



Functional Neuroimaging Studies of the Human Somatosensory System

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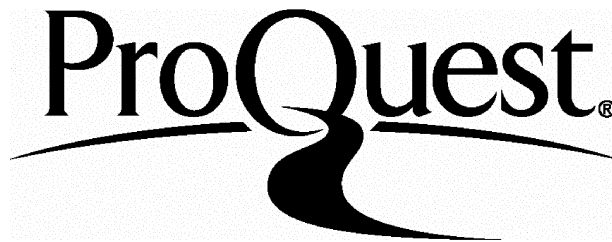
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Abstract

All organisms must possess the ability to detect environmental stimuli and transform them into a form of information that can be utilised to guide behaviour. As the primate sensory systems consist of multiple interconnected cortical areas, it is important to know *where* areas processing different aspects of a sensory stimulus are located, and also *which* dimensions of the stimuli are being processed in each area. The use of functional neuroimaging allows one to address both of these problems.

Although much progress has been made regarding the functional and anatomical organisation of higher order visual areas such as IT (e.g. Milner and Goodale, 1996), there has been comparatively little headway in understanding the functional organisation of somatosensory processing in humans. One problem in particular, the delivery robust somatosensory stimulation in the neuroimaging environment, is not a trivial one. In summary, the field of somatosensory neuroimaging has not received as much interest as other sensory modalities.

In this thesis, I will present the results of my studies, which can be divided into three sections. I) The design and implementation of stimulation within the scanning environment; II) examinations of the topography of digit representations within primary and tertiary somatosensory areas using fMRI, and; III) examinations of sensorimotor transformations and somatoform illusions. My results are discussed with reference to similar studies in other sensory systems, and are placed in the context of investigations using other non-invasive scanning technologies.

Contents

Abstract	2
Contents	3
List of Figures	6
List of Tables	7
Acknowledgements	8
Opening Quotation	9
Chapter 1 The Primate Somatosensory System	
1.1. <i>Studies of Sensory Processing and Perception - General Overview</i>	
1.1.1 Sensing, Perceiving and Knowing	10
1.1.2 Perception: Philosophical Investigations	11
1.1.3 Psychophysics and Experimental Psychology	15
1.1.4 Later work: Gestalt Perception and Dynamic Sensory Processing	17
1.2 <i>The Neuroscience of Sensory Perception</i>	
1.2.1 Basic Principles	19
1.2.2 The Human Somatosensory System	26
1.3 <i>Summary and Aims</i>	38
Chapter 2 Materials and Methods - The Acquisition and Analysis of Functional Neuroimaging Data	
2.1 <i>Non-invasive Imaging Methodologies</i>	
2.1.1 Blood Flow and Neuronal Metabolism - An Introduction	40
2.2 <i>Methodologies Utilising Regional Cerebral Blood Flow : PET & SPECT</i>	
2.2.1 H ¹⁵ O ₂ PET: A Brief Overview	42
2.3 <i>functional Magnetic Resonance Imaging: fMRI</i>	
2.3.1 The Physics of NMR and MRI	47
2.3.2 T ₂ * and fMRI	57
2.4 <i>Characterising Neurovascular Changes With The General Linear Model – Statistical Parametric Mapping (SPM)</i>	
2.4.1 Image Analysis and Pre-processing	61
2.4.2 fMRI and PET: Experimental Design, Statistical Inference and Modeling	65
2.4.3 Experimental Models for fMRI	72
2.4.4 Scanning Protocols for fMRI Experiments	81
Chapter 3 Somatosensory Stimulation in fMRI: Vibrotactile and Airpuff Stimulation, Methodology, and Pilot Studies	
3.1 <i>A Stimulating Problem?</i>	
3.1.1 Somatosensory Stimuli Used in Experimental Studies	85
3.1.2 Interactions Between MRI Environment and Experimental Equipment	87
3.2 <i>Vibrotactile Stimulation of the Digit Pads in fMRI</i>	
3.2.1 Methods - Stimulator Theory	89
3.2.2 Methods - Stimulator Construction	91
3.2.3 Methods - Experimental Setup and Scanning	93
3.2.4 Results	95
3.3 <i>Stimulation of the Digits Using Airpuffs in fMRI</i>	
3.3.1 Methods – Stimulator Construction	104
3.3.2 Methods – Experimental Setup and Scanning	107
3.3.3 Results	108
3.4 <i>Discussion and Conclusions</i>	
3.4.1 Stimulation, Scanning and Analysis Methodology	114
3.4.2 Experimental Design and Task Constraints	117

3.4.3 Postcentral Gyrus Cytoarchitecture, Localising Activation Foci and Receptive Field Properties	119
3.5 <i>Conclusions</i>	
3.5.1 The Sensory-Motor Paradox Revisited	121
Chapter 4 Variability in fMRI: The Generality of Single Session Results	
4.1 <i>The Generality of Experimental Data</i>	124
4.2 <i>Populations, Inference and Multi-Level Modeling</i>	127
4.3 <i>Methods – Experimental Setup and Scanning</i>	
4.3.1 Subject and Scanning Details	129
4.3.2 Experimental Setup	130
4.3.3 Image Preprocessing	131
4.3.4 Data Analysis	132
4.4 <i>Results</i>	
4.4.1 Individual session results	140
4.4.2 Multiple Session Analyses	145
4.5 <i>Discussion</i>	
4.5.1 Differences in the Generality of Different Activation Paradigms	162
4.5.2 Sources of Session by Condition Interactions	163
4.5.3 Stability of fMRI Results across Sessions - Consequences for Longitudinal Studies	165
4.5.4 Use of Thresholded Statistical Maps to Analyse Session Generality	165
4.5.5 Effects of Sample Size on the Analysis of Generality	166
4.5.6 Levels of Inference Arising from Fixed and Random Effects Models	167
4.6 <i>Conclusions</i>	169
Chapter 5 An Examination of Stimulus-Response Functions In Somatosensory Cortex	
5.1 <i>Stimulus-Response Dynamics in the Somatosensory System</i>	
5.1.1 Neural Coding and Sensory ‘Tuning’	172
5.1.2 Convergent and Divergent Connectivity in the Somatosensory System	173
5.1.3 SI Maps: Subthreshold Influences	174
5.1.4 Stimulus Rate and Neuroimaging Studies	175
5.2 <i>Construction and Calibration of Airpuff Stimulator - Mark II</i>	
5.2.1 Design and Construction of Finger-Specific Airpuff Stimulators	176
5.2.2 Calibration And Physical Properties of Airpuff Stimulators	179
5.3 <i>Methods – Experimental Setup And Scanning</i>	
5.3.1 Subject and Scanning Details	186
5.3.2 Experimental Setup	186
5.3.3 Image Preprocessing and Data Analysis	187
5.4 <i>Results</i>	
5.4.1 Single Rate/Digit Contrasts	188
5.4.2 Main Effect Contrasts	193
5.4.3 Rate-Dependent Responses in SI	195
5.5 <i>Discussion</i>	
5.5.1 Aims and Results	197
5.5.2 Rate-Dependent Responses - Methodological Issues	198
5.5.3 Somatosensory Rate-Dependent Responses – Neurobiological Issues	200
5.5.4 Who To Tune?	202

Chapter 6 **The Functional Neuroanatomy of Passive Tactile Discrimination**

6.1 <i>Goal-Directed Tactile Processing</i>	
6.1.1 The Somatosensory System: Beyond SI	205
6.1.2 Previous Studies of Functional Segregation in the Somatosensory Cortices	208
6.2 <i>Materials and Methods</i>	
6.2.1 Stimulus Delivery	211
6.2.2 Behavioural Task – Location and Intensity Discrimination	212
6.2.3 Subject and Scanning Details	216
6.2.4 Experimental Setup	216
6.2.5 Image Preprocessing and Data Analysis	217
6.3 <i>Results</i>	
6.3.1 Behavioural Results	220
6.3.2 Imaging Results	221
6.4 <i>Discussion</i>	
6.4.1 Aims and Results of the Experiment	227
6.4.2 Areas Involved in Attention to and Discrimination of Tactile Stimuli	227
6.4.3 Areas Activated by Location or Intensity Discrimination Task	231
6.5 <i>Conclusions</i>	
6.5.1 Tactile Attention: Modulation of Activity in ‘Early’ or ‘Late’ Cortical Areas?	234
6.5.2 Task-Related Differences in Somatosensory Cortical Areas	237

Chapter 7 **Whose Arm Is It Anyway? : The ‘Action Space’ and Somesthesia**

7.1 <i>Perception for Action...or Action for Perception?</i>	238
7.2 <i>Materials and Methods</i>	
7.2.1 Patient Details – Lesion and Neurological Examination	241
7.2.2 Patient Details – Body Schema Distortions	244
7.2.3 Patient Details – Previous Investigations	245
7.2.4 Experimental Details	245
7.3 <i>Results</i>	
7.3.1 Main effects of ‘Event’ Conditions	251
7.3.2 Contrast of ‘Tonic’ Conditions: ‘Phantom On’ – ‘Phantom Off’	254
7.4 <i>Discussion</i>	
7.4.1 The SMA and ‘Goal-Directed’ Movements	258
7.4.2 Physiological Interpretation of Sustained SMA Activity	260
7.4.3 The Influence of Motor Representations on Subjective Perception	261
7.5 <i>Conclusions</i>	262

Chapter 8 **Discussion And Conclusions: fMRI of the Human Somatosensory System**

8.1 <i>General Discussion</i>	
8.1.1 Somatopy, or Not Somatopy? : Spatial Order in SI	264
8.1.2 ‘Higher Order’ Studies of Somesthesia	266
8.1.3 Don’t Get Touchy: Speculations on the Difficulties of Tactile fMRI	268
8.2 <i>Concluding Remarks</i>	269

References	270
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Appendix 1 - Chapter Four Tabular Data	330
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List of Figures

Figure 1.1 <i>A graph of the Weber-Fechner law</i>	15
Figure 1.2 <i>Examples of the Weber-Fechner law for different sensory modalities</i>	17
Figure 1.3 <i>Schematic representation of the transduction of peripheral stimuli by a first-order afferent neuron/receptor</i>	20
Figure 1.4 <i>Depictions of the defining features of the four types of mechanoreceptor afferents innervating human glabrous skin</i>	27
Figure 1.5 <i>Ascending pathway for discriminative tactile sensations, the medial lemniscal Pathway</i>	29
Figure 1.6 <i>Cytoarchitectonically-defined somatosensory areas of the macaque cerebral cortex</i>	31
Figure 2.1 <i>Link between signal (S) and mental process (M), adapted from Shulman and Rothman (1998)</i>	42
Figure 2.2 <i>'Spin' and 'Precession' of a single proton</i>	49
Figure 2.3 <i>Top. T₁ recovery. Bottom. T₂ decay.</i>	52
Figure 3.1 <i>Principles underlying the construction of the vibrotactile stimulator</i>	90
Figure 3.2 <i>The finished vibrotactile stimulator as used in the scanner</i>	92
Figure 3.3 <i>Examples of peak voxel timeseries' from separate PoG clusters elicited during vibrotactile stimulation in subject BA</i>	99
Figure 3.4 <i>Main effect of D2 stimulation, subject BA</i>	100
Figure 3.5 <i>Group analysis of D2 and D5 stimulation, overlaid on the mean normalised group functional image</i>	102
Figure 3.6 <i>Diagrammatic representation of the airpuff stimulator</i>	106
Figure 3.7 <i>Example of one cycle of airpuff stimulation</i>	108
Figure 3.8 <i>Main effects of single digit stimulation, subject JA</i>	111
Figure 3.9 <i>Group activation, thumb stimulation</i>	113
Figure 3.10 <i>Group activation, index stimulation</i>	113
Figure 4.1 <i>Design matrices used in analysis</i>	134
Figure 4.2 <i>Single session sagittal Maximum Intensity Projections (MIPs) for the motor paradigm</i>	138/39
Figure 4.3 <i>Single session sagittal MIPs for the cognitive paradigm</i>	141/42
Figure 4.4 <i>Single session sagittal MIPs for the visual paradigm</i>	143/44
Figure 4.5 <i>Multisession analyses of the motor paradigm, analysed using a fixed effects model (4.5a), extra-sum of squares F test (4.5b), and a random effects model (4.5c)</i>	146/7/8
Figure 4.6 <i>Multisession analyses of the cognitive paradigm, analysed using a fixed effects model (4.6a), extra-sum of squares F test (4.6b), and a random effects model (4.6c)</i>	151/52/3
Figure 4.7 <i>Multisession analyses of the visual paradigm, analysed using a fixed effects model (4.7a), extra-sum of squares F test (4.7b), and a random effects model (4.7c)</i>	154/5/6
Figure 4.8 <i>Examples of voxels from the multisession motor analyses that typify different kinds of statistical significance</i>	159
Figure 4.9 <i>Session by session plots of the parameter estimates (α_i) and their standard deviations (red bars) of voxels from figure 4.8 (A-D)</i>	161
Figure 5.1 <i>Schematic representation of tuning on sensory systems</i>	172
Figure 5.2 <i>Schematics for a single airpuff 'gutter'</i>	177
Figure 5.3 <i>Single hand setup of airpuff gutters</i>	178
Figure 5.4 <i>Setup of transducer during calibration procedure</i>	179
Figure 5.5 <i>Plot of the weight of objects versus the voltage output of the transducer</i>	180
Figure 5.6 <i>Graphical representation of the low-pass filter used by Spike 2</i>	181
Figure 5.7 <i>Plot of duration of valve opening vs. force of airpuff</i>	182
Figure 5.8 <i>Variables used for analysis of airpuff reproducibility</i>	183
Figure 5.9 <i>Three average waveforms (N=10 for each) from line 3</i>	184

Figure 5.10 Power spectra of rate stimuli used in current experiment	185
Figure 5.11 Representation of the number of activated clusters across all 7 subjects, grouped by cortical area, digit and stimulation rate	191
Figure 5.12 Comparisons between spatial patterns of somatopy between two subjects	192
Figure 5.13 Main effects of middle digit stimulation across all rates of stimulation in four subjects (S1, S2, S3 and S5)	194
Figure 5.14 Effects of stimulation rate on BOLD signal in contralateral SI	196
Figure 6.1 Illustration of the 'dorsal' and 'ventral' pathway hypotheses in vision and Somesthesia	207
Figure 6.2 Airpuff stimulator used in the current experiment	212
Figure 6.3 Schematic illustration of the different components ('target', 'probe' and 'response') comprising each discrimination trial	215
Figure 6.4 Different classification of covariates in each subject's experimental model	218
Figure 6.5 Mean percentage correct trials across all sessions and subjects	220
Figure 6.6 Maximum intensity projection (MIP) of voxels showing a significant ($p < 0.05$ corrected for multiple comparisons) effect in the masked ($A+B+C+D$) – E contrast	222
Figure 6.7 MIPs displaying significantly activated voxels in (Intensity no Motor Response) > (Passive Control) conjunction., and in (Location no Motor Response) > (Passive Control) conjunction	225
Figure 7.1 A three-dimensional rendering of E.P.'s brain constructed from her T1-weighted structural and E.P.'s lesion, shown in greater detail	243
Figure 7.2 Schematic representation of two cycles of the experimental paradigm	250
Figure 7.3 Simple movement-related effects in E.P.'s brain	253
Figure 7.4 Sagittal slice (2mm thick) of E.P.'s T1 scan showing location of SMA cluster in detail and BOLD signal change at peak voxel of SMA cluster	257

List of Tables

Table 3.1 Local maxima within the contralateral postcentral gyrus (PoG)...	96
Table 3.2 Local maxima within the contralateral postcentral gyrus (PoG) ...	110
Table 5.1 Single digit/rate contrasts, listed by subject	189
Table 5.2 Within-rate comparisons of somatopy	190
Table 5.3 Main effects of digit stimulation per subject averaged across all stimulation rates	193
Table 6.1 Areas significantly activated in the masked ($A+B+C+D$) – E contrast	223
Table 6.2 Areas significantly activated in the conjunction analysis (Intensity no motor response) – (passive control)	226
Table 6.3 Areas significantly activated in the conjunction analysis (Location no motor response) – (passive control)	226

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This dissertation has not been submitted in whole or in part for any degree or qualification at any other University. Some of the results of Chapter 4 have been published in the following paper:

McGonigle D.J., Howseman A.M., Athwal B.S., Friston K.J., Frackowiak R.S.J., Holmes A.P.. 2000. Variability in fMRI: An Examination of Intersession Differences. *NeuroImage* 11:708-734 (doi:10.1006/nimg.2000.0562)

I hate quotations.

Tell me what you know.

-- *Ralph Waldo Emerson*

1. The Primate Somatosensory System

1.1. Studies of Sensory Processing and Perception - General Overview

1.1.1. Sensing, Perceiving and Knowing¹

All animals must interact with their environment in order to perform meaningful, goal-directed behaviour. To obtain knowledge about their external surroundings, they must possess the means to detect relevant stimulus features and transform them into information that they can utilise. The mechanisms underlying this process vary significantly between species. At one extreme, single-celled organisms possess rudimentary sensory organs, and can use these in a manner consistent with the sense organs of higher organisms. For example, the eyespots possessed by microorganisms of the genus *Euglena* allow the animal to perform simple phototaxis. Detection of external information relevant to the continued survival of the organism (in this case, energy in the electromagnetic spectrum, light) causes the animal to move towards the source of the energy.

For simple animals like the Euglenoids, it is simple to draw conclusions about *why* the organism is behaving in this manner, because there are few other behaviors that the animal could display in this situation. There are, quite simply, no other ways in which stimulation of the eyespot could produce any other responses. Therefore we could, with a remarkable degree of certainty, predict the behavioural consequences of any possible interactions between the Euglenoid and its environment. By focusing on the mechanisms that the organism uses in its simple form of sensory processing, it is possible to gain knowledge about the organism as a whole.

Not all organisms, however, are as simple as Euglenoids. Humans, in particular, have a vast repertoire of percepts that can be evoked by stimuli with misleadingly similar physical properties (e.g., Gregory, 1997). Even though humans and other primates are immeasurably more complex than Euglenoids,

¹ As it is currently unclear if any stimuli can be regarded as being completely unprocessed by the nervous system, we will not draw a difference between 'sensation' and 'perception'.

they share fundamental similarities in the mechanisms that they employ for perception. In the majority of species, sensory processing involves energy acting upon a specialized *sense organ*, or receptor, with the energy being *transduced* into a form that the organism can use. All nervous systems use electrochemical mechanisms for communication (although some species use electrical synapses as well) and so share basic features. Mammals, however, rarely rely on a single sensory modality. Each of these senses may have a number of receptor sub-classes, each of which in turn may use different transduction mechanisms, or produce a different response from the organism.

Confronted by these levels of complexity, it may initially be difficult to imagine how a purely materialistic description could ever hope to describe sensory processing in all its diverse forms. The approach advocated within this thesis is that if one wishes to study human and animal cognition, it is necessary to first have an appreciation of the neuronal architecture underlying even the simplest of percepts, as ultimately artificial and devoid of context as they may be. The data presented herein concerns the functional organisation of the human somatosensory system, studied using functional magnetic resonance imaging (fMRI). While the nature of sensory processing and perception have only been studied empirically for less than two hundred years, they have been the subject of debate for well over two thousand. As only the methods used in the study of perception have changed, rather than the questions, it is useful to briefly review the history of the study of perception.

1.1.2 Perception: Philosophical Investigations

Investigations of perception in the western world are as old as philosophy itself. The Greek Sophists (5th century BC) questioned how one could obtain knowledge from the external environment. One prominent sophist, Protagoras, taught that each person's opinions were the sole result of their experience, and so in arguments it could be debated that each person's viewpoint was ultimately as valid as the other's. Although from a modern perspective it is easy to sympathise with these views, it is fortunate that the teachings of the Sophists did not become more widespread, as by effectively neutering the power of public

debate they would have greatly damaged the emergence of modern schools of thought. Plato (427-347 BC) answered the Sophists by claiming that there existed a world of *forms* that we gain knowledge of through subjective sense impressions. In addition, he claimed that by studying these forms using abstract methods, such as philosophy, one could overcome the imperfections of the senses.

Aristotle (384-322 BC), a student of Plato, disagreed. He taught that all knowledge *must* come through experience. 'There is nothing in the intellect,' he wrote, 'that was not first in the senses' (Russell, 1975). However, he did not believe that all examples of perception could be explained in this fashion. Aristotle argued that human thought in its highest form (*nous poetikos*, "active mind") could never be explained by mechanistic principles.

From these early debates it is apparent that a number of themes that would later become central to the study of perception and sensory processing were already surprisingly well developed. The struggle to define an epistemologically valid method that would facilitate the integration of different, subjective perceptions of the environment is evident in the work of Plato and Aristotle. However, a major difference was that the Greeks regarded these studies as examinations of the soul, rather of the mind.

It was not until the late seventeenth and early eighteenth century that the *means* for acquiring knowledge began to be actively debated. Earlier philosophers such as Rene Descartes (1596-1650) had attempted to produce explanations of mental processes using examples from then contemporary physiology. Descartes was rare amongst his contemporaries because of his twin interests in the physical and mental world, yet even he regarded the higher faculties as essentially opaque to empirical study. Descartes approach became known as *dualism*, in that both ephemeral (mind) and physical (body/brain) properties were required for life/consciousness.

The English philosophers Thomas Hobbes (1588-1679) and John Locke (1632-1704) did not agree with Descartes. They argued that all human experiences were purely physical processes, occurring within the brain and

nervous system. Just as Aristotle before him, Locke asserted that human knowledge was dependent on the senses, and so humans could not claim to have objective knowledge about the external world. This philosophical school became known as *empiricism*. Like Berkeley (1685-1753) and Hume (1711-1776) after him, Locke believed that a person's mind is a *tabula rasa* (blank slate), and that ultimately all human knowledge comes from sensory experience. In 'A treatise on human knowledge' (1690) Locke stated that 'how comes this [blank slate] to be furnished? [...] To this, I answer, from *experience*'.

The Scottish philosopher David Hume developed the ideas of Locke, and introduced the concept that two sorts of knowledge could be distinguished: knowledge on the *relations* between ideas, and knowledge derived directly from sensory perceptions. The former could be described unambiguously (e.g. mathematical principles), yet carried no information about the world. The latter, while derived from external sources, relied upon cause and effect for their power, and as Hume argued against any logical connection between causes and effects, it was thus impossible to derive measures of objective knowledge. Again, although progress had been made in defining the nature of human knowledge, studies had again reached an *impasse*. What was required was some way to study perception empirically – in effect, to move from philosophical studies to psychological *experiments*. Although Locke, Berkeley and Hume were collectively known as 'the empiricists', there were few planned experiments on perception carried out during their lifetimes (Gregory, 1987). Locke and Newton corresponded frequently, yet little effort was made to put philosophical principles on a similar footing with the physical sciences. However, the work of the three was immensely influential, and came at a time where significant advances were being made in the physical and biological sciences.

The empiricists had their critics, however, and amongst them Leibniz (1646-1716) and Kant (1724-1804) dominated. Kant was particularly vocal in proposing a series of objections as to why mental phenomena would forever remain unknowable and obscure. To Kant, it would forever be impossible to apply the rigorous means of empirical science to phenomena that were internal,

ephemeral and subjective. Taken to its logical conclusions, Kant's philosophy negated the purely objective study of perception. In addition, a number of empirical studies conducted around the same time as Kant's writings strengthened his proposals. The law of specific nerve energies and new discoveries about the wave nature of light suggested that: i) although light energy can cause visual experience, so can mechanical stress to the eyeball, and all one could be sure of was that the optic nerve had been stimulated, *not what had stimulated it*; and ii) although light and sound were waves, humans did not perceive these energies in this form. In common with the humble Euglenoid, *Homo Sapiens* was at the mercy of the transduction mechanism.

The first suggestions of a truly empirical study of mind can be found in the writings of the French philosopher Auguste Comte (1798-1857), the founder of the philosophical school of *positivism*. In his six-volume 'Course of Positive Philosophy' he proposed that in the pursuit of knowledge there were 'three different theoretical states: the theological or fictitious state; the metaphysical or abstract state; and, lastly, the scientific or positive state.' The latter, the scientific state, placed its emphasis on discovering relations between phenomena, and making observations that could later be confirmed by observation. In essence, Comte proposed that behaviour must be studied in the same objective manner as the biological sciences, and implied that human behaviour could eventually be measured and quantified, in contrast to Kant. However, Comte offered few ideas as to how one could actually go about this enterprise (perhaps tellingly, Comte is credited with being the father of Sociology). It was not until the work of Weber (1795-1878), Fechner (1801-1887), Helmholtz (1821-1894) and Wundt (1832-1920) that the study of perception began to use an empirical approach. By instigating a new method to study perception they brought the approach that Comte had advocated to fruition. This marked the beginning of a science devoted to studying the links between physical stimuli and subjective perception: *psychophysics*.

1.1.3 Psychophysics and Experimental Psychology

Although the term ‘psychophysics’ was first defined by Gustav Fechner in his book ‘Elements of Psychophysics’ (*Elemente der Psychophysik*), published in 1860, the ideas proposed within it had not evolved within a vacuum.

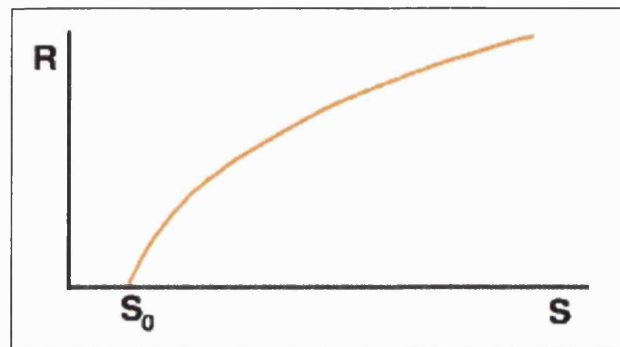


Figure 1.1 A graph of the Weber-Fechner law relating real (R) and subjective (S) stimulus intensities. After S_0 (the smallest stimulus intensity that the subject can perceive), the relationship between R and S is defined by $S = k \log R$, where k is a constant for each sensory modality and S is measured in j.n.d units.

The writings of the Locke contained a number of views that were later echoed by Fechner. Locke proposed that objects could be defined in two ways: by ‘stimulus properties’, which were truly objective physical properties (e.g. the luminance of an object) and by the subjective properties of stimuli (e.g. the *brightness* as viewed by an observer). Fechner resolved this difficulty by deciding that he should study ‘the relative increase of bodily energy...’ and make this ‘...the measure of the increase of the corresponding mental energy’ (Boring, 1950). This initial suggestion built directly on the work of Weber, who had discovered that the ability to discriminate between two things depended not on the absolute difference between them, but instead on the ratio of the two quantities. Furthermore, as measured at the time, this ratio was constant: it became known as the ‘just noticeable difference’ (j.n.d). Fechner used this result to overcome Kant’s earlier assertion that psychology would forever remain outside science, as it required some means of quantifying internal stimuli: Fechner realized the j.n.d could be used to overcome this. It therefore seemed that there were ways in which the ‘inner world’ of subjectivity could be studied in an objective manner².

² Recent studies have challenged the veracity of the jnd as a reliable measure of perception, however.

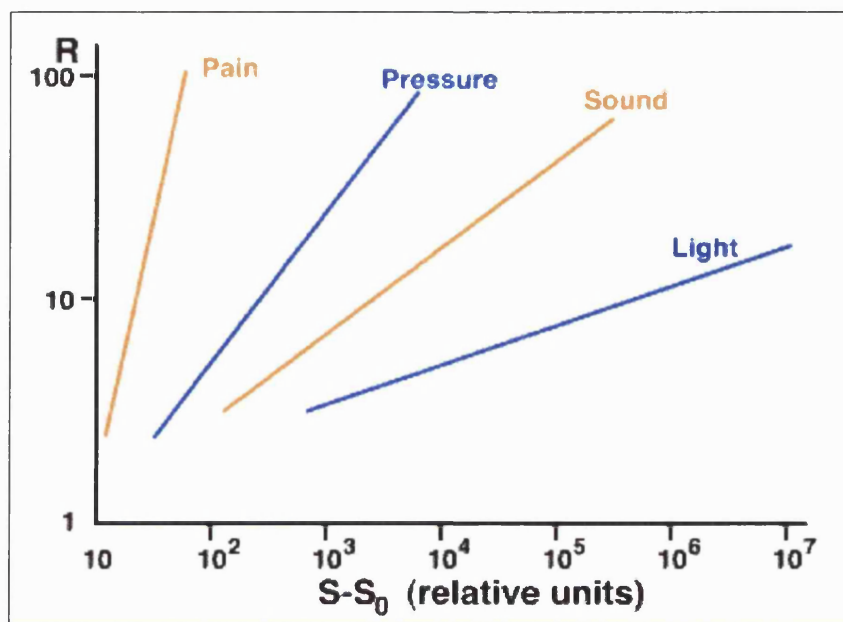


Figure 1.2. Examples of the Weber-Fechner law for different sensory modalities. The figure differs from the previous example because the difference between the two stimuli ($S-S_0$) has been plotted using a semi-log scale.

The work of Hermann Von Helmholtz expanded on these early discoveries by initiating the systematic study of the biological underpinnings of sensory processing and perception. His studies of vision demonstrated that the eye could be treated as though it is an optical instrument, and although it was riddled with imperfections and defects humans nevertheless experience a coherent external visual world. He wrote, 'That the character of our perceptions is conditioned just as much by our senses as by the external things is of the greatest importance'. Helmholtz asserted that physiological and psychological experiments were important, as they allow us to overcome our imperfect sense of perception, and to gain objective experience of the world around us. His work was influential in establishing that mental processes could indeed be studied.

1.4 Later work: Gestalt Perception and Dynamic Sensory Processing

Although late nineteenth century experimental psychology advocated the study of the senses, a committee set up by the British Association for the Advancement of Science in 1932 came to a different conclusion: internal sensation could not be measured, or at least could not be measured using similar techniques as those employed to study the objective qualities of objects. The English experimental

psychologist Edward Titchener called this problem the ‘stimulus error’. Titchener believed that the kinds of judgements that we make are very dependent on the contexts in which they are made i.e. the effects of preceding stimuli on category judgements. However, psychology was saved again from recourse to sterile analysis by a new school of psychology (*Gestalt* psychology) that built on the work of Kant, in particular his theory of *pre-knowledge*. Kant influentially claimed that sensory experiences do not only depend on the percepts themselves, but crucially on the way in which sensory experience is organised - the pre-knowledge. To the Gestaltists, *form* was the primitive of perception - they were most interested in the relative relationships between the elements that made up a unified conscious percept. This does not mean that they sought to ignore individual elements or features – merely to advance the idea that the *configuration* of these elements was also important.

Views of perception as essentially dynamic were further advanced by the British psychologist F.C. Bartlett (1932), who believed that perceiving, remembering, imagery, and recall were all dynamic processes, influenced by the current state and needs of the organism *at the time of the process*. These views regarded animals as goal-orientated organisms that actively *sought* stimulation, re-casting sensory perception as an active process – a concept that will be revisited in Chapters 6 and 7. The foremost proponent of this school of psychology was J.J. Gibson (1904-1979). Gibson developed an ‘ecological’ approach to the study of perception, asserting that sensory data are obtained directly from the environment without the kind of ‘unconscious inference’ that Helmholtz had proposed almost a century before.

This brief outline of the history of the study of sensory processing has been designed to stress two important points: i) whenever people have been adamant that perception involves something ‘more’ that cannot be measured or quantified, they have invariably been proven wrong, and ii) perception and knowledge may seem to be internal, subjective and ephemeral, yet yield to materialistic enquiry. Advances have only been made, however, when investigations have built on basic physiology – for example, without

Helmholtz's knowledge of the basic structure of the eye, his theories of visual perception would have lacked a solid foundation. The pioneering combination of electrophysiological and psychophysical methodology made by Mountcastle and co-workers (for review see Mountcastle, 1995) is another example of this. Before studying the neuroscience of perception and sensory processing, one must first study the basic architecture underlying subjective experience – in the present case, the architecture of the somatosensory system.

1.2 The Neuroscience of Sensory Perception

1.2.1 Basic Principles

1.2.1.1. *Structure of Primate Sensory Systems: Peripheral and Central Organisation.*

Although the remainder of this thesis will focus almost exclusively on the organisation of the somatosensory system in man, the sensory systems of higher mammals are organised in a similar manner. It is useful to briefly consider this before proceeding, as the results from later chapters will be compared to current knowledge from other mammalian sensory systems, in particular the visual system (Chapter 6 focuses on the possible functional homologies between information processing in the somatosensory and visual systems).

As a general rule, the first neural event in sensory processing is the stimulation of a *receptor*, a specialised cell designed to *transduce* energy into electrochemical events i.e. a pattern of changes in cell membrane potential ultimately leading to the cell firing. As noted previously, the method of transduction varies widely across species and sensory modalities. For example, in the vertebrate eye, transduction involves a complicated chain of interactions between light-absorbing visual pigments and various second-messenger molecules (Tessier-Lavigne, 1991), culminating in a change in the photoreceptor's membrane potential. At the other end of the spectrum, the human somatosensory system contains free nerve endings, lacking any kind of accessory structure – perhaps the simplest receptors possible (yet not the oldest phylogenetically; e.g. Halata, 1993) However, although the actual physical

energy transduced can be very different, the result is almost exclusively electrochemical.

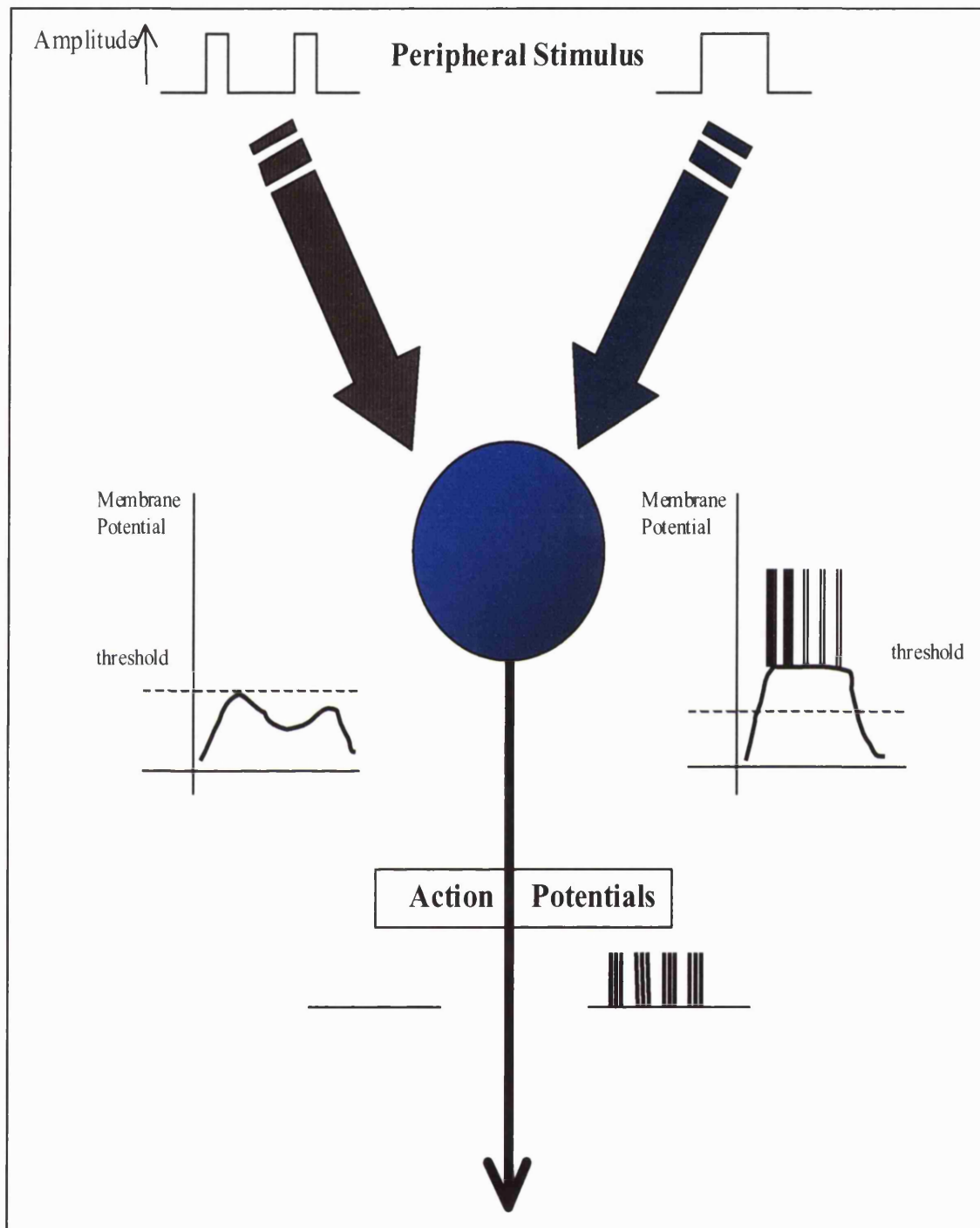


Figure 1.3. Schematic representation of the transduction of peripheral stimuli by a first-order afferent neuron/receptor. The stimuli on the left do not cause the neuron to depolarise sufficiently to trigger an action potential, while the stimulus on the right causes the neuron to fire repeatedly

Figure 1.3 above shows a simplified diagram of the peripheral events accompanying stimulation of a receptor/sense organ with a stimulus that it is 'tuned' to detect (i.e. photons for rods and cones, mechanical deformation for Pacinian corpuscles, etc.). The somatosensory system contains by far the most receptor types of any of the primate sensory systems, as it possesses mechanoreceptors, chemoreceptors, nociceptors and thermoreceptors. In addition, like olfactory receptors but unlike visual and auditory systems, the somatic receptors are actually neurons that must transduce and represent the stimuli as a neuronal code.

1.2.1.2 *Neuroanatomical Pathways from Periphery to Centre in Sensory Systems.*

In the majority of sensory systems, information takes a similar path after transduction has taken place. The first neuron in the ascending sensory pathway (the *primary afferent* in the somatosensory system) synapses with a neuron whose cell body lies in the dorsal horn of the spinal cord, although the afferent fibres of some of the cranial nerve first synapse with their own associated nuclei (i.e. the spinal trigeminal nucleus in the medulla). There is no simple point-to-point relationship between the projection of the primary afferent and the second-order spinal neuron that it synapses with. Primary afferent fibres branch extensively in both superior and inferior directions in the spinal cord. For example, in the feline somatosensory system each afferent fibre class has a distinctive terminal pattern of arborization (Brown, 1981). Even at this relatively early stage of the ascending neuraxis, an anatomical substrate for the integration of afferent information exists. In general, however, there is a segregation of submodalities along ascending pathways.

Before reaching the cortex, the second order neuron will typically synapse with the thalamus before entering the cortex. In humans, only the olfactory system bypasses this structure. Ascending information arises to the cortex in a thick bundle of fibres known as the ascending limb of the *internal capsule*. The thalamus plays an important role in sensory processing, forming a richly reciprocated loop with cortical areas. These 'reentrant' loops have been

suggested by some observers to be a substrate for ‘higher-order’ aspects of human cognition, such as consciousness (e.g. Edelman, 1992). It is sufficient to say that the thalamus, although a subcortical structure, is more than a mere ‘pit stop’ for axons as they make their way to the cortex.

1.2.1.3 *The Receptive Field*

Any neuron involved in the processing of sensory information has a receptive field (r.f.), a location in the peripheral receptor sheet that optimally excites the neuron under normal physiological conditions. The concept of the receptive field can be applied to each successive level of the processing hierarchy, so that the r.f.s of primary afferents can be contrasted with the r.f.s of central neurons. However, the further away from the periphery one proceeds, the more abstract the concept of the r.f. becomes.

The r.f.s of receptors occupy a position within a ‘space’, which is spanned by the different stimulus dimensions that excite the sensory modality in question. The receptor’s r.f. is the portion of this space that excites it. This can have a direct spatial interpretation, like in the primate visual and somatosensory systems: r.f.s occupy a spatial position within the peripheral receptor sheet, and are excited when stimulation impinges upon that location. The space can be highly abstract, however, as in the primate auditory system – here r.f.s are defined by the receptors sensitivities to particular frequencies of sound energy. Similarly, the r.f.s of chemoreceptors within the gustatory and olfactory systems are defined by variations along a chemical dimension. In addition, r.f. dimensions can be described as varying in time – spatiotemporal variations in peripheral r.f.s have been shown to exist in the somatosensory system (DiCarlo et al., 1999).

1.2.1.4 *Coding of Stimulus Attributes By Neuronal Firing*

A major problem for any study of sensory physiology is to bridge the gap between the external, physical quantities of stimuli and their eventual representation by internal electrochemical events. As discussed previously, the stimulation of tactile receptors or visual receptors is experienced as very different subjective percepts. However, once the stimulus has been transduced

(whether it is visual or somatic) *all* physical features are represented as electrochemical changes. Therefore, any attempt to examine in detail the neuronal implementation of sensory processing must first explain how stimulus features such as location and intensity are *encoded* in the firing patterns of neurons at different levels of the nervous system. If the code is known, it is possible to construct a model of how the feature is encoded, and employ this to predict how the system will behave when any value of the stimulus is presented to the organism, under any context.

Adrian and Zotterman (1926) were the first to record that the discharge frequency of a single nerve fiber increased with the intensity of the stimulus applied to it. This is an example of a frequency or rate code. According to this theory, the number of spikes fired by each neuron in a set time interval represents stimulus features in the periphery. To reconstruct the stimulus feature, or have some idea of what the pattern of stimulation that the neuron is receiving represents, one merely has to record the number of spikes from a particular neuron or group of neurons (e.g. Parker and Newsome, 1998).

The other major theory of neuronal coding is temporal coding. Temporal coding asserts that the temporal relationship *between* spikes is the appropriate metric for the encoding of information. In these models, neurons act as coincidence detectors to certain patterns of spikes, rather than reproducing in an isomorphic fashion the actual pattern of the spikes themselves as they arrive (e.g. Singer and Gray, 1995). In addition, there are suggestions that transitions between firing rates are equally important (Bodner et al., 1998), although fewer studies have examined this possibility.

In addition, the fundamental unit that the nervous system employs to analyse sensory information is controversial. Is the signal from one neuron sufficient for an organism to base a perceptual judgement, or does pooling of neuronal information occur? Do different principles occur at the periphery of the nervous system versus more central structures? Early analyses emphasised the importance of single neurons, as outlined by Barlow (1972): 'The central proposition is that our perceptions are caused by the activity of a rather small

number of neurons selected from a very large population of predominantly silent cells. The activity of each single cell is thus an important perceptual event...’.

More recent analyses take a more measured approach. Parker and Newsome (1998) argue that although evidence from biophysics, psychophysics and neurophysiology support a pooling approach in central structures, there are discrepancies between sensory systems. For example, while motion processing in VS appears to require the pooling of signals from a large number of neurons (~100, Shadlen et al., 1996), a single action potential in a somatosensory primary afferent fibre appears sufficient to produce a behavioural response in human subjects (Valbo and Johansson, 1976).

The resolution of this debate is vital for neuroimagers. Human neuroimaging examines the behaviour of large groups of neurons (a typical voxel of size 3x3x3mm may contain 200,000 neurons if centred on cortical grey matter). If one wishes to directly examine and correlate behavioural variables with measures of neuronal activity (e.g. the BOLD measure in fMRI), it is necessary to demonstrate that the averaged signals of large populations of neurons are a metric that is used by the CNS. In addition, if temporal coding is used, the neuroimaging method in question may not possess the temporal fidelity to unravel this measure (e.g. neuroimaging techniques that employ measures of blood flow as their dependent variable). However, while the exact coding strategies employed by single neurons in isolation may be a matter of contention, the experiments described in this thesis are motivated by the numerous experimental demonstrations of a consistent relationship between metabolic mapping and neuronal dynamics at the level of large, cytoarchitectonically-defined areas (e.g. Woolsey et al., 1996). In addition, I assume that it is feasible and reasonable to describe systems-level neuronal processing at the gross level allowable using functional magnetic resonance imaging (fMRI).

1.2.1.3 *Isomorphic Maps in Sensory Systems*

A ubiquitous feature of mammalian sensory systems is the presence of ordered ‘maps’ of stimulus features. The principal is best illustrated by an examination of the mammalian somatosensory and visual systems. The peripheral receptor

sheets of both systems (the retina for vision, the skin for somesthesia) are represented in the primary sensory areas such that the spatial relationship between points in the periphery is preserved. For example, the primate visual field is mapped in an orderly fashion onto the calcarine cortex (reviewed in Zeki, 1993). Similarly, in the rat primary somatosensory cortex, there is an almost perfect isomorph of the peripheral arrangement of the rodent's vibrissae, or whisker system. Early investigations of the organisation of human (Penfield and Boldrey, 1937) showed that consistent patterns of electrically excitable regions existed in cortex, and that gross patterns of similarities existed between brains.

The maps that exist can be, as with the receptive fields of neurons, highly abstract constructs. For example, a complete map of the arrangement of peripheral proprioceptors exists in mammalian brain (Huffman et al., manuscript in preparation). Conceptually, this map is very different to other somatosensory maps - there is no peripheral sheet of muscle spindles or tendon organs. Instead, the topography of area 3a in primates relates to positions within a 'space', like that previously defined for receptive fields.

The existence of sensory cortical maps has led to a number of hypotheses on their existence. These range from regarding sensory maps as an epiphenomenon arising from the common migrational routes taken by neuronal progenitors during development, to those asserting that the existence of topographic maps is a fundamental organisational feature of sensory systems. This debate will be expanded upon in Chapters 3 and 5, in the context of topographic order within human primary somatosensory cortex (SI). For now it is sufficient to note that, while most researchers would argue that topographic maps serve *some* computational need, the exact nature of this is currently unclear.

1.2.2 The Human Somatosensory System

1.2.2.1 *Peripheral Organisation*

The glabrous skin of the human hand is innervated by a number of different peripheral afferent fibres that are commonly differentiated into four broad subclasses. Most studies use the definitions developed by Johansson, Valbo and colleagues (e.g. Johansson, 1976; Johansson and Valbo, 1979; Valbo and

Johansson, 1978), which differentiates the receptors according to and physiological criteria. This gives four classes of receptors (Figure 1.4), delineated by two dimensions: their innervation density on the skin, and responses to tonic levels of stimulation ('adaptation properties'). Evidence supports that the four classes of afferent fibre are each associated with a specific receptor type in the periphery: 'Fast-Adapting type I' (FAIs) with Meissner's corpuscles; FAIIs with Pacinian corpuscles; 'Slowly-Adapting type I' (SAIs) with Merkel complexes; and SAIIs with Ruffini endings. The somatosensory periphery is usually thought of as possessing a 'labeled-line' code, in stimulation of specific receptors results in particular patterns of ascending information in segregated processing channels in the periphery. The majority of experimental evidence supports this, although some researchers believe that, as receptors are not always found connected to certain classes of primary afferents, it is stimulation of the fiber that is primary for sensory processing, not the transduction mechanism of the fiber itself. In the cornea there are few specialized receptors, yet different sub-modalities of somesthesia can be distinguished.

Whatever the resolution of this debate, it is sufficient to note that different afferent fibre populations transmit different submodalities of tactile experience to the CNS. Therefore, it is possible to have deficits that may affect a particular tactile submodality without affecting another (e.g. Cole and Waterman, 1995). In addition, there is a large body of literature that suggests the existence of independent processing channels for vibrotactile perception (Bowlanowski et al., 1988), perhaps in a similar fashion to the parvo- and magnocellular channels of the human visual system.

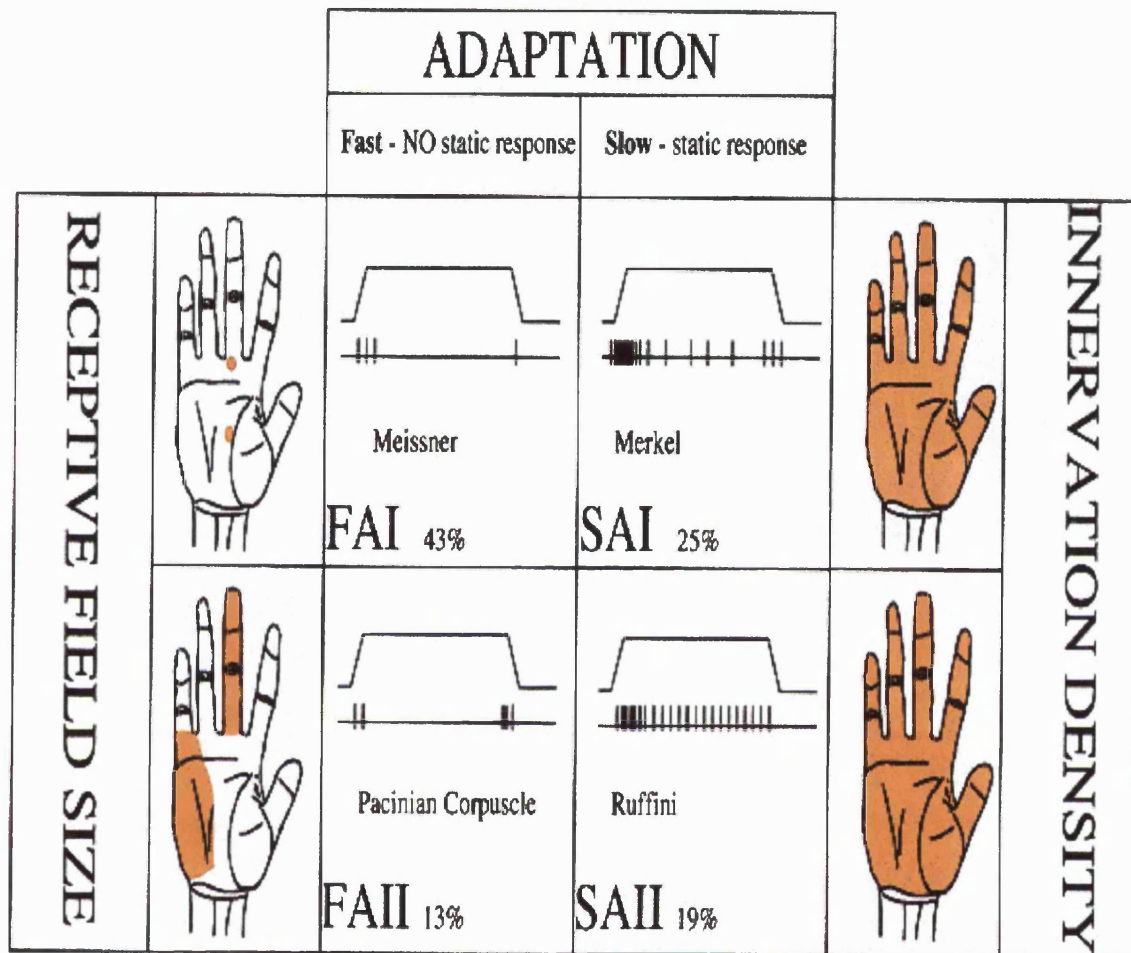


Figure 1.4. Depictions of the defining features of the four types of mechanoreceptor afferents innervating human glabrous skin. The centre figures are representations of 'canonical' responses of the afferents to the ramp-and-hold stimulus depicted as the upper trace. The hands to the left show typical receptive field sizes between type I and type II afferents, while the hands on the right indicate the relative densities of the afferents (darker colours represent greater density). Adapted from Westling, 1986.

Although mechanoreceptors contribute to touch sensations, there are a number of other processing channels within the somatosensory system: nociception, proprioception, and temperature or thermal sense. Proprioception is often defined as 'muscle sense', as proprioceptive afferents carry information from receptors which signal muscle length (muscle spindles), and joint position (Golgi tendon organs). The role of proprioception in contributing to the

conscious appreciation of the body in space, at one time controversial, was conclusively demonstrated by the work of Matthews and colleagues (see Matthews 1988 for review). Information from proprioception is essential for accurate goal-directed movement: however, in this thesis I will be most concerned with the role of proprioception as a perceptual modality (*c.f.* Chapter seven).

1.2.2.2. *Central organisation: spinal cord, brainstem nuclei and thalamus*

Primary afferent fibres enter the spinal cord via the dorsal horn of the spinal cord. The cell bodies of primary afferents are located in the dorsal root ganglion - only their axonal processes enter the grey matter of the dorsal horn, where they synapse with second order somatosensory neurons, or *projection neurons*. Similar to elsewhere in the somatosensory system, the patterns of termination of primary afferents in the dorsal horn are complex. As noted above, the work of Brown (1981) illustrates this point elegantly: different classes of primary afferent have stereotypical patterns of terminal axonal collaterals. In the cat somatosensory system, in some cases the terminal arborization of primary afferent fibres can carry on for several dermatomes (Brown, 1981). The spinal grey matter is divided into laminae using the classification scheme of Rexed, again developed in the cat. Different tracts have their cell bodies in different spinal laminae, and while ascending information is grossly segregated, cross talk between ascending fibre systems is possible (e.g. Burke et al., 1982). These results demonstrate that, even at the early stages of spinal processing, incoming information is processed in a manner reliant on the history of processing in a particular region. This is not merely a facile point: in cognitive neuroscience it is common to talk of information arriving at sensory cortical areas ‘unaffected’ by context or the behavioural state of the organism.

There are two major ascending fibre systems that convey somatosensory information to cortical structures: the dorsal column and anterolateral projection systems. As the dorsal column system mediates discriminative touch and limb proprioception, it will be outlined in detail.

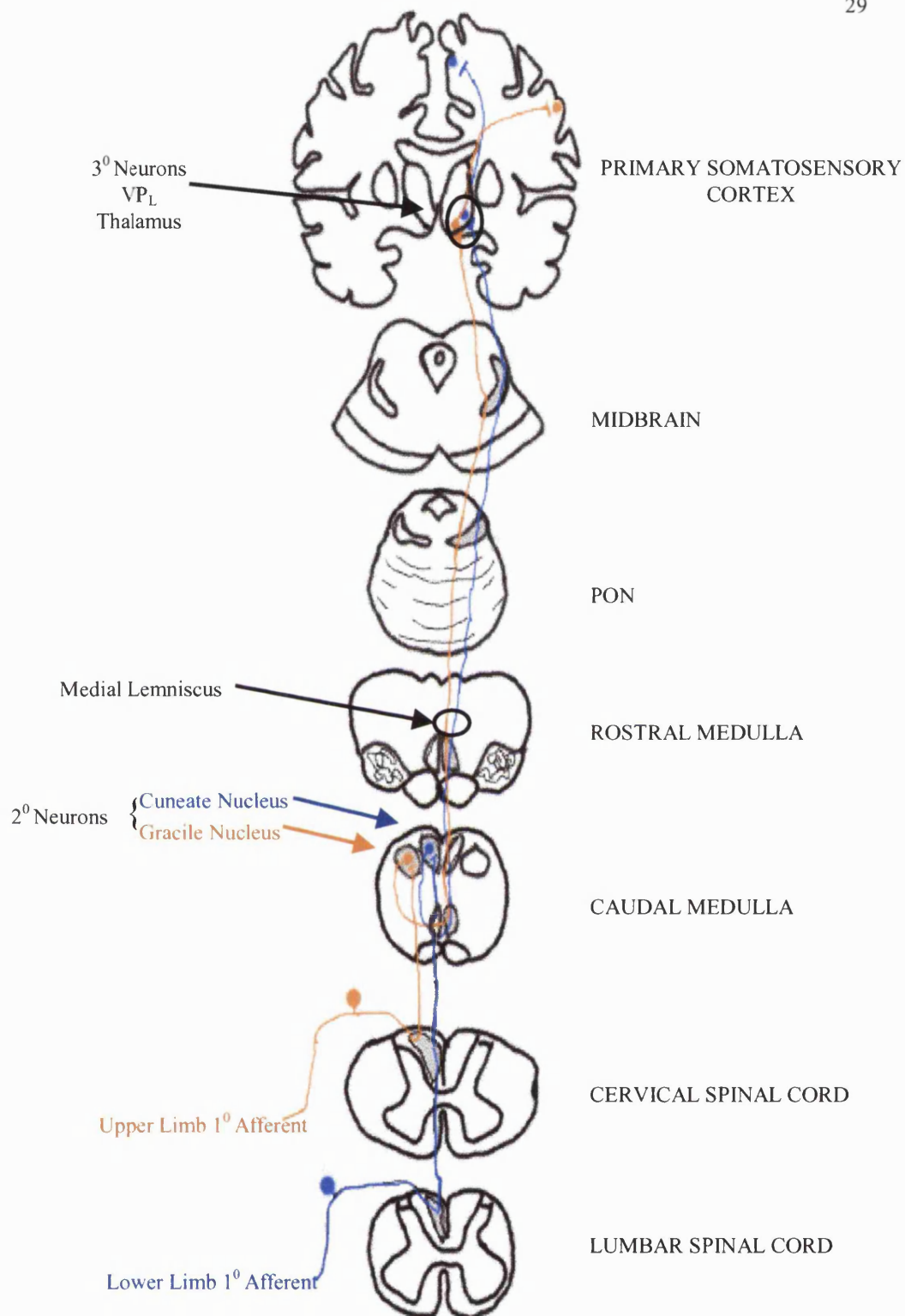


Figure 1.5. Ascending pathway for discriminative tactile sensations, the medial lemniscal pathway. Note the decussation of fibres at the level of the caudal medulla: afferent information from the left side of the body is processed by the right hemisphere, and vice versa. Axial slices are shown at each level, except cortex (coronal). Redrawn from Barr and Kiernan, 1993.

The ascending primary afferent fibres form two major ascending spinal tracts: the gracile fasciculus, which consists of fibres entering below the midthoracic level, and the cuneate fasciculus, which contains fibres from the upper thoracic and cervical levels. These tracts synapse with second order neurons in the gracile and cuneate nuclei respectively, at the level of the lower medulla. The second-order neurons then decussate (cross the midline), and ascend as the medial lemniscus. Topography is maintained within the medial lemniscus: the more medial a fibre, the later it entered the spinal cord. Thus, second-order cervical fibres will be more medial than lumbosacral fibres.

The majority of medial lemniscal fibres terminate in the venterior posterior lateral (VPL) nucleus of the thalamus. Although the topographic order of the medial lemniscal pathway is, to some extent, preserved, the location of the third-order somatosensory projection neurons determines the cortical area that they project to. The central region of VPL sends the majority of its projections to Brodmann's area (BA) 3b. BA1 receives projections from a band of fibres located throughout the entire extent of the VPL, while BA2 primarily receives input from the dorsal and rostral extents of VPL (Burton and Sinclair, 1996). In addition, BA3a receives extensive VPL projections.

Thalamic projections to areas of somatosensory cortex preserve the pattern of peripheral topography: there is a mediolateral organisation that reflects the terminations of the medial lemniscus and is the basis for the somatopical organisation found in cortical areas. This does not imply that there is a simple promulgation of peripheral information to the cortex through segregated transmission pathways (see Chapter 5's introduction for a more detailed discussion): rather, although gross somatopy is preserved between periphery and center, there is in addition convergence at each synaptic relay point of the medial lemniscus. Convergence in somatosensory projection pathways has been demonstrated in a number of studies (see Jones, 2000 for a review). It is useful to consider each stage of the ascending pathway as putative loci for the integration of ascending information. Other thalamic cortical regions receive thalamic projections. The somatosensory cortex of the lateral sulcus (SII and

related areas) receive direct projections from both the VPL nucleus and the ventral posterior inferior nucleus (VPI), although the relative importance of these is unknown. In addition, the posterior parietal cortex receives sparse thalamic projections (Burton, 1986). The existence of direct thalamic projections to the lateral sulcus, traditionally regarded as ‘higher’ somatosensory cortex, poses a number of questions about the functional organisation of somatosensory cortex. How this reflects the functional organisation of the somatosensory system is addressed in Chapter six.

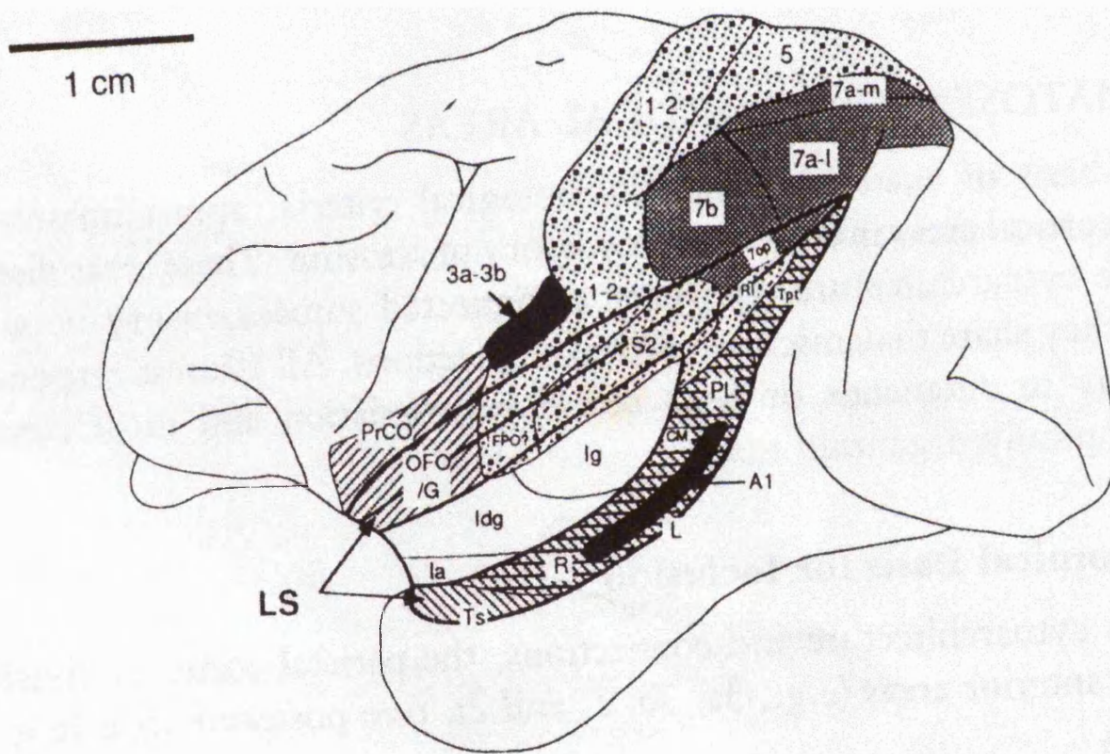


Figure 1.6. Cytoarchitecturally-defined somatosensory areas of the macaque cerebral cortex. Each area is numbered by the definitions of Brodmann (1909). The lateral sulcus has been exposed to show the heterogeneity of fields within its depths. Adapted from Preuss and Goldman-Rakic, 1991.

1.2.2.3 Cortex – Primary Somatosensory Cortex (SI)

Initially, according to physiological criteria, it was believed that the somatosensory cortex was composed of a primary somatosensory area, SI, and a second somatosensory area, SII, buried in the lateral sulcus (Woolsey and Fairman, 1946). However, modern connectivity and cytoarchitectonic analysis has defined at least ten separate areas. Burton and Sinclair (1996) divide primate parietal (somatosensory) cortex into four anterior areas (3a, 3b, 1 and 2), two posterior areas (5 and 7b), and four lateral regions (SIIrostral, SIIposterior, retroinsular and granular insula). Roughly 11% of the macaque brain is occupied by somatosensory areas (Fellman and Van Essen, 1991).

As a major question of this thesis was to define the topographic structure of the primary somatosensory cortex (SI) in man, it is important to note at this early stage that this area comprises multiple sub-areas – BA1,2 and 3a and 3b. Although the initial studies of Brodmann (translated 1994), in which he identified three parallel strips of anterior parietal cortex were viewed with suspicion, recent cytoarchitectonic studies using modern neuroanatomical techniques have confirmed these findings (Geyer et al., 1997,1999,2000). These observer-independent classification schemes have overcome many of the critiques put forward by researchers distrustful of previous cytoarchitectonic findings.

The discovery of two distinct patterns of cytoarchitecture within area 3 prompted its division into areas 3a and 3b: 3a has an extended layer IV when compared to areas 4 (primary motor cortex) and 3b, and larger pyramidal cells in its supra - and infragranular layers (Jones *et al.*, 1978; Jones *et al.*, 1980). The topography of these areas and the properties of individual neurons within them have been extensively investigated (e.g., Phillips et al., 1971; Paul et al., 1972; Dreyer et al., 1973; Merzenich et al., 1978; Jones and Porter, 1980; Nelson et al., 1980; Sur et al., 1982; Iwamura et al., 1983; Pons et al., 1985; Carlson et al., 1986; Phillips et al., 1988; Sinclair and Burton, 1991; Hsiao et al., 1993; Iwamura et al., 1995; see Kaas, 1983 and Iwamura, 1998 for review). The most striking feature of this area is that it contains an isomorphic

representation of the periphery – a ‘homuncular’ pattern in which the size of an area’s mapping reflects the density of the peripheral fibres innervating it.

As well as the presence of complete topographic maps in each, the different areas of the postcentral gyrus in man are differentially responsive to peripheral stimulation. In general, it is believed that an anteroposterior gradient neuronal complexity exists in anterior parietal cortex (see Iwamura, 1998, for review). Thus receptive fields are smallest in BA3b, the most anterior area, and enlarge as one records from areas progressively posterior (3b-1-2), with multidigit receptive fields present in BA2. Investigations by Burton and colleagues (1995) echo this view. Thus, even in ‘early’ cortical areas, a surprising amount of specialisation exists – even ‘primary’ cortex contain multiple, functionally distinct mappings.

1.2.2.4 Areas 5 and 7 – Posterior Parietal Cortex

The somatosensory areas of the posterior parietal cortex (PPC) are defined almost arbitrarily, as in the human PPC includes everything posterior to BA2 that is not adjacent to the Sylvian fissure. In the monkey, posterior parietal areas involved in somatosensory processing include areas 5, 7a, LIP and VIP (see Kaas and Pons, 1988; Andersen et al., 1997 for review), but the exact human homologues of these areas are the subject of controversy. These areas are believed to be involved in coding the spatial location of goal directed movements, converting sensory locations into motor coordinates for directed or intended movements (Snyder et al., 1997; Andersen et al., 1997 for review), and for the perception of the body and its movements in extrapersonal space (see Mountcastle et al., 1984 for review).

Area 5 was shown to be a somatosensory area by the clinical studies performed by Critchley (1953) – it was originally placed in posterior somatosensory cortex by Brodmann, then ‘reclaimed’ as a somatosensory parietal area. There have been a great number of single unit recordings from area 5. The most salient features of neurons in area 5 are: their responsiveness to light mechanical or deep stimulation of the arm, hand, hindlimb or trunk, and to wrist rotation (Sakata et al., 1973); bilateral receptive fields (Iwamura et al.,

1994); directed arm movements, reaching and grasping (Chapman et al., 1984; Iwamura et al., 1995; 1996; Jiang et al., 1997); integration of visual inputs regarding target location and kinesthetic information regarding the position of the limbs in space (Ferraina and Bianchi, 1994); instructed movements (Seal et al., 1983); and attention (Iriki et al., 1996). BA5 neurons here respond to visual stimulation, and they change receptive field size and configuration with changes in perceptions of extrapersonal space through tool use (Iriki et al., 1996). In monkeys, lesions of cortex in and around the intraparietal sulcus, including areas 5 and 7, result in deficits in reaching and a misalignment of digits, with or without visual guidance. Some studies suggest that area 5 has 2 separate subdivisions (e.g. Jiang et al., 1997); but there has been no attempt to subdivide this region anatomically, histologically or functionally. For the purposes of this thesis it will be considered to be a functionally homogeneous region.

Neurons in area 7a are active under a variety of conditions that involve goal directed reaching, and ‘body centered’ movements. Both the connections (see below) and responses of neurons in area 7a suggest that this field is related more to visual processing than somatosensory processing (see Andersen et al., 1990). For instance, neurons here have large, often bilateral visual receptive fields, change their discharge rate at different fixation locations, and are active during instructed saccades. Although neurons in 7a do not respond to somatic stimulation, they clearly have access to somatic inputs since they are most active when the monkey brings its hand to its mouth, and when the monkey is exploring with its lips or chewing (Leinonen and Nymen, 1979).

The posterior parietal regions are densely connected to a number of other somatosensory cortical areas. Connections of the hand and wrist representations of area 5 with the SII region, and portions of areas 7 have been described. However, the connections of these areas to more caudal areas is less certain. Although tracing studies have been performed in non-human primates (Cavada and Goldman-Rakic, 1989a; 1989b; Andersen et al., 1990), electrophysiological identification of injections sites or target areas was done *across* different animals. Accepting these caveats, the connections of 7a and 7b (although the

location of 7b in Cavada and Goldman-Rakic studies is different to recent studies) were with extrastriate visual areas, areas of prefrontal cortex, and regions of the temporal lobe (for a more review of cortical connections see Darian-Smith et al., 1996)

1.2.2.5 *The Somatosensory Areas of the Lateral Sulcus*

Classification schemes of subdivisions of cortex in the superior lateral sulcus (above the Sylvian fissure) have recently undergone substantial modifications. The relative inaccessability of this area to traditional multiunit electrode recording may explain why only recent attempts (see below) have been able to study the physiology of this region in detail. In the region of cortex traditionally identified as the second somatosensory area, SII (Woolsey and Fairman, 1946), previous investigations in non-human primates (Robinson and Burton, 1980a and 1980b) described multiple representations of similar body parts. More recent investigations have prompted a redefinition of the cortical areas contained within this region (Cusick et al., 1989; Alloway et al., 1990; Krubitzer and Kaas, 1990; Burton et al., 1995; Krubitzer et al., 1995; Disbrow et al., 1998). At least two separate representations are present, SII (SIIp of Burton et al., 1995), and the parietal ventral area, PV (Krubitzer et al., 1995; SIIa of Burton et al., 1995; SIIr of Whitsel et al., 1969; Disbrow et al., 2000). A third area, the ventral somatosensory area, VS, has also been identified in owl monkeys (Cusick et al., 1989), and a partial map of VS has been described in macaque monkeys (Krubitzer et al., 1995). Partial maps of adjacent fields such as 7b and Ri have been generated (Robinson and Burton, 1980b; Krubitzer et al., 1995), but the data obtained in these studies were too sparse to allow for accurate descriptions of these areas.

Studies of single units in awake monkeys demonstrate that some neurons in SII respond during active touch, are less modality specific than neurons in SI, and have larger receptive fields than neurons in SI (e.g. Sinclair and Burton, 1993). In addition, neurons in SII have been shown to change their discharge rate with shifts in attention (Hsiao et al., 1993; Burton et al., 1997b). Finally, studies in which SII was lesioned (e.g. Murray and Mishkin, 1984) demonstrate

that animals are impaired in discriminating texture and shape. However, given that the anatomical definitions of this region have only recently been revised, the ‘SII’ defined by earlier studies (i.e. Robinson and Burton, 1980a and 1980b) may not be consistent with later investigations. Furthermore, while much is known about the physiological properties of single identified neurons within the lateral sulcus, less is known about the functional roles of these areas as a whole.

More is known about the connectivity of these cortical areas. There have been several studies of the connections from anterior parietal areas (i.e. SI) to the SII region (e.g., Friedman et al., 1980; Pons and Kaas, 1986; Cusick et al., 1989; Krubitzer and Kaas, 1990; Burton et al., 1995). However, as with the single unit studies listed above, most of these were carried out before the complexity of this region was fully appreciated. Only a few studies have directly examined the connections of SII in primates (Friedman et al., 1986; Krubitzer and Kaas, 1990; Krubitzer and Kaas, 1992; Disbrow et al., 1998), and these were carried out before the separate subdivisions of motor, prefrontal and lateral sulcal cortex were re-evaluated. In addition, while studies have been carried out on the connections of area 7b with other somatosensory areas (Andersen et al., 1990), the precise location of this area remains controversial.

1.2.2.6 *Neuroimaging Studies of Somatosensory Cortex*

While accepting that there is still a great deal of neurophysiological data on the somatosensory areas of the parietal cortex to be acquired (which would facilitate the analysis of human studies), there have been a number of neuroimaging studies of somesthesia. These will be discussed in more detail in subsequent chapters, and the following brief discussion is presented as an overview.

The human somatosensory cortex has been studied using a variety of non-invasive imaging techniques. In particular, a number of studies have focused on the somatotopic organisation of SI (along the postcentral gyrus): in electroencephalography (EEG) and magnetoencephalography (MEG; Suk *et al.*, 1991; Baumgartner *et al.*, 1991; Hari *et al.*, 1993; Nakamura *et al.*, 1998), positron emission tomography (PET; Fox *et al.*, 1987), and in addition fMRI

(Gelnar *et al.*, 1998; Sakai *et al.*, 1995; Puce *et al.*, 1995; Kurth *et al.*, 1998; Disbrow *et al.*, 1998; Maldjian *et al.*, 1999; Francis *et al.*, 2000; Kurth *et al.*, 2000). While the majority of MEG studies have been able to show the ‘somatotical’ mapping of the body in SI as predicted from invasive mapping procedure (e.g. Penfield and Boldrey, 1937), results from fMRI have been more variable. The experiments of Chapters 3 and 5 were performed to examine this issue in more detail.

The first metabolic-based mapping (PET) of SII was carried out by Burton and colleagues in 1993 using vibrotactile stimulation. They located SII in the region of the parietal operculum on the upper bank of the sylvian fissure. Similar imaging studies demonstrate that SII has activates during simple somatosensory stimulation (Coghill *et al.*, 1994; Burton *et al.*, 1997a). In addition, SII activation has been observed in sophisticated somatosensory tasks including micro and macrogeometric discrimination (Ledberg *et al.*, 1995; Roland *et al.*, 1998), tactile attention (Burton *et al.*, 1999; Mima *et al.*, 1998) and tactile memory (Bonda *et al.*, 1996). Further experiments examining sensorimotor integration have shown differential SII activity (Huttunen *et al.*, 1996). Furthermore, SII has been implicated in human bimanual coordination (Simoes and Hari 1999; Disbrow *et al.*, in preparation). The topographical organisation of this area has been studied in less detail (Disbrow *et al.*, 2000).

Several studies have demonstrated increases in activity in posterior parietal cortex during visually guided and exploratory reaching tasks (Gitelman *et al.*, 1996; Kertzman *et al.*, 1997), complex sequential finger movements (Catalan *et al.*, 1998; Gordon *et al.*, 1998), and shifts in attention (e.g. Pugh *et al.*, 1996). However, few studies have focused *specifically* on the role of these areas in tactile perception. This issue is explored in Chapter 6.

1.3 Summary and Aims

It is evident from the previous sections that there is a rich and detailed literature outlining the properties of single and small groups of neurons in the somatosensory areas of primates. Similarly, the gross inter-areal connectivity of the cortical areas of the somatosensory system have been adequately defined in non-human primates. However, though animal studies are necessary, studies involving human subjects are really necessary for questions relating to sensory perception (not least because of the significant time and effort that it takes to train primates on behavioural tasks). While a great deal of progress has been made regarding the functional and anatomical organisation of ‘higher order’ areas in other sensory modalities in humans (such as IT and posterior parietal cortex; e.g. Milner and Goodale, 1996), there has been comparatively little headway made in understanding the functional organisation of somatosensory processing. MEG has been used successfully to examine changes in the topographic maps of anterior parietal cortex after injury or perceptual learning (Flor et al., 1995). Yet MEG is less useful for the study of deep signal sources, such as the thalamus.

If one wishes to examine whole-brain responses to somatosensory stimulation in the human brain, without spatial bias, metabolic mapping measures are ideal. fMRI in particular is attractive, as it combines high spatial and temporal resolution with non-invasiveness. However, there are a number of obstacles associated with the use of fMRI as a tool to study somesthesia. First, the high ambient magnetic field means that it is not trivial to be able to deliver somatosensory stimulation during scanning. Second, although it is often noted that fMRI is completely non-invasive and thus an excellent putative method for longitudinal studies, little is known about the reproducibility of sessions sampled over a discrete time period from the same subject. Finally, compared with the great number of studies performed in non-human primates, only a small number of imaging studies have specifically focused on the somatosensory system. This may relate to a concept introduced by Ingvar in 1975 – the ‘sensory-motor paradox’. Ingvar’s early PET activation studies found that pure somatosensory

stimuli appear to cause rCBF increases in prefrontal, not parietal, cortex. I will discuss this concept in more detail in Chapter three.

This thesis is thus an attempt to overcome the methodological difficulties that have posed problems to previous investigators wishing to use fMRI to study somesthesia. In Chapter Two, I outline the basic physics of fMRI, and summarise the statistical techniques used to analyse fMRI data. In Chapter Three the design, construction and calibration of vibrotactile and airpuff stimulators for fMRI are described. Chapter Four focuses on the variability of fMRI responses in the same subject when scanned on separate occasions. Chapter Five is an investigation of the frequency-dependence of the BOLD signal within SI. Chapter Six details the differential activation patterns found in somatosensory cortical regions when subjects perform either intensity or location discrimination tasks, and Chapter Seven is a study of a single patient with a somatoform disorder. In Chapter Eight the results of the previous chapters are discussed.

2 Materials and Methods - The Acquisition and Analysis of Functional Neuroimaging Data

2.1 Non-invasive Imaging Methodologies

Since the first non-invasive recordings of the electrical activity of the human brain (published by Berger in 1929) the number of non-invasive techniques available to cognitive neuroscientists has grown. In addition to human electroencephalography (EEG), it is now possible to record the minute fluctuations in magnetic fields produced by the electrochemical activity of the brain (magnetoencephalography or MEG). Arguably the most widely used mapping techniques are those that employ a metabolic metric to indirectly measure neuronal activity. All data in this thesis were collected using such a technique: functional magnetic resonance imaging (fMRI). The methodology behind this technique will be subsequently reviewed. First, as much of the assumptions concerning the relationships between neuronal metabolism and neuronal activity assumed in fMRI are inherited from an older technique (positron emission tomography - PET), this method will be briefly discussed.

2.1.1 Blood Flow and Neuronal Metabolism - An Introduction

All imaging modalities that measure regional cerebral blood flow directly (PET) or the indirect effects of marker substances in blood (fMRI) rely on local flow as a window to the hidden processes of regional cerebral metabolism. The assumption is that ‘the energetic requirements associated with synaptic function represent the indicators detected with functional brain imaging techniques’ (Magistretti and Pellerin, 1999). Synaptic interactions require energy - in particular, adenosine triphosphate (ATP), produced from glucose by oxidative phosphorylation and the Krebs’s cycle. The brain is unique amongst other human physiological systems in that it has a very high energy demand: weight ratio (in humans, the brain takes up only 2% of body weight, yet requires roughly 20% of oxygen consumption and 15% of blood flow). In addition, the brain appears to lack a ‘functional reserve’, in that it is almost completely reliant on oxygen

delivered via the blood to fuel the biochemical processes vital for synaptic transmission. Although the human brain contains a greater concentration of glycogen than other animals, the greatest concentrations of glycogen are found in glial cells, not neurons. Oxygen must therefore be delivered to neurons via local blood supply to supply the energetic processes underlying neurotransmission. As the majority of this oxygen is used in oxidative metabolism (Hyder et al., 1997), local oxygen consumption should act as a sensitive marker of local neuronal activity.

One of the first (and certainly one of the most famous) papers to relate blood flow to local cerebral metabolism was published by Roy and Sherrington in 1890. Their animal work led them to postulate that the brain's blood supply was locally regulated, so that those areas that required energy would receive the highest proportion of global flow. They concluded '...the chemical products of cerebral metabolism contained in the lymph which bathes the walls of the arterioles of the brain can cause variations of the calibre of the central vessels: that in this reaction the brain possesses an intrinsic mechanism by which its vascular supply can be varied locally in correspondence with local variations of functional activity' (Roy and Sherrington, 1890). This remarkably prescient statement is a precise summary of the main assumptions underlying modern neuroimaging.

Since this pioneering work, evidence has steadily accrued supporting a link between local blood flow and local oxidative metabolism. However, while few would debate the *existence* of a relationship between regional cerebral blood flow and cerebral metabolism, there is still much work to be done on clarifying the exact *form* of this relationship. The current situation faced by cognitive neuroscientists using imaging technologies is succinctly summarised by the figure from Shulman and Rothman (1998) below.

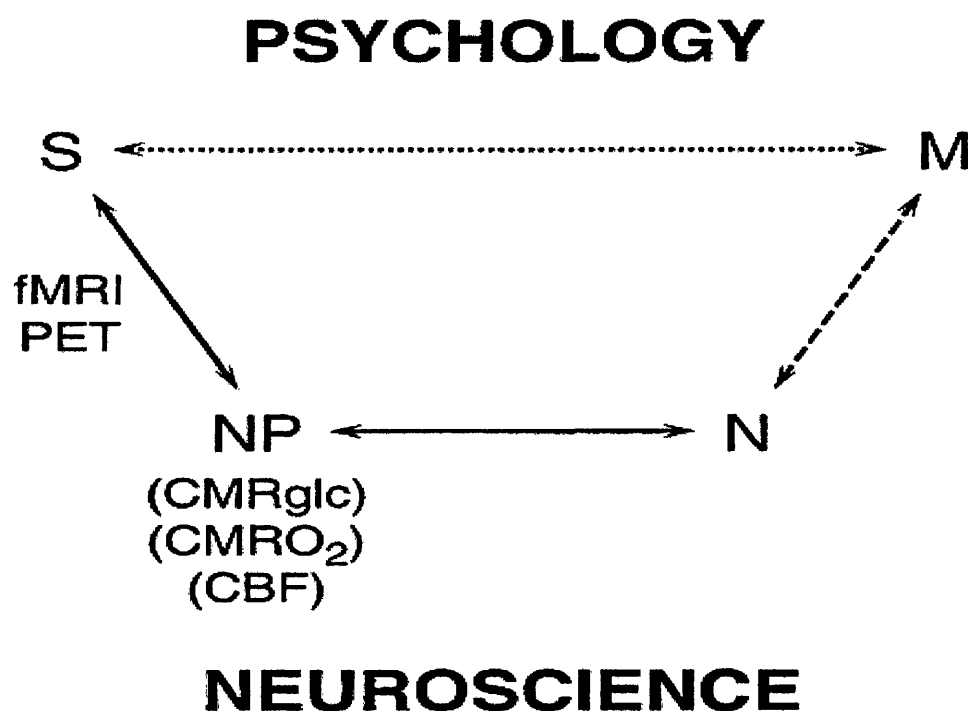


Figure 2.1. Link between signal (S) and mental process (M), adapted from Shulman and Rothman (1998). NP – parameters used to measure neuronal metabolism. N – neuronal activation. CMRglc – cerebral metabolic rate of glucose. CMRO₂ – cerebral metabolic rate of oxygen. CBF – cerebral blood flow.

Shulman and Rothman (1998) correctly point out that there are a number of intervening layers between S and M that are often conveniently ignored in functional neuroimaging experiments. One has to consider how the signal (S) relates first to the physiological parameters used to measure neuronal metabolism (NP), and how NP is related to N, the dynamics of neuronal activation. While uncertainties remain about the exact nature of the relationship between N and M, there has been a great deal of progress in tracing the successive links between the imaging signal and the metabolic processes underlying it. An excellent example of these advances is the family of rCBF mapping techniques represented here by PET and SPECT.

2.2 Methodologies Utilising Regional Cerebral Blood Flow (rCBF): PET & SPECT

The earliest attempts to produce standardised instruments and methodologies that could be utilised to link local flow and metabolism were carried out by Kety and Schmidt in the 1940s (Kety and Schmidt 1945). These first attempts used freely diffusible, inert tracer substances to calculate cerebral blood flow. Using nitrous oxide (NO) as an indicator, it was possible to calculate the difference between the arterial and venous concentrations to work out how much O₂ had been taken up by the brain. Attempts to apply these techniques to the study of human functional neuroanatomy were largely unsuccessful, as an obvious disadvantage of this method was that only global flow could be measured. Animal studies using autoradiographic techniques were more successful (for review see Sokoloff et al., 1977). However, these techniques rely upon sacrificing the subject at the end of the experiment: thus the procedure does not lend itself to ethical human experiments.

The early work of Kety and Schmidt was subsequently refined by a number of investigators. Ingvar and Lassen were the first to develop methods which took Kety and Schmidt's earlier work to its logical conclusion - the ability to measure regional CBF in humans (reviewed in Lassen et al., 1991). Building on this work, Glass and Harper utilised Xe-133 (a gamma ray emitter) and used intravenous injections of the tracer and multiple external detectors to develop a much less invasive method. This was then extended with the introduction of computerised tomography to develop Single Photon Computed Tomography (SPECT). The main attraction of SPECT amongst the other imaging techniques available to a 21st-century neuroscientist is its cheapness: it will not be discussed further.

PET has better temporal and spatial resolution than SPECT because the radionucleotides used in PET are positron emitters, resulting in two gamma rays per disintegration. They have short half-lives, especially those that substitute for stable biologically relevant elements such as carbon, nitrogen or oxygen, and thus allow a number of images to be collected from each subject. This latter ability makes PET a good technique for conducting activation studies. Although fMRI is

less expensive and has better temporal and spatial resolution, PET allows one to image radiolabelled neurotransmitters and thus obtain a more direct metric of neuronal activity (e.g. Cherry and Phelps, 1996). However, to date there have been few studies that have successfully overcome the complications of modelling the tracer kinetics of neurochemical processes, let alone been able to apply these in a cognitive activation paradigm. The recent work by Koepp and colleagues is a notable exception (Koepp et al, 1998).

2.2.1 H^{15}O_2 PET: A Brief Overview

As the experimental results presented in this thesis were collected using fMRI, the theory and practice of PET will be discussed in less detail. However, the theoretical issues underlying flow-activation coupling and statistical modelling in PET are maturer than comparable concerns in fMRI, and so serve as a useful introduction.

2.2.1.1 *The PET Camera*

While there are no theoretical limits on the choice of tracers used for human and animal brain mapping, there are a number of practical considerations to acknowledge. These include the type of emitter used, the half-life of the radioisotope, and the energy of the emitted particles. We will concentrate on the ^{15}O method pioneered by Frackowiak and colleagues at the Hammersmith hospital in London (1980).

^{15}O is a positron emitter with a half-life of a little over two minutes. When an atom of ^{15}O decays, it emits a positron and a neutrino. While the neutrino rapidly passes through biological material without any interactions, the positron loses energy through encounters with negatively charged electrons. Eventually, the positron will annihilate with one of the electrons. The distance that the particle travels before annihilation depends on the energy of the positron emitter (Derenzo, 1979). This distance will ultimately affect the spatial resolution of the technique: the further that the positron travels from the tracer, the lower the spatial resolution possible. In human tissue the positron typically travels less than 2mm before annihilation (Cherry and Phelps, 1995).

The signal in PET is not the positron itself, but rather the gamma rays that are produced by the positron/electron reaction. The PET 'camera' comprises a ring of detectors surrounding the object being imaged: in the case of human brain mapping, the subject's head. In modern PET cameras there are a number of detector rings, each one comprising an imaging 'plane'. The more rings, the greater the coverage of the subject's head in the inferior/superior plane (commonly labelled the 'Z' axis in imaging experiments). Each ring consists of arrays of positron detectors - dense crystalline materials such as bismuth germanate (BGO) or sodium iodide (NaI). The more crystals that one has in each ring, the greater the possible spatial resolution. Modern PET cameras may have as many as 1024 crystals per ring (reviewed in Roland, 1993).

The materials used in modern PET cameras *scintillate* when they encounter a gamma ray: in a similar fashion to the processes occurring in scintillation counters, the energy of the gamma rays causes the detector crystals to emit photons. These photons are converted into an electrical signal by a photomultiplier, which uses a photocathode to convert the photons to electrons. The actual signal caused by the interaction of the gamma rays with the crystals is small, however, and so the photomultiplier tubes amplify the signal as well. It is estimated that for every electron caused directly by the interaction of photons at the photocathode, 10^6 electrons are produced at the output of the photomultiplier tube (Cherry and Phelps, 1996).

The rings of detectors in the PET camera are designed to register 'coincidence' events: as positron annihilation causes two gamma rays to be emitted, 'true' PET counts are those that cause simultaneous events in two spatially opposed detectors. It should be noted that modern PET cameras allow for coincidence detection between imaging planes, to enable detection of those gamma-ray pairs that are emitted obliquely with respect to the imaging plane. This mode of acquisition is known as 3D data acquisition. It is estimated it offers a five-fold increase in sensitivity over 2D acquisition, in which only coincident events in the same imaging plane are detected (Townsend et al., 1991).

2.2.1.2 *Spatial Resolution in PET*

In practice, the path between annihilation of the positron and the subsequent detection of gamma rays by the PET camera is not as error-free as described above. There are two hard constraints on PET scanner resolution. The first is the distance that the positron travels before annihilation. The second is caused by the fact that, as the positron and electron are not completely at rest when they annihilate, the emitted gamma rays rarely emit at *exactly* 180° to each other. This smooths the PET signal, and in doing so lowers the spatial resolution (Derenzo et al., 1982).

In addition to the above constraints, further artefacts can contaminate PET data. The gamma rays can be partially or completely absorbed by tissue: these events give rise to the phenomenae of *scatter* and *attenuation* (reviewed in Roland, 1993). Attenuation can be corrected in an efficient manner by using an external source of positrons: from examining the attenuation of this known source, one can efficiently calculate attenuation coefficients (Ranger et al., 1989). Scatter is caused by interactions between gamma rays and other substances (primarily biological material here) before the rays are detected. If one of the gamma rays is scattered and goes on to strike the ‘wrong’ detector, the ‘true’ position of the event will be lost, and a reduction of image contrast will result. Most modern PET cameras employ some means of scatter correction (e.g. Grootenboer et al., 1992). In addition to problems arising from scatter and attenuation, the presence of background radiation can cause the detection of false positives due to random coincidences at pairs of detectors. Automatic correction algorithms (Hoffman et al., 1981) ably deal with this final noise source.

2.2.1.3 *Image Reconstruction In PET*

The process of image reconstruction in PET aims to produce a tomographic representation of the concentration of tracer activity. However, the raw data from the PET scanner represents not point activity, but *projection* activity: the value of the activity detected by each pair of detectors. Raw PET data is usually represented as a sinogram, a 2D matrix whose dimensions represent the angle of the gamma ray projection (ϕ) and the distance the projection line lies from the

centre of the field of view (r) (Cherry and Phelps, 1995). Each element in the sinogram matrix represents a single coincidence line. The difference in computational complexity between 2D and 3D PET can be easily appreciated by considering the massive increase in the number of sinograms which will result when one includes oblique detection planes.

It is usual to employ a backprojection algorithm to reconstruct an image from sinogram data. Backprojection has been likened to ‘...drawing the floor plan of a house by looking in the windows’ (Croft, 1986). The more windows (imaging planes/projection lines) that one has the better the floor plan (final image). Just as a greater number of windows would facilitate a better sampling of the form of the house’s floor, the greater the number of detector rings has a similar effect on the PET image. Here, the usefulness of 3D-acquisition mode can be appreciated.

The backprojection method converts the raw data from a Fourier space representation back into image space (Brooks and De Chiro, 1976). In effect, each element of the sinogram is backprojected to the line it represents in image space. The data are usually filtered before backprojection to improve the signal: noise ratio, although this will decrease in the spatial resolution of the data. Backprojection methods for fMRI image reconstruction will be discussed in more detail in the next section.

2.3 functional Magnetic Resonance Imaging: fMRI

2.3.1 The Physics of NMR and MRI

While PET uses exogenous substances injected into the bloodstream as signal, modern fMRI relies on *endogenous* contrast mechanisms to produce its signal. fMRI is a special form of magnetic resonance imaging (MRI), and both fMRI and MRI rely on the principle of nuclear magnetic resonance (NMR), discovered independently by Bloch and Purcell in the 1940s (Bloch et al., 1946; Purcell et al., 1945). The first application of NMR as a topographic imaging modality came in 1973, using NMR of hydrogen atoms in the human body (Lauterbur, 1973). This early study paved the way for MRI images which contain not only structural but also functional information - the techniques underlying fMRI. The basic physical principles underlying both MRI and fMRI are very similar.

2.3.1.1 *Spin Physics*

Subatomic particles, such as protons, electrons and neutrons all possess a property known as *spin*. Spin is measured in multiples of $\frac{1}{2}$, and can be either positive or negative. It is possible for particles with opposite spin values (i.e. $\frac{1}{2}$ and $-\frac{1}{2}$) to combine or pair - this negates the physical properties of spin. In this brief review, we will concentrate on particles which are unpaired, in particular the hydrogen nucleus, ^1H (the proton).

When elements with an odd atomic weight (an odd number of protons) are placed within an external magnetic field they will align themselves with the direction of the field. When one places protons in a strong external magnetic field, the protons will occupy one of two possible energy levels. The difference in energy levels is related to the frequency of the two states by Planck's constant (h):

$$\Delta E = h\nu \quad (1)$$

The lower energy level is preferred, although the number of protons occupying either level is very similar (as a rough example, for every 1×10^7 protons in the higher energy state, there will be 1.0000007×10^7 protons in the lower state). Nevertheless, this difference means that the population magnetic vector (the vector sum of all individual nuclei) points in the direction of the external field. This is called 'longitudinal magnetization' as it is 'along' the direction of the external magnetic field.

While within the field the protons are not stationary - they spin or *precess* (Figure 2.2.) around the magnetisation vector (in the direction of the external field) with a certain frequency.

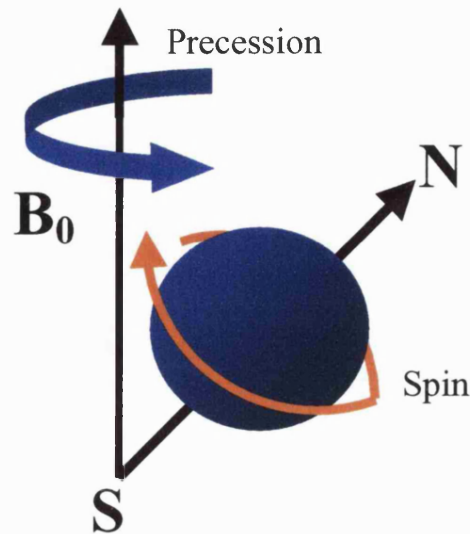


Figure 2.2. 'Spin' and 'Precession' of a single proton. The proton possesses the quantum quality 'spin' (outlined in red). When placed within an external magnetic field, the proton 'precesses' around the longitudinal magnetic field vector (indicated by the blue arrow). This proton will precess at roughly 43 MHz/Tesla (see the Larmor equation below).

The precession frequency is proportional to the magnetic field strength, and to the type of nuclei within the field. Precession frequency and magnetic field strength are related according to the *Larmor equation*:

$$\omega_0 = \gamma B_0 \quad (2)$$

where ω_0 is the precession frequency (Hz), B_0 is the strength of the external magnetic field (Tesla, T), and γ is a constant, the *gyromagnetic ratio*, which varies depending on the nuclei within the field.

In living organisms, the most abundant atom with spin is the hydrogen atom in the form of water (the human body is roughly 63% hydrogen atoms). From above, it is clear that placing a source with a high water content (such as a human) within a static magnetic field will cause the sample to become magnetized after a certain period of time. The rate constant that governs the time for a sample to reach magnetic equilibrium is known as T_1 . While in the field, the hydrogen nuclei within the water precess with their Larmor frequency. However, the net magnetic vector ($\mathbf{M}$) of the source is still in the direction of the static field. As MRI relies upon measuring the signal that is produced when precessing atoms are perturbed

from magnetic equilibrium, the protons must be somehow 'shifted' from this state in order to use them as a signal source.

2.3.1.2 *Magnetic Resonance*

Although $\mathbf{M}$ is in the direction of the static B_0 field, each individual proton has a component of magnetization that is at right angles (orthogonal) to the B_0 field. This component is caused by precession, and because each individual proton will precess with a slightly different phase, there is no *net* transverse magnetization. It is possible to change this arrangement by exposing the protons to radio frequency (rf) pulses of a particular frequency. Only when the rf pulse matches the frequency of precession (which happens to be the Larmor frequency) can energy be transferred between the pulse and the protons. This phenomenon is known as *resonance*.

The energy from the rf pulse is absorbed by the protons, causing some of them to occupy the higher energy state. This reduces the net magnetization vector in the B_0 direction (the longitudinal magnetization) - in effect, disrupting the magnetic equilibrium of the sample. This rf pulse is referred to as the $\mathbf{B}_1$ or rf field. In addition to its effects on the longitudinal magnetization, the rf pulse works to focus the phases of the precessing photons. This means that it induces a component of transverse magnetization at the same time as the longitudinal magnetization decreases in magnitude. The resulting transverse magnetization is essential for fMRI studies, and its kinetics are described by the T_2 time constant. Whereas before the moving electrical charge of the proton induced the magnetic field of the proton, after the rf pulse the precessing transverse magnetization vector produces a changing magnetic field. This in turn induces an electrical current. The electrical current is the basis of the MRI signal, and causes a signal current to be induced in an antenna in the MRI hardware.

2.3.1.3 *T_1 and T_2 Effects in MRI*

Once the rf pulse is turned off, protons gradually decay or *relax* back to their original energy levels. This causes the longitudinal magnetization vector to return to its original value. This process is called T_1 or *spin-lattice relaxation*, as the energy emitted from the protons as they return to the lower energy state is

transferred to their local tissue environment. The exact composition of that environment will affect T_1 - for example, the protons in water have a longer T_1 than those in fat as the carbon bonds in fat resonate near the Larmor frequency, facilitating the transfer of energy. In the human brain, the different water content of grey and white matter (71% and 84%, respectively) means that T_1 contrast can be used to provide contrast between these tissues, although this does not mean that it is possible to *unambiguously* differentiate them.

As mentioned above, the focusing effect of the rf pulse introduces a component of transverse magnetization. Again, after the rf pulse is switched off, the protons gradually lose their phase coherence, and this component is similarly lost. This is known as T_2 or *spin-spin relaxation*, as in this case energy is lost due to both local variations in B_0 and interactions between the protons themselves. The combination of these factors is known as T_2^* , and is related to both sources thus:

$$1/T_2^* = 1/T_2 \text{ (molecular effects)} + 1/T_2 \text{ (B}_0 \text{ field effects)} \quad (3)$$

fMRI sequences usually measure T_2^* , and rely on the fact that T_2^* is affected by local field inhomogeneities. In modern MR scanners, local variations in magnetic field are unlikely to dominate the above equation: it is possible to achieve magnetic fields that are uniform to 2 ppm over an imaging volume of 40cm (Cohen, 1996).

As mentioned, T_1 and T_2 are also used to describe the time-constants affecting recovery and relaxation, respectively. Both processes can be described by simple first-order exponential equations

$$M_z = M_0(1 - e^{-t/T_1}) \quad (4)$$

$$M_{xy} = M_0 e^{-t/T_2} \quad (5)$$

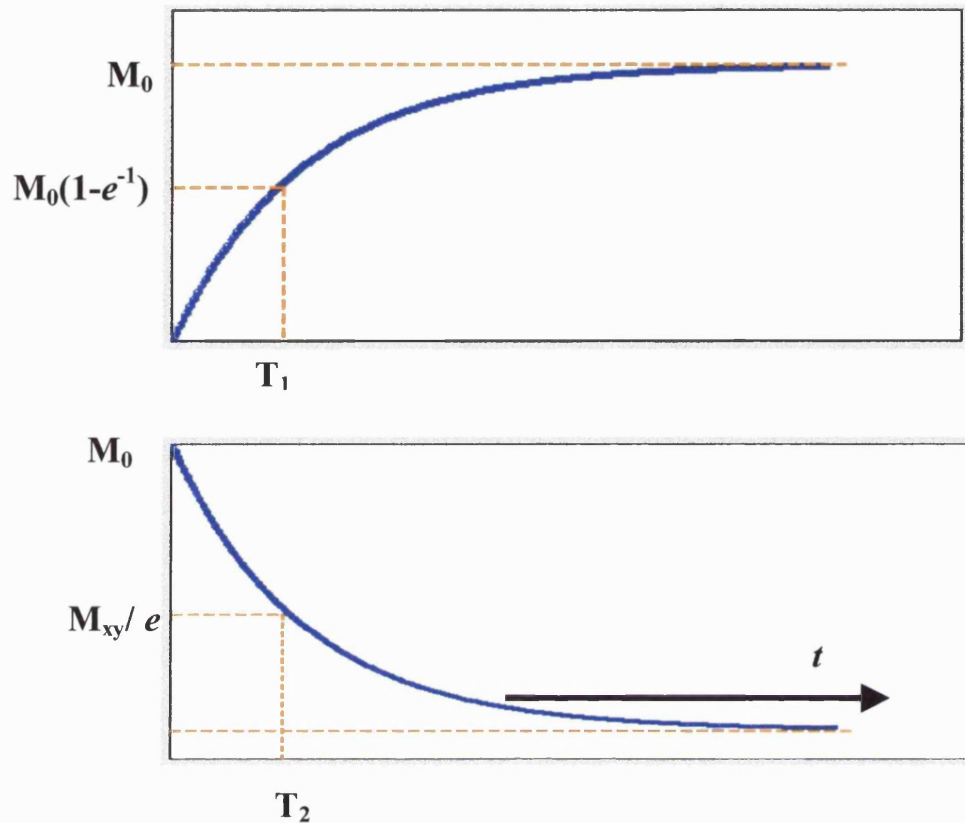


Figure 2.3. *Top.* T_1 recovery. The blue timecourse is a plot of Eqn. 4 above.
Bottom. T_2 decay. The blue timecourse is a plot of Eqn. 5 above.

M_0 is the net magnetisation vector at equilibrium, and lies in the direction of the applied field (the B_0 field). T_1 is defined as the time taken to reduce the difference between the longitudinal component of magnetization and its steady-state value by a factor of e . Similarly, T_2 is defined as the time to reduce transverse magnetization by e . An important difference to note is that after the rf pulse T_1 *recovers* back to its original value, whereas T_2^* *decays* back to zero. M_z and M_{xy} are the component of magnetisation in their respective planes.

The combination of T_1 and T_2 effects after the rf pulse is usually known as the *free induction decay*, or F.I.D. The F.I.D is caused by the decay of the magnetisation vector over time, and describes a spiralling motion in three dimensions around the static longitudinal magnetization vector. This change in magnetic field is responsible for the changing electrical current that is detected by the receiver coil.

2.3.1.4 Image Formation in MRI

To produce tomographic MR images, placing the sample (in fMRI, the patient's head) within a homogeneous B_0 field is not enough. If all the subject's protons are experiencing (roughly) the same magnetic field, the frequency of their emitted signal will be the same - in effect, there will be a single peak in the magnetic resonance spectrum. All the protons will be excited in a similar fashion by a similar rf pulse, because they will all have the same Larmor frequency. This is not particularly helpful to the average imaging neuroscientist.

If, instead, the sample being imaged is exposed to an inhomogeneous magnetic field, protons within the sample will emit different frequency signals that are dependent on their spatial position. In MRI, a second magnetic field (called a gradient field) is applied to the sample to achieve this. This principle is known as *frequency encoding*, and underlies the acquisition of spatial information from the acquired MR spectrum. Put simply, the frequency of each proton will be proportional to its position within the magnetic field gradient.

How does one form a three-dimensional image from this principle? Originally, one-dimensional field gradients were used in a process called *back projection* (directly comparable to PET back projection, discussed in section 2.2.2.3) adapted from methods employed in computerised tomography. To produce two-dimensional image planes, the one-dimensional gradient is applied at a number of imaging angles in sequence, and the frequency spectrum recorded each time. This information was used to reconstruct the imaging plane. To select the plane of interest in the sample (a process known as slice selection), a further magnetic field gradient was used in conjunction with the frequency encoding pulse. A simple back projection *pulse sequence* (the sequence of external magnetic fields applied to the sample during imaging) would consist of a slice selection pulse, followed by a frequency-encoding gradient.

As can be appreciated, the above procedure is rather laborious, as it is necessary to continually rotate the one-dimensional gradient around the sample to produce a 2D image. It is now commonplace and more efficient in MRI to employ Fourier transform (FT) imaging techniques. The Fourier transform is an integral transform

that allows one to express time domain data (such as a neurophysiological timeseries) in the frequency domain. It is equally able to express frequency domain data (for example, the different frequencies that together make up complex auditory tones) in the time domain. FT principles are particularly important in modern MRI, as they allow one to quickly compute tomographic information.

In addition to the two gradient fields discussed above (the frequency-encoding and slice selection gradients), FT imaging employs a third class of gradient - the *phase encoding gradient*. As the image that will be acquired is three-dimensional, three orthogonal magnetic field gradients are required. However, one cannot simply use two orthogonal frequency-encoding pulses to acquire 2D information about the slice, as they would interact and confound the acquired signal (in effect, the combination of the two fields would simply rotate the frequency-encoding gradient in plane). The use of phase encoding principles combined with frequency encoding allows one to circumvent this problem. After the slice selection pulse (the method used almost universally is that pioneered by Mansfield in 1977), the phase encoding pulse is applied along one of the axes of the slice. The net effect of this pulse is to impart a phase difference in spins relating to the local magnetic field strength. Although the frequency of the spins is affected as well, enough time is allowed between the phase-encoding pulse and the frequency-encoding pulse for any frequency differences to die away. But though the spins are now precessing again with the same frequency, they now possess phase information.

The final, frequency encoding, pulse is applied along the remaining axis of the slice. It is therefore possible to 'read-out' 2D spatial information according to phase information along one axis and frequency information along the other. In effect, 2D FT MRI renders precession frequency spatially dependent by the application of two orthogonal magnetic field gradients. The raw data in MRI is thus composed of data in the frequency domain.

2.3.1.5 *k* Space

Although the concept of frequency domain data is common to a number of analytical techniques, and the use of the Fourier Transform itself a common procedure, the raw fMRI data are slightly more complex. Typically, the Fourier transform is used to express temporal domain data in the frequency domain, and vice versa. Frequency data are commonly only composed of a single dimension (e.g. time). This is merely a one-dimensional example of *k* space. The two orthogonal gradients applied during phase encoding and frequency encoding in MRI mean that it is more parsimonious to consider MRI data as lying in 2D Fourier space, or *k* space, and data within *k* space as corresponding to the MR data before its transformation into an image. The two axes of *k* space in the current example are k_x and k_y , corresponding to the frequency and phase-encoding directions within the imaging slice. *k* space is therefore equivalent to the space defined by the frequency and phase encoding directions. Therefore one can think of the image's representation within *k* space as the area that must be optimally sampled to obtain a veridical image of the sample.

2.3.1.6 *Ultrafast MRI Sequences and Echo-Planar Imaging (EPI)*

When imaging dynamic processes such as cardiac motion, MRI images that take minutes to form are not useful, and will be seriously confounded by bulk motion of the sample – for example, early spin-echo (SE) MRI sequences could take 1-2 hours to acquire. Although gradient-recalled echo (GRE) sequences have brought imaging time down to seconds, the use of echo-planar imaging (EPI; Mansfield 1977) sequences means it is theoretically possible to obtain a whole brain image of decent in-plane resolution in a *fraction* of a second. A major difference between EPI and other MR imaging sequences is the manner in which the sequence samples *k* space. The method described by Kumar and colleagues (1975) is an efficient way to sample *k* space: a successive series of lines through *space* is sampled, with one of the gradients being pulsed briefly between each acquisition to ‘move on’ the imaging line. This is usually done in the direction of the phase-encoding pulse, and so any increase in the spatial resolution in the

phase-encoding direction will bring with it a corresponding increase in imaging time.

In contrast, EPI measures *all* lines of k space in a single excitation, vastly reducing the imaging time and making it an ideal sequence for dynamic MRI techniques such as fMRI. In order to acquire all the data in a single sample of k space, the gradient amplifiers are usually charged to their maximum, and are switched rapidly. The resulting time varying magnetic field can induce physiological stimulation in human subjects (Cohen et al., 1990). While it is possible to use other ‘single-excitation’ sequences for fMRI (such as spiral scanning sequences), EPI imaging was used exclusively to collect the data in this thesis.

2.3.2 T_2^* and fMRI

The T_2^* of water protons is influenced by molecule-molecule interactions between the protons themselves, but also by local B_0 inhomogeneities caused by the different magnetic properties of various molecules. In the human body there are a number of molecules that have endogenous magnetic properties. Some of these molecules are called *paramagnetic* (the antonym is *diamagnetic*) because they will magnetize to a slight degree when exposed to an externally applied field (the B_0 field). Paramagnetic molecules will affect T_2^* times, as an area of the body with a high concentration of paramagnetic molecules will have a local magnetic gradient. This local gradient will contribute to the decay of transverse magnetization and consequently shorten the T_2^* decay time. This difference between the field experienced locally at given locations and the applied field is known as *magnetic susceptibility* (χ). The problems that susceptibility poses for imaging neuroscience will be briefly revisited later.

Serendipitously for neuroscience haemoglobin (the primary oxygen-carrying molecule in blood) is more paramagnetic in its unbound state (deoxyhaemoglobin) than its oxygen-bound state (Pauling and Coryell, 1936). Therefore changes in the ratio of deoxyhaemoglobin to oxyhaemoglobin should result in changes in T_2^* . This effect was demonstrated empirically *in vivo* in animal work carried out by Ogawa and colleagues (1990a, 1990b) and Turner and

colleagues (1991). Both groups showed that by experimentally manipulating the ratio of deoxy- to oxyhaemoglobin (usually by the induction of hypoxia) one could image contrast changes around blood vessels using MRI. Changes occurred not only in blood water, but also in the tissue water around vessels.

2.3.2.1 *BOLD Contrast in fMRI*

Taking the work of Turner and Ogawa to its logical conclusion, Kwong and colleagues (1992) and Ogawa and colleagues (1990c) showed that the susceptibility differences caused by deoxyhaemoglobin concentrations *in vivo* in humans were sufficient to act as a contrast source. Although Belliveau and colleagues (1991) had already used an exogenous contrast agent to examine blood volume changes in human visual cortex during simple photic stimulation, the work by Kwong and Ogawa demonstrated the potential of fMRI as a truly non-invasive imaging technology. This signal source was dubbed the blood oxygenation level dependant, or 'BOLD', contrast mechanism. Using MRI pulse sequences that have a long TE (i.e. a long time between the initial excitation of protons and the measurement of signal, on the order of 20-80ms for fMRI) and a short TR (e.g. EPI) it is possible to collect whole-brain data from subjects in a matter of a couple of seconds.

As blood occupies only a small fraction of grey matter, BOLD signal changes are on the order of a few percent at best. Additionally, the dynamics of the neurovascular response mean that the BOLD signal is delayed in time: whereas neuronal dynamics are measured on the order of milliseconds, the BOLD response takes a number of seconds to evolve. This means that although one can theoretically acquire several MR images in a second, the temporal smoothing of the underlying neuronal signal effected by the BOLD response ultimately decides the effective temporal resolution. Determining the *temporal point spread function* (Friston et al., 1994) of fMRI data is therefore important.

In addition, although very high-resolution fMRI images are theoretically possible, there may be other constraints on the effective spatial resolution of the BOLD signal. The relationship between the BOLD signal and the

neurophysiological events that generate it are therefore of great interest to imaging neuroscience.

2.3.2.2 *Brain, Vein or Oxygen Drain? : Neurophysiology and BOLD*

While local cerebral blood flow and glucose consumption increase locally and co-localise with the site of increased neuronal metabolism in a robust fashion, the local metabolic rate of oxygen (CMRO_2) does not change correspondingly (Fox and Raichle, 1986). Since the first demonstration of this effect in 1986, different groups have shown varying relationships between oxygen consumption and flow/glucose consumption, either confirming (e.g. Madsen et al., 1995) or contradicting (Hyder et al., 1996) the findings of Fox and Raichle. While at present this remains a controversial topic, it is widely accepted that the delivery of oxygen to functionally activated neuronal tissue overcompensates for initial oxygen demand. There is therefore a surplus in the increase of local oxygenated haemoglobin. Some studies have suggested that this increase is the only way that the diffusion-limited qualities of arterial oxygen can be overcome (e.g. Buxton and Frank, 1997).

The uncoupling or weak link between the changes in rCBF and rCMRO_2 , with CBF changing more than local oxygen uptake, leads to a decrease in deoxyhaemoglobin concentration in local capillaries. This reduction in signal is the basis of the BOLD effect - the ratio of deoxygenated to oxygenated haemoglobin in blood within a voxel. The increase in rCBF delivered in response to functional activation results in more oxygenated blood in local capillaries and venous vascular beds, which in turn results in lower field gradients around the vascular beds. It is this decrease in the effects of deoxyhaemoglobin on T_2^* that causes the increase in signal within voxels.

The ambiguities surrounding the relation of BOLD to actual neuronal activation (i.e. an increase in the production of action potentials) have caused some scientists to be wary of over-interpreting the results of functional imaging studies. For example, some have argued that BOLD is inherently non-physiological, an epiphenomenon that accompanies neuronal activation, and it may be dangerous to treat it as a true indicator of underlying neurophysiology. However, there is now a

large body of data to support the use of BOLD as a tool for neuroscience. A number of studies have used optical imaging techniques to study neurovascular coupling. These techniques record reflectance changes from the exposed cortical surface caused by a number of optically active processes. However, it is difficult to separate out these different sources when using traditional optical imaging. A series of experiments performed by Arminen Grinvald and colleagues have provided crucial insights into both the spatiotemporal limitations of fMRI, and of the sources underlying responses to local increases in neuronal metabolism. Expanding on early work in cat visual cortex (Grinvald et al., 1986), they used optical imaging spectroscopy (Malonek and Grinvald, 1996) to obtain detailed information on the temporal pattern of oxy- and deoxyhaemoglobin changes in activated tissue after simple visual stimulation. Finally they used an oxygen-sensitive dye method (Vanzetta and Grinvald, 1999) to study oxygen uptake during stimulation with greater temporal resolution.

The results from this series of papers support a triphasic model. Initially there is an increase in oxygen consumption, caused by an increase in oxygen metabolism in 'active neurons'. This results in an increase in local deoxyhaemoglobin concentrations, and begins around 100ms after initial sensory stimulation (the so-called 'initial dip'). This component is well localised to the actual site of neuronal activity (in the Grinvald experiments, as columnar-specific stimuli were used, this translates into columnar-specific signals). This finding has been confirmed by high-field fMRI studies, using field strengths of 4T and higher (e.g. Hu et al., 1997).

This phase is followed by an increase in blood volume caused by capillary dilation beginning around 300-500ms later, which is less well co-localised with the site of electrical activity. Finally, there is an increase in local blood flow that begins around 500ms - 1s after stimulation. This decreases deoxyhaemoglobin concentrations and increases oxyhaemoglobin concentrations, and is the primary cause of the BOLD effect. This third phase of the neurovascular response causes a much larger decrease in deoxy- concentration than the initial increase (on the order of x4 difference). The cat experiments of Grinvald suggest that this late

response is not localised to the activated cortical columns, but is spread over neighbouring columns as well.

Quite apart from the relationship between the BOLD signal and neuronal 'activation' is the relationship between fMRI signal as acquired by the scanner and the actual spatiotemporal characteristics of the BOLD signal. One good example is the 'brain or vein' problem (e.g. Kleinschmidt and Frahm, 1997): as BOLD signal can also be detected in the macrovasculature surrounding areas of activation (e.g. Segebarth et al., 1994), how confident can one be that BOLD signal in voxels truly represents activation of the underlying cortex and not vessels? The high-resolution images of ocular dominance columns produced at high field strengths suggest, at least in visual cortex, this obstacle can be overcome.

These difficulties apart, the difference between the 'initial dip' and the later BOLD response suggests that imaging studies using the initial dip will produce more spatially veridical data. However, the use of 'the dip' remains controversial. While some investigators have published impressive demonstrations of the localising power of the dip (Kim et al, 2000), others have remained more cautious. There are practical (the dip has not been observed at field strengths of lower than 4T in humans) and theoretical (e.g. Logothetis 2000) reasons why this controversy continues.

The problems associated with the initial dip illustrate the problems of imaging small signal changes in MRI. Even the positive-going component of the BOLD response only produces signal changes of the order of 2-4% in primary sensory areas at 1.5T (Cohen, 1996). Because of this, sophisticated image processing and analysis techniques must be used to ensure that signal and not noise is being studied. These issues and techniques will be discussed in the next section.

2.4 Characterising Neurovascular Changes With The General Linear Model - Statistical Parametric Mapping (SPM)

2.4.1 Image Analysis and Pre-processing

All of the techniques described above have a common goal: to produce an image that contains relevant information relating to underlying neurophysiology. In PET and fMRI, three-dimensional images are acquired that be divided into volume elements or *voxels*, each with its own intensity value. The voxel intensity value is the value of the dependent variable (rCBF or BOLD contrast) averaged over the volume of brain tissue that the voxel covers. The size of each voxel determines the resolution of the image. Voxel size, however, is often not the ultimate determinant of the *true* resolution of the image. While the resolution of modern PET scans is around 6-8mm, one could conceivably resample PET images into an almost infinite number of voxels. This procedure would not represent a gain in information, as one would not gain any (effective) resolution. As pointed out by Friston and colleagues in their original work on statistical parametric mapping (Friston et al., 1991), the spatial point-spread function of the underlying signal is larger than the voxel size. In addition, artifacts caused by the acquisition of images in *k*-space can cause dependence between spatially non-contiguous voxels (the ‘Gibbs phenomenon’). However, it is important to note that the ‘point-spread’ of the physiological process being imaged determines the true resolution of the images. In addition, artefactual activations can be caused by the method of acquisition.

2.4.1.1 *Realignment*

Effective data analysis in functional imaging experiments relies on the ability of the experimenter to compare like with like over a series of scans acquired over a period of time. For example, if a voxel moves its position between scans so that its intensity value no longer reflects differences from the same spatial location but differences due to different areas being sampled in subsequent scans, it is difficult for the experimenter to unambiguously interpret the data. The higher the spatial resolution (i.e. the smaller the voxel size), the greater this problem becomes.

Indeed, it was common for early fMRI studies to be viewed with some suspicion due to the problems caused by subject motion (for example see Hajnal et al., 1996). However, if one can ensure that any motion is detected and controlled these problems can be addressed. It is now standard in functional neuroimaging experiments for researchers to employ a *realignment* algorithm to ensure that the confounding effects of movement are reduced.

Typically, realignment algorithms move all images into a standard ‘space’, so that the data from each voxel represents an intensity value from the same position over subsequent scans. The approach used in all work described in this thesis is that used by Ashburner and colleagues (Friston et al., 1995a; Ashburner et al., 1999). The framework involves treating images as scalar fields - in effect, as a series of points (or vectors), each with an intensity value. The problems posed by subject movement on the eventual analysis of imaging data suggest that steps should be taken before analysis to remove or reduce residual movement effects.

The Ashburner approach treats each image (or scalar field) as a *rigid body*. A rigid body is an object in which the relationship between each element (voxel) of the body remains constant under all possible motions. It is easy to appreciate how this simplification of each image renders the problem of realignment more computationally tractable. Briefly, by considering images as scalar fields, the differences between images can be solved by linear algebraic methods. One of the simplest of spatial transformations is the *affine transformation*, a class of transformation that preserves collinearities. In realignment, the differences between images are assumed to be describable by six parameters: three translations (in the x, y or z axes respectively) and three rotations (about each of the axes). The transformations described by these parameters are applied iteratively until the sum-of-squares difference between the two images is minimised: this typically requires only five iterations of the algorithm (Ashburner and Friston, 1997).

It is simple to acknowledge the problems of movement when it is of a large enough magnitude to be appreciable by eye, but even sub-voxel movement can be a serious problem. As well as introducing false positive activations at tissue

boundaries, movement will reduce the signal:noise ratio of the image. Perhaps most significantly, uncontrolled motion introduces an unmodelled source of variance into voxel time series, affecting the assumptions underlying the modelling of fMRI time series. This issue will be revisited in the subsequent discussion of linear models for image analysis.

2.4.1.2 *Between Modality Coregistration*

Often in neuroimaging the functional data are of a low enough resolution to make unambiguous anatomical localisation a problem. It is common practice to acquire a T1-weighted structural image of the subject during the scanning session. As well as having a higher spatial resolution, this image typically has better white:grey matter contrast. Once acquired, the researcher often wishes to display the lower resolution data in the same space as the higher-resolution data to facilitate localisation. Even if the subject has not moved between the acquisition of the functional and structural images, the different kinds of sequence used in their acquisition require a different approach to combining them. This problem is conceptually similar to realignment - two images are not spatially contingent, and the researcher wishes to minimise the differences between them. However, the assumptions that any differences between images are now merely down to subject movements are no longer tenable. The differences between high-speed EPI functional images and slower MPAGE structural images are quite pronounced even to the untrained eye, and there are significant differences between PET and MPAGE images.

One approach to this problem is to pre-process the images from both modalities. This is achieved by ‘partitioning the MR image and then recombining the partitions such that they emulate an [...] image [of whatever modality the researcher requires]’ (Ashburner and Friston, 1997). This ‘partitioning’ approach is formally known as *segmentation*. Segmenting an image involves applying an algorithm that attempts to classify each voxel as a distinct tissue type based on its intensity value. In semi-automated segmentation routines, it is common for the operator to select an exemplar voxel from each tissue type (here, GM, WM and CSF) by eye, and use these as starting or seed values for the classification

algorithm. However, the ultimate goal of these routines is to escape observer bias. *Cluster analysis* is a technique that finds similarities in a body of data and uses this to group the data (for an interesting practical application of this technique, see LaPointe and Legrande, 1994). While cluster analysis is usually an assumption-free technique, it is possible to incorporate prior knowledge into the algorithm's computations. The approach used herein utilises prior knowledge of the spatial distribution of voxels of a particular tissue class taken from work carried at the Montreal Neurological Institute (Evans et al., 1993). This prior information is incorporated into the clustering algorithm's computations (here, the ML 'Mixture Model' algorithm is employed; Hartigan, 1975). After the images have been segmented into images of the different tissue compartments (voxels are also clustered into scalp values, and so segmentation is a quick way to effect *de facto* scalp editing), a rigid-body transformation is used to coregister the images.

2.4.1.3 *Linear and Non-linear Spatial Normalisation*

The above techniques for the spatial transformation of images allow one to solve the problems of differences in reference space within modalities (realignment), and the comparison of images between modalities (coregistration). The questions posed by most neuroimaging studies require the researcher to perform group-wise or even population-wise statistical inferences. Before beginning these types of analysis, some way must be found to allow structurally analogous areas to be compared between different subjects' brains. Human brains vary in anatomical details at a number of spatial scales: studies have shown significant variation at the macroscopic (Armstrong et al., 1995) and microscopic levels (Rademacher et al., 1992). To ensure the validity of any between-subject comparisons, each subject's brain must be transformed into a common reference space, just as successive images from the same subject are during realignment. This process of 'normalisation' seeks to remove confounding anatomical differences at one spatial scale so that comparisons at another can be effected. However, affine transformations or other classes of linear spatial transformations are not powerful enough for this task. To enable the comparison of between-subject imaging data, images must be 'warped' into a standard reference space

that contains a template image – a standardised brain. Warping is a class of spatial transformation that acts to change the global shape of the subject's brain while preserving the spatial relationships of local structures.

First, each subject's brain is mapped roughly into the space of the template using an affine transformation, similar to during realignment. However, how one proceeds from this initial step remains contentious. Different kinds of warping algorithm use different constraints: for example, viscous fluid models (e.g. Lester and Arridge, 1998) are powerful warping algorithms that can effectively transform one image into the space of another. In the context of neuroimaging analysis the appropriateness of such a transform is debatable. The variability between individual brains is an important expression of the structural organisation of each brain. If the 'warping' algorithms used to map between subject brains and standard space are run until they converge, interesting variations in local anatomy may be lost. This may influence subsequent functional analyses. Although we accept that each brain is different and it may not make sense to employ warping techniques that will remove all local structural variance, it is difficult to decide how to compute a 'goodness of warp' estimator, or even the parameters that one would use. The approaches used within this thesis are widely used and constantly subject to improvement as better heuristic measures of the 'goodness' of normalisation are formulated. If warping performs its task efficiently i.e. by minimising the global shape differences between different subjects' brains while maintaining local structural information, then multi-subject analysis techniques can be utilised.

2.4.2 fMRI and PET: Experimental Design, Statistical Inference and Modeling

PET and fMRI characterise neurovascular activity using different dependent variables. These differences will influence subsequent data analysis. While PET averages over a time period of around half a minute and each scan is treated as independent, fMRI data are time series data with a theoretical resolution of less than a second. Accepting these differences, PET and fMRI analyses still share a common core of theoretical concepts. A common approach to the analysis of data

from both modalities is the use of a form of the *general linear model* (GLM). One of the most popular embodiments of the GLM in neuroimaging analysis is the Statistical Parametric Mapping (SPM) software package (<http://www.fil.ion.ucl.ac.uk/spm>), which is used throughout this thesis. The GLM will be introduced herein by first describing the terminology and some issues regarding its application to neuroimaging data. Issues specifically pertinent to the analysis of PET scans and fMRI timeseries will be introduced subsequently.

2.4.2.1 *Statistical Parametric Mapping (SPM)*

The concept of Statistical Parametric Mapping was introduced by Friston and colleagues, and although the approach owes much to previous work on change distribution analysis pioneered by the St.Louis group (Fox and Mintun, 1989) there are substantive differences. SPMs are three-dimensional images of statistical values, such as *ts* or *Fs*, recorded over a volume of interest that can range from the entire brain to a single plane through a structure of interest. The intensity of each voxel (volume element) represents the value of the statistic in question under the particular hypothesis being examined. The underlying philosophy of SPM is ably summarised by the following quote: ‘...one proceeds by analyzing each voxel using any (univariate) statistical parametric test. The resulting statistics are assembled into an image that is then interpreted as a spatially extended statistical process.’ (Friston et al., 1995b). SPMs efficiently summarise a vast body of data in a form that is by far easier to examine and interpret.

2.4.2.2 *Gaussian Fields and Non-Independence*

Before introducing the GLM, it is important to discuss some issues that frequently arise in the analysis of neuroimaging data. In a typical single fMRI volume there can be as many as 200,000 voxels. As the researcher typically wishes to test a regionally specified hypothesis, it is necessary to perform the appropriate univariate statistical tests *at each and every voxel*. At the standard rejection rate of $p < 0.05$, we would expect by chance to reject the null hypothesis (H_0) of no experimental effects in a twentieth of our sample i.e. 5% of 200,000 - 10,000 voxels! One can therefore obtain a perfectly reasonable number of activated voxels in the imaging volume by simply testing one’s hypothesis

enough times, and reporting only the instances in which H_0 is rejected while ignoring the times it is not (called the '*file drawer*' problem; Abelson, 1989).

The standard solution to this problem is to use a technique called Bonferroni correction, which simply adjusts the p value at which H_0 is rejected such that it reflects the number of tests being performed. For example, in the above case one would divide the usual p value of 0.05 by 200,000, to get a corrected p value of 25×10^{-7} . However, although *separate* univariate tests are performed at each voxel, the resolution of most neuroimaging data renders voxels non-independent (see section 2.4.1 above). The Bonferroni correction is therefore too conservative.

Instead, the crucial statistic level to reject H_0 in the univariate tests used by SPM is calculated by the application of *Gaussian random field* (GRF) theory. GRF deals with 'the behaviour of stochastic processes defined over a space of D dimensions' (Poline et al., 1997). Knowing about the behaviour of Gaussian fields under certain constraints (Adler 1981; Worsley, 1994) it is possible to determine the probability of a given 'local excursion' of the Gaussian field at any location: in simpler terms, to assign the correct significance to activations at a voxel-specific spatial scale.

Without dealing with this theory in exhaustive detail, it is important to appreciate that the pre-processing of neuroimaging data is necessary before GRF theory can be utilised. Images must approximate 'a continuous, zero-mean, unit variance, homogenous, smoothed Gaussian random field' (Poline et al., 1995). To fulfil the latter part of this assumption and to ensure that the spatial correlation structure of the data is stationary the images must be spatially smoothed using Gaussian filter kernels, lowering the resolution of the data from its 'raw' state. The full-width-half-maximum (FWHM) of the smoothing kernel should typically be at least 2 or 3 times larger than the initial voxel size - for example, it is common practice to smooth fMRI data with a 'raw' resolution of $2 \times 2 \times 2$ mm with a Gaussian kernel of 6 mm FWHM. Although this may appear to defeat the purpose of acquiring high-resolution functional data, it is important to remember that the underlying neurovascular signal has already spatially smoothed the BOLD signal. While it is possible to acquire functional data of submillimeter

resolution, the *effective* resolution of the data is determined by the spatial congruence between metabolic demand and vascular supply.

Smoothing neuroimaging data is an important process, for a variety of reasons: it raises the signal: noise ratio of the data; it facilitates the detection of activations which have the same size as the filter kernel (by matched filter theorem); and, perhaps most importantly, smoothing facilitates the detection of group-level activations by removing residual differences in functional neuroanatomy that remain after normalisation.

A further point to note when using Gaussian field theory is that the statistic must have enough degrees of freedom (dfs), or Gaussian field assumptions break down. It is usually the case that one has more than enough dfs in the analysis of fMRI data, but in single subject PET designs with a large number of conditions this can be problematic. In these cases it may be more useful to use non-parametric analysis methods (Holmes et al., 1996).

2.4.2.3 *The General Linear Model*

At present there are a number of different analysis ‘packages’ used by the neuroimaging community. As mentioned above, the great majority of these packages employ univariate linear tests at each and every voxel to attempt to reject the H_0 . All parametric versions of these tests, ranging from simple correlation tests of a single stimulus vector (e.g. STIMULATE; Strupp, 1996) to more sophisticated analysis frameworks employing ANCOVAs, can be thought of as singular cases of a unifying analysis framework, the general linear model. The general linear model lies at the heart of the SPM package, and was used for all subsequent analyses.

The GLM allows for a great deal of flexibility in the design and analysis of experiments. Variation in the dependent variable Y (rCBF or BOLD contrast for PET and fMRI respectively) is modeled as a linear combination of a number of explanatory variables, plus an error term. The explanatory (independent) variables are each denoted by x_{jl} (where L is the total number of explanatory variables). An important point to note is that the use of the GLM is predicated upon the

assumption that the variance attributable to the explanatory variables is linearly separable. The GLM formulation for a single observation at a voxel is:

$$Y_j = \beta_1 x_{j1} + \dots + \beta_L x_{jL} + \epsilon_j \quad (6)$$

The errors (ϵ_j) are assumed to be independent and Normally distributed with zero mean and variance σ^2 . This particular error term is between-scan or intra-session variance, and is denoted by σ_ϵ^2 throughout the remainder of this thesis. Fitting the GLM at a voxel allows for different σ_ϵ^2 across voxels, but does carry with it the assumption that σ_ϵ^2 is constant across experimental conditions and different subjects. The x s can take two forms: *covariates* ('real' levels of a particular variable, such as time or the concentration of a pharmacological agent) and *indicator* variables (in which different values of an experimental factor are assigned integer values, i.e. using VAS measurements of subject pain as an explanatory variable) (Friston *et al.*, 1995b). As the above difference does not influence the evaluation of the GLM, I will use the catchall term 'covariate' when referring to explanatory variables from hereon in. To fit the model of x_{jL} s to the data Y_j , the parameters of the model must be estimated (β_L). For the single observation of Eqn. 6, a relationship between the values of each experimental factor x and Y must be evaluated. Although in neuroimaging experiments there are usually more than one x to fit to Y , it is helpful to remember that in the limiting case of $L=1$, Eqn. 6 reduces to:

$$Y_j = x_{1j}\mu + \beta_2 x_{2j} + \epsilon_j$$

which is simply linear regression! The ' $x_{1j}\mu$ ' term is the Y -axis 'intercept', and introduces the use of a 'dummy' variable (x_{1j}) whose values is one for all J scans. This allows mean or 'constant' terms to be included in the GLM formulation, and so explicitly model condition, subject or even population means in the design matrix.

The above example usefully illustrates that the β s may be helpfully thought of as 'regression slope' co-efficients, describing the size of the relationship between Y and the x s. However, it is rare for a neuroimaging experiment to reduce to

simple linear regression. Similarly, it is rare for only one observation to be taken of each voxel, and so for every scan j there is a corresponding Eqn. 6, such that:

$$Y_I = \beta_I x_{I1} + \dots + \beta_I x_{Il} + \dots + \beta_L x_{IL} + \epsilon_I$$

$$\cdot \quad \cdot$$

$$\cdot = \cdot$$

$$\cdot \quad \cdot$$

$$Y_j = \beta_I x_{j1} + \dots + \beta_I x_{jl} + \dots + \beta_L x_{jL} + \epsilon_j$$

$$\cdot \quad \cdot$$

$$\cdot = \cdot$$

$$\cdot \quad \cdot$$

$$Y_J = \beta_I x_{J1} + \dots + \beta_I x_{Jl} + \dots + \beta_L x_{JL} + \epsilon_J$$

This rather cumbersome formulation can be summarized by:

$$\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\epsilon} \quad (7)$$

which is a multivariate GLM where $\mathbf{Y}$ is a column vector of observations, $\boldsymbol{\beta}$ a column vector of parameter estimates and $\boldsymbol{\epsilon}$ a column vector of error terms. $\mathbf{X}$ represents a concept that is essential in the application of the GLM in neuroimaging analysis: the *design matrix*. To summarize, to test for experimental effects at a given voxel the data $\mathbf{Y}$ are collected over J scans, the experimental model of explanatory variables $\mathbf{X}$ is fitted to the data, and the column vector of parameters $\boldsymbol{\beta}$ is estimated. The ‘goodness-of-fit’ of the model to the data is indexed by the errors $\boldsymbol{\epsilon}$. Maximizing the fit of the model to the data will increase subsequent calculations of statistical significance. Intelligent formulation of the experimental model is therefore extremely important.

2.4.2.4 Model Fitting: Estimation, Overdetermination and Inference

Estimation refers to the process of generating values for the model parameters β_{1-L} (the parameters must be *estimated* as there are typically less parameters in the model than there are scans). The ‘best’ values of β s are those that minimise the total distance between the model and the data. This quantity is formulated as the *sum of squared error (S)* - the sum of the squared distances between each Y_j (data) and $\hat{Y}_j$ (model). Fitting the model to the data such that S is minimized is an example of *least squares* fitting. The parameter estimates that minimise S are denoted $\hat{\beta}$ such that:

$$\hat{\beta} = (X^T X)^{-1} X^T Y \quad (8)$$

Eqn.8 is solvable if and only if $(X^T X)$ is invertible - that is, there is a unique solution to $(X^T X)^{-1}$. As X is the design matrix, $(X^T X)$ is invertible if X is of full rank or non-singular - in matrix algebra terms, there are no columns that can be formed by a linear combination of the other columns (X does not show *linear dependence*). Such a matrix is *overdetermined*. Consider the simple 2x3 matrix X :

$$X = \begin{bmatrix} 0 & 1 & 1 \\ 1 & 0 & 1 \end{bmatrix}$$

The third column of X is a linear combination of columns one and two, so X is overdetermined. This causes serious problems. Because there are an infinite number of matrices whose inverse is X , there are also an infinite number of least square estimates $\hat{\beta}$. As it is a simple fact of experimental design that one will often be faced with the above problem (i.e. in almost all PET studies), it must be overcome. The approach used within SPM to constrain the infinite set of $\hat{\beta}$ s is to compute the *pseudo-inverse* of X , or $\text{pinv}(X^T X)$.

After fitting the model and determining the parameters, the variance of the model fit is estimated by *residual mean squares*: the residual sum of squares divided by the degrees of freedom ($df = J - p$, where p is the rank of X). Usually in neuroimaging, one is less interested in disproving the null hypothesis for the entire design matrix (i.e. $H_0 =$ ‘the entire experimental model does not

significantly reduce the error variance') and more concerned with seeing how much experimental variance can be explained by some linear combination of the model parameters. Linear combinations of the parameter estimates that are invariant over the space of possible parameters are called *contrasts*. A contrast vector in SPM is one whose elements sum to zero. Contrasts are important when the design matrix is not of full rank.

The eventual output of the above steps is an image where each voxel's intensity value corresponds to a statistic value (usually a t or an F). The probability assigned to each statistic is achieved by treating each image volume as a Gaussian random field (reviewed in Poline et al., 1997), reviewed in section 2.4.2.2 above.

2.4.3 Experimental Models for fMRI

The versatility of the GLM allows for a large number of possible experimental designs to be tested. While not wanting to list an extensive taxonomy of design forms (interested readers should consult Friston et al., 1997), it is important to introduce a number of terms that will be used in the following chapters.

Usually experimenters will want to test for the significance of a particular linear combination of the explanatory variables: the significance of these variables is computed after the remainder of the experimental model has been fitted to the data. While there are an almost infinite number of different contrasts arising out of larger design matrices, the evaluation of linear combinations of design matrix columns can usually be classified according to a small number of experimental designs.

While early PET designs were dominated by 'region-of-interest' (ROI) approaches where researchers limited the brain areas that they evaluated according to *a priori* information, the introduction of 'subtractive methodology' allowed for assumption-free analyses. Frans Donders, pioneer of reaction time experiments introduced the subtractive method to experimental psychology in the 19th century. By subtracting the time subjects took to respond to a simple stimulus from a more complex stimulus Donders claimed that he could isolate the time that subjects needed to perform the 'differentiation' inherent in the complex task. Donders' methodology allowed researchers to isolate specific cognitive task

components: for example, if a researcher was *only* interested in the time for subjects to react to differently coloured stimuli, they could use this approach to design a similar control task that differed *only* in presenting monochrome stimuli. In neuroimaging, acquiring images of two different cognitive states that differ only in the *cognitive component of interest* (CCI) should allow the experimenter to isolate the CCI by subtracting the less complex image from the other. One of the biggest practical problems in neuroimaging is ensuring that a control task is good enough for the hypothesis in question.

Subtractive designs make the assumption of ‘pure insertion’; that is, it is possible to introduce a different category of the factor in question without it having any effect on the neurovascular processes mediating the base/control task. To use the example of Donder’s experiment, the ‘insertion’ of the more complex task should not cause any *interactions*. The presence of interactions makes subtraction analyses ambiguous, and violates the assumptions embodied in the simple subtraction design. Although rightly criticised (Friston et al., 1996), subtractive designs can be useful as long as the caveats accompanying their use are kept in mind.

The approach suggested by Friston and colleagues to overcome the problems of cognitive subtraction is that of the *factorial* design (after Sternberg’s similar extension to Donder’s method; Sternberg, 1969). A factorial design allows one to explicitly examine interactions between experimental factors consisting of a number of levels. While there are a great many possible ways to conceptualize factorial experiments, it is useful to think of a factorial experiment as measuring a ‘difference of a difference’. Whereas a simple subtractive design is interested in the difference in Y between two categories ($Y_1 - Y_2$), the factorial design allows one to evaluate this difference under two different contexts ($Y_1^A - Y_2^A$) and ($Y_1^B - Y_2^B$). A psychopharmacological study is a good example: the experimenters are usually interested in drug effects on a particular cognitive process. This can be formulated as a subtraction - say ‘reaction time on the colour Stroop task’ (Y_1) versus ‘reaction times on veridical colour/word pairs’ (Y_2). However, if data are only acquired while subjects are exposed to the drug the experimenter cannot

unambiguously attribute the difference in RTs to the drug itself. By acquiring data while the subject receives the drug in one instance and receives a placebo in the other (the two levels of factor two, A and B above), specific *drug x task* effects can be examined. As well as the increased power of such a design to unambiguously isolate cognitive components, the very non-linear nature of cognitive dynamics at the neuronal level suggests that experimental designs examining interaction effects are those that will produce the most ‘interesting’ results. However, one caveat is that however hard one tries, some experimental designs cannot be formulated as factorial designs. Experimenters may find that by forcing their design into a factorial framework they ultimately lose rather than gain sensitivity.

2.4.3.1 SPM formulations of GLM designs

As detailed above, neuroimaging seeks to explain variance in Y at each voxel by applying the GLM and fitting X (the design matrix) at each and every voxel. It is common in neuroimaging to graphically illustrate the design matrix as an ‘image’. The values of X are represented by grayscale values, so that a value of -1 will be black, 0 mid-gray, and +1 white (Holmes et al., 1997). Using the SPM software package it is possible to test a great variety of different contrasts (and thus hypotheses) by assigning different weights to the columns of the design matrix (and thus the experimental effects). One can think of this as ‘partitioning’ the design matrix so that the significance of particular weightings of its columns that specify a unique hypothesis can be evaluated.

Not all of the columns of the design matrix will necessarily be of interest to the experimenter for a given contrast. Furthermore, some columns of the design matrix may model effects that the experimenter is *never* interested in evaluating. These effects are usually classed as ‘confounds’. A typical confound in PET imaging is global flow. Neuroimaging hypotheses are typically predicated on the assumption that the effects of interest are expressed in a regionally specific manner. Global effects i.e. those that are not regionally specific will potentially confound any analyses. As global flow is simply the mean intracerebral rCBF (or BOLD signal), a column modeling global flow can be easily incorporated into any

design matrix. A further common confound arises when a multisubject design matrix is used - the experimenter is typically interested in changes in Y that are *relative* to the subject-specific mean values of Y . Including in the design matrix subject-specific mean terms solves this problem.

Modeling confounds in the design matrix will improve the sensitivity of the model, as the maximum amount of experimental variance will be modeled, resulting in a better model fit and smaller ϵ . However, the degrees of freedom of the model are $J-p$. Increasing the rank of the matrix (p) will therefore decrease the degrees of freedom. Yet not modeling structured sources of variance in the data will increase ϵ and result in smaller significance (not to mention invalidating the assumption of Normality for ϵ). This ‘Catch-22’ situation is rife in linear modeling, and is formally known as *model selection*. In multilinear regression there are two different schemes of model selection: *forward* and *backward selection* (Draper and Smith, 1998). In forward model selection, the simplest possible model is used to start, and columns are successively added one at a time. The significance of adding these terms to the model is assessed using the F statistic and the ‘extra-sum-of squares’ principle. Here, H_0 can be formulated as ‘the addition of this extra term does not explain a significant amount of variance over the current model’. If H_0 is rejected, the term is added to the model, and so on. Backward model selection is analogous: one starts with the full model and assesses the effects of removing terms from it. Formal model selection is rarely performed in neuroimaging, although whenever an F test is used on a single column of the model it is being used implicitly. A practical example of model selection will be presented in Chapter 4.

2.4.3.2 Modelling of fMRI Timeseries - Signal Processing Issues

A significant difference between PET studies and fMRI studies is evident in the title to this section: while PET measurements are independent, fMRI produces *time series* data. This introduces additional issues for analysis and inference of fMRI data. As well as dealing with additional sources of noise, the temporal dynamics of the ‘haemodynamic transfer function’ of neuronal effects to vascular effects must be considered.

In PET scanning each scan is treated as an independent observation, but fMRI scans occur in a continual series. As for PET studies, to increase the signal: noise ratio the experimenter rarely collects a single set of data for each of the experimental conditions. As this will involve the repetition of experimental conditions over a set period of time, it is possible to describe the occurrence of experimental conditions in fMRI as obeying a certain frequency. For example, consider a single subject fMRI study with a TR of 4s in which photic stimulation is delivered to the subject for a period of five scans, followed by five scans of 'rest' (i.e. no photic stimulation). The frequency of the delivery of photic stimulation is therefore 0.025HZ, as it takes 40s or 10TRs for the stimulation cycle to repeat.

Knowing the frequency spectra of the experimental conditions is crucial, because in fMRI the noise spectra (the distribution of noise across all frequencies) is not uncorrelated (white). A number of empirical studies (e.g. Zarahn et al., 1997a; Boynton et al., 1996) have shown that fMRI data are coloured under the null hypothesis, violating the assumptions of the GLM. Although the exact shape of fMRI noise spectra is contentious, the $1/f$ (frequency) model proposed by Zarahn and colleagues (1997a) is accepted as a good approximation. As one can appreciate, because of the approximate $1/f$ form the power of the noise is highest at low frequencies. Reasons for these low-frequency components range from periodic physiological noise (Jezzard, 1993), scanner 'drift', or more complex time x task interactions. Whatever the underlying cause, low frequency noise presents two problems for the analysis of fMRI data. As mentioned above, it violates the assumptions of traditional parametric statistics. In addition, it reduces the sensitivity of fMRI designs where the frequency of the experimental effects are similar to the intrinsic noise spectrum, as the experimental model will end up fitting noise as well as signal.

The fMRI noise spectra are not only characterised by low frequency confounds, however. The smoothness of the haemodynamic response smooths the BOLD signal so that signal in the n th scan will be contaminated by the BOLD signal from previous scans. Formally, as '...the sampling interval of ...[f]MRI...is

typically much shorter than the time-constants of haemodynamic changes, the resulting timeseries can show substantial autocorrelation' (Friston et al., 1994). The smoothness of the haemodynamic response smooths the BOLD signal so that signal in the n th scan is contaminated by the BOLD signal from previous scans. Just as low-frequency noise presents problems at one end of the noise spectra, the smoothness of the haemodynamic response function (hrf) presents additional problems as it will attenuate high-frequency experimental designs.

As eloquently summarised by Aguirre and D'Esposito (1999), the $1/f$ noise spectrum and the smoothness of the hrf are the '...Scylla and Charybdis of fMRI experimental design: experimental variance must be present at sufficiently low frequencies to pass through the haemodynamic transfer function but at sufficiently high frequencies to avoid the elevated noise range'. The fMRI researcher has two means with which to circumvent these problems. The first is effective experimental design: ensuring that the fundamental frequency of experimental variance is concentrated in a region high enough to escape the $1/f$ spectra, yet low enough so that its power is not reduced by the hrf. The second approach is temporal filtering, analogous to the spatial smoothing used to ensure that the data conform to GRF assumptions. Filtering fMRI data before the experimental model is estimated and inference made is an effective way to 'regularize' the temporal autocorrelation structure. The approach implemented in the current version of the SPM software (SPM99) is to use bandpass filtering, using a convolution matrix K that effects both low-pass and high-pass filtering simultaneously.

However, the temporal autocorrelation inherent in fMRI data also affects calculations of statistical inference. As the data are temporally autocorrelated, the residual degrees of freedom are no longer $J-p-1$. If the autocorrelation structure of the data is known in advance, this information can be used to calculate the *effective* degrees of freedom of the model (Friston et al., 1994). However, instead of estimating the autocorrelation structure itself, the approach advocated by Friston and colleagues (1995c; and extended by Worsley and Friston 1995) is to use the convolution matrix K , as the low-pass component of K is effectively smoothing the data.

The smoothing kernel K is applied such that Eq.7. is now:

$$KY = KX\beta + K\epsilon \quad (9)$$

Although the raw errors ϵ are autocorrelated, by choosing a kernel of a larger size than the endogenous autocorrelation it is assumed that these serial correlations are ‘swamped’ by K (Friston et al., 1995c). Statistical inference is then possible as the effective degrees of freedom are used to calculate the corresponding t or F statistic. Again, by analogy with the application of matched filter theorem to spatial smoothing, conditioning the frequency structure of the data and excluding noise frequencies makes it more likely that ‘interesting’ frequencies of variance i.e. experimental effects will be recovered. The approach above is by no means the only way to solve this problem: other methods to model or remove the serial correlations in fMRI have been proposed (Bullmore et al, 1996; Purdon and Weiskoff, 1998; Aguirre et al 1997; Zarahan et al, 1997a).

2.4.3.3 Event-Related fMRI

The use of event-related fMRI is becoming increasingly popular in fMRI, yet the technique itself is still relatively immature. Initial demonstrations of detectable fMRI signal changes to relatively brief stimulus (on the order of 2s) presentations were made as early as 1992 (Blamire et al., 1992). Subsequent studies demonstrating the ability of fMRI to detect neurovascular events of even shorter duration (e.g. Savoy et al., 1995; Boulanouar et al., 1996; Konishi et al., 1996) showed that fMRI has the power to resolve transient events. Following on from this initial work Dale and Buckner (1997; following an initial empirical example in Buckner et al., 1996) proposed an analysis framework influenced by techniques commonly in use to analyse event-related potentials (ERPs) for the analysis of transient haemodynamic events. Event-related fMRI (efMRI) was thus born.

Subsequent to the Dale and Buckner formulation, a number of analytical frameworks for the analysis of efMRI were published (Josephs et al., 1997; Zarahan et al., 1997b). The approach used herein is that described by Josephs and colleagues (1997), which is an extension of the basic SPM framework to encompass the modelling of single events or ‘transients/delta functions/stick

functions' as they are variously described. While at heart the SPM implementation of efMRI can be simplified for those familiar with the block-mode fMRI by considering a design matrix with an extremely brief block (in effect a temporal singularity), efMRI demands that a number of additional issues are addressed. Although block design fMRI was used for the majority of experiments in this thesis (except Chapters 6 and 7), an examination of some of the assumptions underlying efMRI is useful as it makes the presence of these assumptions in block-mode fMRI transparent.

efMRI is extremely useful from an experimental design perspective as it allows '...new *genres* of fMRI experiment' (Josephs et al., 1997). An oft-quoted example is the 'oddball paradigm', in which the experimental effects of interest are the subject's responses to transient, infrequently presented stimuli that break the 'set' of the context established by preceding stimuli. Similarly, efMRI is extremely useful for stimuli over which the experimenter has no control (i.e. any form of pathological episode, or spontaneous shifts in perception e.g. Kleinschmidt et al., 1999). In addition, most experimenters would agree that modelling subject responses to stimuli over a protracted period of time as is done in block-mode fMRI is often not the most sensitive way to proceed - effectively the assumption is that the subject's responses are invariant over the time of the block. Modelling each trial as a separate event and thus allowing for within-block or trial-to-trial variation will be a more sensitive way to model the experimental variance (e.g. Price et al., 1999).

As well as increasing the number of possible fMRI experiments, efMRI experiments present an opportunity to explicitly test some of the assumptions of the GLM - namely, the linear transform assumptions. The study by Boynton and colleagues (1996) was one of the first to address the linear assumptions underlying the transfer of neuronal activity to the vascular response. While showing that the response was approximately linear over a range of Stimulus Onset Asynchronies (SOAs), the Boynton study demonstrated that some non-linearities in the hrf exist at short SOAs, which the authors thought may be due to neuronal adaptation (Boynton et al., 1996). At present it is unknown whether

nonlinearities in efMRI are due to the BOLD response itself or the underlying neuronal response (e.g. Friston et al., 1998).

The delayed yet transient form of the hrf presents challenges when performing efMRI experiments. One significant problem to models using phase-dependent regressors is the non-simultaneous acquisition of imaging data in a single volume. During sequential scanning protocols, the last slice is acquired a TR after the first slice. Yet each fMRI volume is treated as though each slice is acquired simultaneously. The relatively long state-related designs used for block-mode fMRI will be minimally affected by this fact. However this may significantly bias efMRI results, because the experimental model will fit some slices better than others (Price et al., 1999). In addition, if the experimental stimulus is time-locked to a slice consistently throughout the experiment, the hrf will be sampled very sparsely. Josephs and colleagues (1997) proposed a way to circumvent both problems by ‘jittering’ the phase of data acquisition relative to the stimulus. This provides greater *effective* temporal resolution, and also goes some way towards reducing the effects of non-simultaneous slice acquisition. To effectively overcome different slice-timing problems, it is often necessary to use a temporal interpolation algorithm (Josephs and Henson, 1999). In the absence of such schemes, the choice of *basis functions* can help to overcome slice-timing issues (for example, using a Fourier set of basis functions; Henson et al., 1999). ‘Basis functions’ are defined formally as a set of mutually orthogonal vectors that span a ‘space’ such that each element of the space can be uniquely expressed by a linear combination of the functions. In the current context the ‘space’ is defined as containing all possible spatial expressions of the hrf to a transient event. However, when the dimensions of the space are not known in advance, it becomes difficult to choose the most efficient set of basis functions, or whether to use a single function or a combination.

The single Poisson function suggested by Friston and colleagues (1994) may not be as efficient as other possible formulations. For example, Boynton and colleagues (1996) showed that the time constant chosen by Friston for the Poisson response was several seconds slower than the form suggested by data from V1.

However the method employed by Boynton involved averaging over all the voxels within a selected ROI in the calcarine sulcus. The spatial smoothing effected by Boynton may bias results towards a model which is consistent with the spatially averaged activity of a group of voxels, and not single voxel estimates, although the reasons for this are not obvious. Aguirre and colleagues (1998) suggested that as between-subject variance in efMRI responses was greater than within-subject variance, empirically derived subject-specific hrfs would be the most efficient basis functions. However, although it makes intuitive sense to obtain a good estimate of each subject's hrf for use in subsequent analyses, the Aguirre results remain to be confirmed across different brain areas and different cognitive paradigms. Other analysis frameworks (Lange and Zeger, 1997; Kruggel and von Cramon, 1999) allow for a more complete specification of the hrf, and can thus model non-stationary hrfs well. However the use of multiple basis functions in the GLM allows for good approximations to these more complicated specifications.

2.4.4 Scanning Protocols for fMRI Experiments

The content of most fMRI experiments is very similar to experimental psychology; the main difference being that fMRI experiments are carried out in while the subject lies supine within the cylindrical bore of the MRI scanner. To illustrate the 'fMRI experience' from the subject's point of view, I will describe a typical scanning session. All of the data in this thesis were collected from subjects using a 2T Magnetom VISION (Siemens) whole body MRI system equipped with a volume head coil.

All subjects are checked for contra-indications that may endanger them in the MRI scanner before commencing the experiment, and sign a consent form as standard. This procedure typically lasts 15-20 minutes. Subjects are then familiarised with the experimental task. While it is certainly possible to take a long time doing this, for the majority of the experiments in this thesis the subjects had only to attend to patterns of tactile stimulation. The subjects are then escorted to the scanning suite, and relinquish all metal objects on their person. They are finally led into the scanner and asked to lie supine on the scanner's bed, which is

retracted from the scanner bore. If the experiment involves the delivery of auditory stimuli to subjects, they are fitted either with pneumatic sound tubes or with MR compatible headphones driven from a custom-built noise-cancellation amplifier (Palmer et al., 1999). If this is not the case, subjects are given earplugs to wear. The subject's head is positioned in the head-coil using standard SIEMENS foam cushioning for subject comfort. A number of other laboratories use vacuum 'bean bags' to assist with head stabilisation during scanning – however the extra time spent molding it to each subject's head does not seem to result in a significant improvement in data quality.

It is important to be able to trigger stimuli with exact timing during scanning. In the following experiment, and in all experiments described in this thesis, the stimuli were delivered using an Apple Macintosh computer running in-house experimental protocol software (COGENT; John Romaya, LoN and Oliver Josephs, FIL). COGENT is triggered by serial codes sent from a PC running PLSCNT software (Oliver Josephs, FIL) that allows the user to synchronise serial codes to specific slice numbers. As the subject is lying supine and staring upwards, the delivery of visual stimuli in the scanner is a potential problem. A half-silvered mirror angled at 45 degrees that fits on the top of the head coil. Visual stimuli are back-projected onto the screen using a Proxima 8400e video projector mounted in the scanner control room. Using this simple system it is possible to quickly and with ease present the subject with timelocked visual stimuli. Responses to stimuli are made using a simple MRI-compatible button box. The button box typically lies on the subject's hip. No obvious artifacts have been noted from the slight magnetic field induced by the presence of the device in the B_0 field of the magnet, although these problems have driven other labs to develop fibre-optic button boxes. The exact form of the scanning session is determined by the experimental question. However long each individual session is, the functional EPI sequence data is usually acquired first, followed by the structural MP-RAGE sequence. After each experiment, subjects are debriefed about the purpose of the experiment, and are reimbursed for travelling expenses.

While an effective experimental design is extremely important in neuroimaging, a further level of complexity is added by the need to ensure that the psychological parameters of the experimental model are efficiently controlled. In the current context (the study of the somatosensory system) the psychological parameters of the model are to the different forms of peripheral stimulation delivered to the subject. The methodological challenge presented by this will be covered in the next chapter.

3 Somatosensory Stimulation in fMRI: Vibrotactile and Airpuff Stimulation, Methodology, and Pilot Studies

3.1 A Stimulating Problem?

Before 1900 most of biology was primarily concerned with description. By detailing and classifying the relationships between organisms a *taxonomy* of the natural world slowly took shape. Darwin's theory of evolution by natural selection (1859) was one of the first attempts to begin to explain *why* such diversity existed. Without the taxonomists who preceded him, Darwin would not have possessed the rich fund of data that allowed him to make his conclusions. This pattern is common in science – descriptive explanations are typically superseded by theories with predictive power.

Although experimental neuroimaging is a new science, it is already sufficiently mature for there to exist a number of attempts at proceeding beyond an initial taxonomic level of description. Methodological advances have allowed investigators to show that brain regions can be involved in a number of roles depending on their connectivity and the task being performed (e.g. MacIntosh and Gonzalez-Lima, 1994; Friston et al., 1995d). However, like Darwin's theory, these advances relied upon earlier, simpler studies to describe the form of the systems under investigation (e.g. to form the structural anatomical models essential for structural equation models). Furthermore, current levels of knowledge are not sufficient to allow these kinds of analyses to be performed in all sensory systems - as described in Chapter one, there is still much to be learned about even the basic connectivity and number of cortical areas involved in human somesthetic processing. My objective was to form and address simple hypotheses initially, with a view to addressing more involved questions subsequently. The experiments presented in this chapter focus on two aims: i) the construction of an 'MR friendly' somatosensory stimulator, and ii) an evaluation of the stimulator's ability to produce statistically significant changes in BOLD signal in cortical somatosensory areas.

3.1.1 Somatosensory Stimuli Used in Experimental Studies

Choosing one stimulation technique over another in neuroimaging experiments should be primarily informed by the researcher's experimental hypothesis. In studies of the visual system this is usually easy to ensure, as there are few appreciable differences between delivering a visual stimulus during a psychophysical experiment and a neuroimaging experiment (as long as one can project images into the scanning environment). The situation is very different for other sensory modalities. While auditory studies can be easily performed in PET, the presence of periodic wide-frequency noise during fMRI studies can present serious problems (see Eden et al., 1999; Hall et al., 1999). Somatosensory stimulation paradigms are arguably even worse off. Although presenting somesthetic stimuli during PET scanning is of a comparable difficulty to using the stimuli in behavioural experiments, the magnetic environment of the MR scanner presents serious problems for somatosensory activation studies in fMRI. These problems hinge upon the submodality of stimulation employed.

At present there are a number of techniques used in experimental studies of the somatosensory system. Early behavioural studies of touch were constrained by the technology available to investigators (Weber's early studies used coins and compasses; later investigators employed horse hairs [Von Frey hairs] calibrated to bend under known pressures). Similarly, initial attempts at mapping the spatial organisation of somatosensory cortex were far cruder than current non-invasive methods. Penfield and Boldrey (1937) were first to describe the somatosensory homunculus in human subjects using direct stimulation of the exposed cortical surface. This paper represents the beginning of 'cartographic' electrophysiology in the somatosensory system, in which the primary aim was to examine the spatial layout of receptive fields - how the body's surface was mapped or represented in the brain. These early studies tend to be quoted extensively, and are frequently referred to as 'gold standards' with which to compare the efficacy of novel techniques for non-invasive mapping of human somatosensory cortex.

Most of subsequent research extending Penfield's work was carried out in non-human primates: e.g. the initial single cell somatosensory studies carried out by Mountcastle (1957); the work of Werner and Whitsel on transforming the three-

dimensional representation of the body onto a 2D plane (reviewed in Dykes and Ruest, 1986); and finally the first demonstration that the cytoarchitectonic areas of primary somatosensory cortex in monkeys each contain a map of the body surface (Merzenich et al., 1978). Human neurophysiological studies have necessarily lagged behind. Until the advent of somatosensory evoked magnetic fields (SEFs), somatosensory evoked potentials (SEPs) and PET and fMRI, most human data was acquired during invasive procedures on patients in a similar manner to Penfield's original study. Early fMRI studies used simple yet hard to quantify stimulation methods such as rubbing the subject's hand with the investigator's hand (Yetkin et al., 1995). More sophisticated stimuli followed (textured surfaces, Lin et al., 1996; median nerve stimulation, Puce et al., 1995; peripheral electrical stimulation, Kurth et al., 1998), but few systematic studies of which stimuli optimally cause SI 'activation' were carried out. One of the few studies to do this compared two manual stimulation paradigms (air blowing over the palm vs. brushing the fingers) to median nerve stimulation (Puce et al., 1995). Median nerve stimulation was found to be less reliable than other methods of stimulation, but the authors' sample size was low. Certainly activation of SI is inconsistent in neuroimaging studies, and even a detailed examination of the parameters of each study do not greatly assist the choice of new stimulation methods.

While a number of early neuroimaging studies used somatosensory stimulation (e.g. Ingvar, 1975) it was apparent even at this stage that it was more difficult to elicit significant rCBF changes in the primary somatosensory cortex (SI) than, for example, in the primary motor cortex (M1). Ingvar's early work showed that somatosensory stimulation produced more robust changes in frontal areas than parietal areas, contrary to evidence from human and non-human primate studies. He coined the term 'sensory-motor paradox' to describe his findings. A number of investigators have referred to this finding (e.g. Paulesu et al., 1997) as a reason why PET and fMRI studies of the somatosensory system (and SI in particular) are rarely as informative as those from other modalities (e.g. MEG, Yang et al., 1993; Nakamura et al., 1998). This is not to say that there have been no successful neurovascular neuroimaging studies of the somatosensory system – merely that it is tacitly accepted that somatosensory fMRI studies are difficult.

In clinical situations, it is common for investigators to use peripheral nerve stimulation: in particular, median nerve stimulation is used in both SEP and SEF studies (for reviews see McLaughlin et al., 1993 (SEPs) and Kakigi et al., 2000 (SEFs)). While this technique is a reliable test of peripheral nerve function, it is an inherently non-physiological method of stimulation – analogous to attempting to study the normal functioning of the visual system by direct stimulation of the optic nerve. Although microneurography and microstimulation allow (careful) investigators to stimulate and record from single primary afferent fibres in unanaesthetised humans, and this has both clinical and experimental value, it is an invasive procedure with some morbidity, requiring skilled researchers and dedicated subjects. For these reasons and others, most neuroimaging studies use von Frey hairs, brushes or other stimuli manually administered by the investigator or a confederate during the scanning procedure. The motivation behind these techniques is often that they are simply and easily applied. However, if one wishes to go beyond categorical tactile activation studies and deliver calibrated, reproducible stimuli, more sophisticated methods are required.

3.1.2 Interactions Between MRI Environment and Experimental Equipment

During MRI procedures, the subject is exposed to three different forms of electromagnetic radiation: the static field (B_0 field), gradient magnetic fields (B_1 field), and radiofrequency fields (the r.f. pulses used in image formation; see Chapter two). It is generally believed that no significant health effects arise from patient exposure to the above sources of radiation during routine MR investigations. Studies have failed to find any effects of static fields on skin temperature (Tenforde, 1986), ECG waveforms (Dimick et al., 1987), or the CNS itself (up to fields of 2T; Kanal et al., 1990). The effects of gradient fields are more obvious. Fast switching of magnetic fields will induce current in appropriately orientated conductors, including biological tissue. There are a great number of variables that influence the strength and direction of induced currents in the body: for example, the effects are likely to be strongest in distal tissue (i.e. towards the periphery). The bioeffects of the induced fields can be of two forms: thermal (unlikely to be of great consequence; Kanal et al., 1990), or caused by the direct effects of the current itself, such as direct nerve stimulation. The latter is

rarely seen, even when using rapid gradient switching techniques such as EPI. The final effect is from exposure to rf fields, which are thought to be principally thermogenic, (Shellock et al., 1986).

It follows from the evidence above that a standard MR procedure should not pose a significant health risk to normal subjects. However, the minor effects produced by the combination of static, rapidly shifting and r.f. fields can seriously disrupt the functioning of pieces of electrical equipment. Moreover, the electromagnetic interference generated by the presence of electronic circuitry within the magnet itself can be problematic. Thus the MR environment presents its own unique challenge to the delivery of physiological stimulation to experimental subjects, and to the recording of electrophysiological data.

3.2 Vibrotactile stimulation of the digit pads in fMRI

Arguably the most frequently used method of stimulation currently in use in somesthetic studies is vibration or vibrotactile stimulation, in part due to the influence of the early work of Geldard (Geldard 1940a, 1940b and 1940c). One of the attractions of using vibrotactile stimulation is that, since the stimulation parameter is a periodic waveform, the physical properties of the stimulus can be completely specified by its phase, amplitude and frequency.¹ Vibrotactile stimuli are also temporally dynamic (i.e. they are not merely static impressions of the skin), and so should be less likely to cause habituation/adaptation of the responses of peripheral and central neurons. In addition, vibrotactile stimuli were used as stimuli in the first experiments explicitly designed to explore how the dynamics of peripheral stimuli are encoded or represented in the central nervous system (Talbot et al., 1968; Mountcastle, 1969). This class of stimuli is therefore a logical choice. In addition, vibrotactile stimulation is known to cause robust changes in rCBF in primary somatosensory cortical regions (Fox et al., 1987, 1988; Meyer et al., 1991; Burton et al., 1993). I therefore chose to begin using vibrotactile stimuli, as they had been most successful in producing signal change in previous PET studies.

¹ In practice the mechanical properties of the skin make it difficult to confidently measure the shape of any applied stimulation. For simplicity, I assume throughout this thesis that the skin is an incompressible medium (Phillips and Johnson, 1981).

3.2.1 Methods – Stimulator Theory

It is possible to turn the very qualities that make the magnet an inhospitable environment for electrical devices into the driving force for a stimulator. When a current-carrying conductor is located in an external magnetic field perpendicular to the conductor, the conductor experiences a force perpendicular to itself and to the external magnetic field. This is known as the *motor principle* in physics. Using the ‘right-hand’ rule: if the right thumb points in the direction of the current in the conductor and the fingers of the right hand point in the direction of the external magnetic field, then the force on the conductor is directed outward from the palm of the right hand (Figure 3.1A). As discussed above, these effects can affect electrical equipment while located within the B_0 field, and are most marked when wires cross the bore of the magnet at right angles. If the conductor (the current-carrying wire for present purposes) is shaped into a rectangular coil and placed within the B_0 field of the magnet again, it experiences a turning force around its central axis (Figure 3.1B); torque (τ). If the coil is then suspended so that it turns freely, it describes a circular motion in one direction. This direction reverses when the flow of current is reversed.

This effect can be used to power a simple vibrotactile stimulator. If the coil is placed within a container within the magnet’s bore such that it is restrained from turning fully around its axis, and the direction of input current is rapidly alternated, the coil will vibrate with the frequency of the input current (Figure 3.1C). The probe transduces this movement to the area being stimulated.

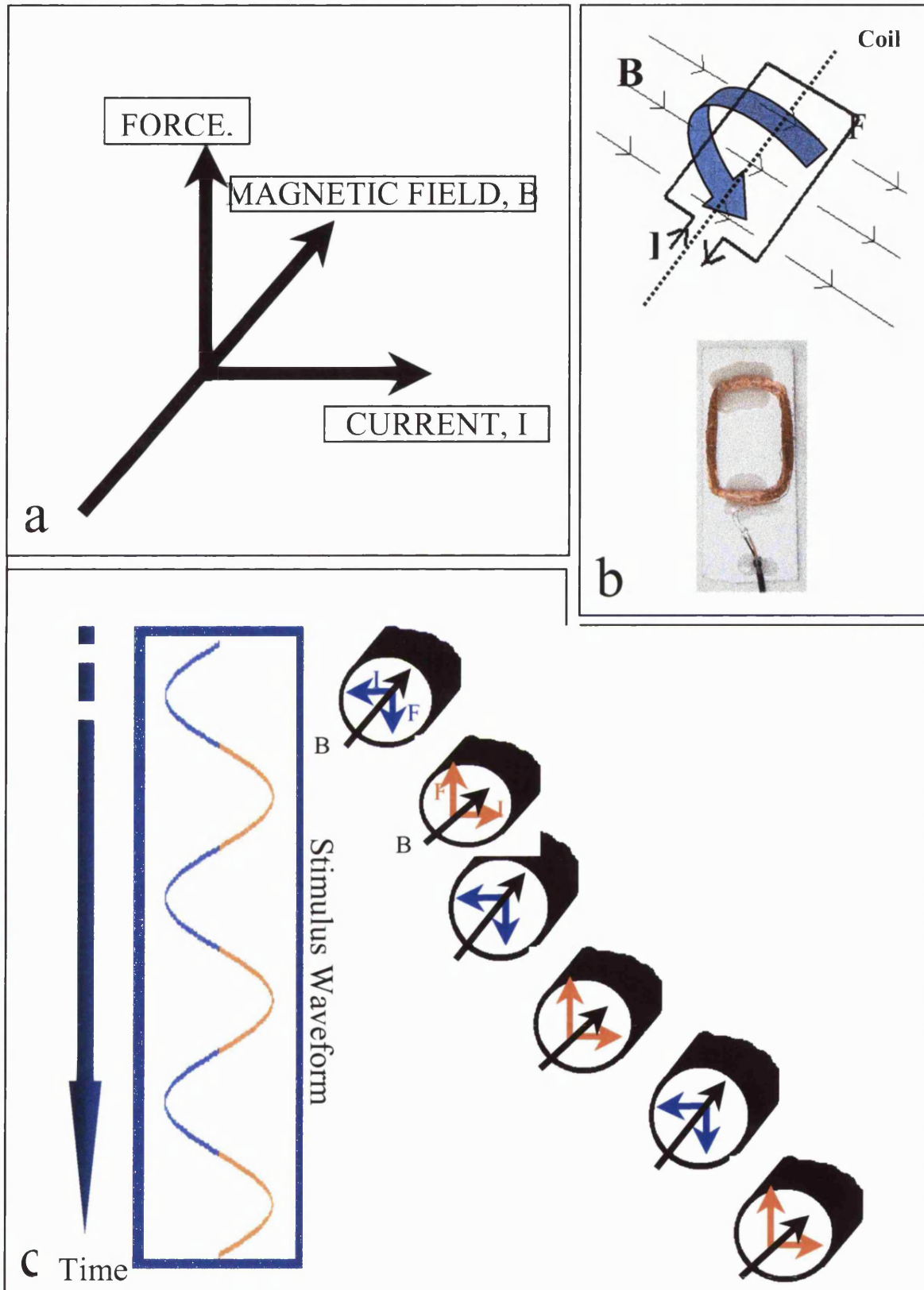


Figure 3.1. Principles underlying the construction of the vibrotactile stimulator. A) The 'motor principle'. B) The behaviour of a rectangular conductor when placed in a uniform magnetic field, and a picture of the conductor used in the stimulator. C) Schematic display of the behaviour of the conductor when driven with an alternating current in the magnet bore: the force **F** alternates its direction with the stimulus waveform.

3.2.2 Methods – Stimulator Construction

The stimulator consists of three parts – the central coil, the non-magnetic housing, and the vibrotactile probe. The coil was made from ~120 turns of copper wire shaped into a rectangular coil (6 x 4cm). This was glued to a plastic board that was subsequently fitted within a plastic component box (stock no. 222-812, R&S, Northants, UK) to serve as housing for the coil. The box was padded with foam rubber to dampen vibrations transmitted from the coil to box, and to reduce the humming noise produced by the stimulator. The stimulating probe was a 5cm long piece of plastic doweling, fitted with a circular head (head area 1cm²). This was attached to the remainder of the stimulator by drilling a hole in the component box and gluing the base to the coil and card. Two stimulators were made in this fashion.

During operation, the stimulators were driven using stimulus waveforms generated using 'Sound Effects' software. To allow the stimulators to be triggered independently, the left and right audio channels of an Apple Macintosh 1760 computer were used. The two outputs from the Macintosh were conditioned by being fed through an op-amp before entering the stimulators. To drive each of the stimulators, the input waveforms were 'played' through either the right or left audio channel of the Apple Mac. Input to the stimulators was filtered before entering the scanner (stock no. 225-3521, RS, Northants UK). Running the stimulators both with and without filtering while scanning a phantom demonstrated that the filters effectively removed obvious r.f. artifacts.

It is important that passive movements are kept to a minimum during scanning to ensure that only 'pure' cutaneous tactile stimuli are delivered. To hold the subjects' hand in position a pre-formed anti-spasticity splint was used (North Coast Medical, component NC158187). During scanning, the subject's fingers were held in the splint using padded supports. The probes fitted under the splint and stimulated the glabrous skin of the subjects' exposed D2 (index finger) and D5 (little finger) digit pads (Figure 3.2, below).

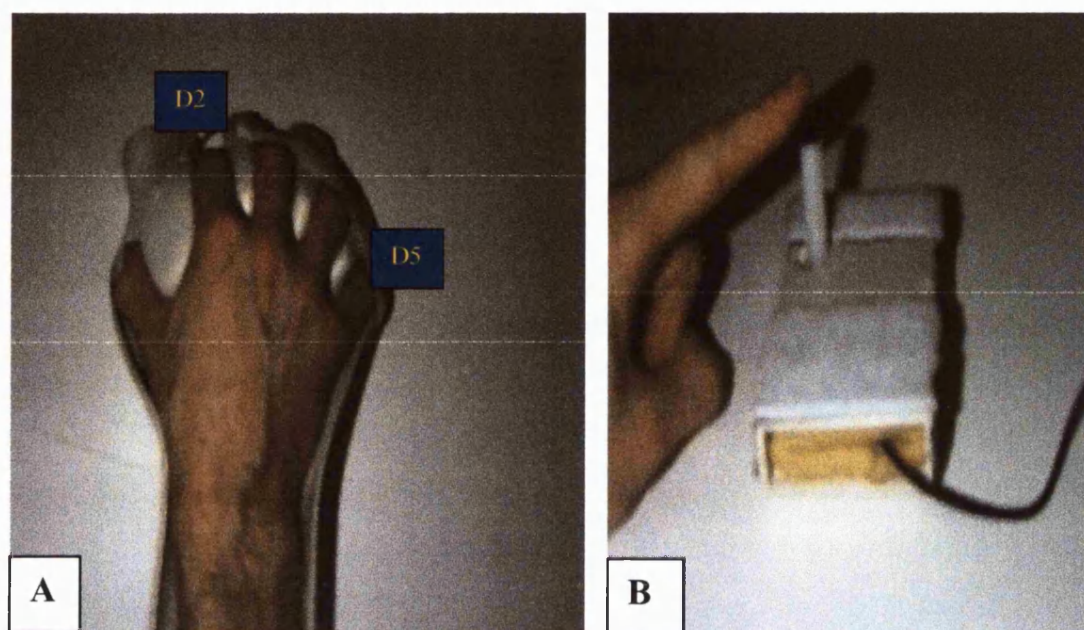


Figure 3.2. A) Each subject's hand was held firmly in a thermoplastic splint during scanning, with the digit pads of D2 and D5 exposed to the heads of the vibrotactile stimulators. B) The finished vibrotactile stimulator as used in the scanner. Two identical units were used to stimulate D2 and D5 independently.

As previous studies had reported varying success in delineating patterns of somatopy in the postcentral gyrus digit stimulation studies (Kurth et al., 1998; Gelnar et al., 1998), I chose to stimulate two fingers separated by a large 'cortical distance' to maximise my ability to detect each digit. While the greatest possible distance between digit representations is between the thumb and little finger, and the area of cortex responsive to the thumb is the greatest of all digits, I chose to stimulate D2 and D5. The digit pad of the thumb (D1) is orientated differently to the rest of the hand while it is held at rest, limiting its accessibility to the current method of stimulation.

3.2.3 Methods - Experimental Setup and Scanning

3.2.3.1 *Subjects and Scanning Details*

Five right-handed males (mean age 27, age range 23-33) served as subjects. The local ethics committee approved the experimental procedure, and all subjects signed a consent form before being scanned. All subjects had no history of neurological intervention and were drug free when scanned. Differences in skin condition (e.g. calluses) were not controlled for.

As in all subsequent studies, the functional data were acquired using echo-planar imaging (EPI) {TE=40ms; in-plane matrix 64x64 pixels [19.2cm x 19.2cm] giving 3mmx3mm pixels; TR=4.1s}. Forty-eight 2.5mm thick slices with a .5mm inter-slice gap were obtained per volume measurement. Ninety-eight functional volumes were acquired per subject in a single experimental session. A T1-weighted MP-RAGE structural image of each subject (voxel size 1x1x1.5mm) was acquired to facilitate anatomical localization of the functional data.

3.2.3.2 *Experimental Setup*

Subjects rested their right hand in a plastic anti-spasticity splint mounted on a Perspex base. The two vibrotactile stimulators were mounted such that the head of each probe was in contact with the exposed glabrous skin of the D2 and D5 fingerpads, but did not support the weight of the fingers. During scanning, subjects lay supine on the scanner bed with a Perspex sheet positioned on the torso. Before the start of scanning each subject received practice trials of the stimulus to ensure that they could feel the stimulation, and that the subjective intensity was comparable between digits. Stimulation epochs (24s/6 volume scans in length) were alternated with periods of rest in a counterbalanced design to minimise possible order effects (e.g. ABACACAB... 'A' rest, 'B' D2 stimulation, 'C' D5 stimulation). During stimulation epochs, 1s bursts of 125 Hz vibrotactile stimulation was delivered to the glabrous digit pads of *either* D2 or D5. Each burst of stimulation within a stimulation block was alternated with a 0.5s interval to reduce within-session habituation or adaptation that may result from constant exposure to a tonic stimulus. Subjects were instructed to close their eyes during scanning and concentrate on the sensation of vibration in their fingers.

3.2.3.3 Image Preprocessing

Data preprocessing was carried out using SPM97 (Wellcome Dept. of Cognitive Neurology, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>) implemented in Matlab4 software. After removal of the first two scans to allow for T_1 saturation effects, subjects' scans were realigned to the first volume of the series (Friston *et al.*, 1995a) and a mean realigned volume was created. Each subject's T_1 structural image was coregistered to their mean EPI image. The mean functional volume was used to determine the parameters applied to all volumes during spatial normalisation and resampling (2x2x2mm; Ashburner *et al.*, 1997) to a standard template (Evans *et al.*, 1993). All functional volumes were smoothed using a 6mm FWHM isotropic Gaussian kernel.

3.2.3.4 Data Analysis

Data analysis used SPM99 (authorship as SPM97) implemented in Matlab5 software. The functional volumes from each session were treated as a time series, and experimental effects were estimated using a multi-subject² design matrix that included subject mean terms and session by condition interactions for all explanatory variables. Each single subject partition of the design matrix contained eight covariates: two 'boxcar' reference functions that had a value of 1 when either D2 or D5 stimulation was applied and zero during no stimulation, and six covariates representing the estimated movement parameters for each scan (obtained from the realignment parameters). The boxcar functions were convolved with a synthetic 'canonical' haemodynamic response function to increase sensitivity to the evoked BOLD responses. To remove low-frequency noise the data were high-pass filtered using a set of discrete cosine basis functions with a cutoff period of 296s. Temporal autocorrelation was dealt with using the method of Worsley and Friston (1995), by temporally smoothing the session time series with a Gaussian kernel of 6s FWHM.

². It may seem counterintuitive to enter data into a multisubject model when it is entirely possible that local anatomical and physiological variability may produce few significant 'group' activations. This is certainly true: however, by using the appropriate contrasts it is still possible to examine single-subject activation patterns. This produces similar results to examining single session results

Linear contrasts of the covariates were evaluated for the main effects of D2 and D5 stimulation within and across subjects. These results were displayed as a voxelwise statistical parametric map (an SPM) of t values. As I predicted that contralateral postcentral gyrus and bilateral superior lateral sulcal areas would be activated, voxels in these regions were reported as significantly active with a p value of $p < 0.00001$ (corrected for the number of voxels using the areas' estimated volumes; Kennedy et al., 1998). The exact number and function of cortical areas within the lateral sulcus is currently a matter of contention (see Burton et al., 1995 and Krubitzer et al., 1995). For the purposes of this thesis, the superior bank of the lateral sulcus including the central and parietal operculum (using the definitions of Kennedy et al., 1998) was used to calculate the number of voxels. Voxels in other brain areas were reported as significant if they survived a correction for multiple comparisons over the entire scan volume ($p < 0.05$ corrected). A cluster threshold of three contiguous voxels ($k=3$) was used.

3.2.4 Results

3.2.4.1 *Single Subject Results*

The results of each single subject analysis are summarised in Table 3.1 below. Statistically significant changes in BOLD contrast were found in the contralateral Postcentral Gyrus (PoG) for stimulation of both fingers in three out of five subjects. For the remaining two subjects, activation was found for D2 stimulation in one subject, while the remaining subject had no significant voxels in any of the locations examined. Only one of the three subjects who had significant activation foci for both D2 and D5 stimulation showed a pattern of somatopy that agreed with the pattern defined by the classical 'Penfieldian' homunculus (subject BA – but see below).

in isolation (although significance levels change due to the different numbers of d.f.s, parameter estimates do not).

	<u>Contralateral PoG</u>				<u>Contralateral PO</u>				<u>Ipsilateral PO</u>			
	<i>X</i>	<i>Y</i>	<i>Z</i>	<i>T</i>	<i>X</i>	<i>Y</i>	<i>Z</i>	<i>T</i>	<i>X</i>	<i>Y</i>	<i>Z</i>	<i>T</i>
AH D2	-42	-24	60	7.27	-62	-16	16	5.33	64	-18	12	6.01
D5	-	-	-	-	-	-	-	-	50	-16	18	5.70
BA D2	-56	-14	42	8.71	-50	-36	26	6.40	56	-34	24	7.70
D5	-40	-16	46	5.51	-64	-8	12	5.02	-	-	-	-
DM D2	-60	-26	40	8.14	-54	-38	18	8.16	66	-24	16	8.04
D5	-60	-26	40	6.48	-54	-38	18	7.39	66	-24	16	7.09
EM D2	-42	-6	52	6.18	-62	-14	12	7.01	42	-20	16	6.55
D5	-44	-8	48	5.37	-56	-16	12	7.74	-	-	-	-
RH D2	-	-	-	-	-	-	-	-	-	-	-	-
D5	-	-	-	-	-	-	-	-	-	-	-	-

Table 3.1. Local maxima within the contralateral postcentral gyrus (PoG), contralateral parietal operculum (PO) and ipsilateral parietal operculum for digit 2 and digit 5 stimulation per subject. The Talairach coordinates of each voxel are listed along with its T score for each subject. All local maxima reported are either significant at a $p < 0.05$ corrected for multiple comparisons over the entire image or corrected for a 32.4cm^3 volume as suggested by the measurements of Kennedy and colleagues (1998) for the PoG and bilateral frontal and parietal opercula.

Table 3.1 lists the most significant voxels within each area for each subject. While some subjects (DM) displayed statistically significant patterns of activation across all contrasts tested, other subjects (RH) had no significantly active voxels in *any* contrast. In the interests of parsimony, Table 1 lists only the most significant voxels in each contrast by area: in most subjects several maxima were found in each region. This is illustrated in Figure 3.3. below.

Patterns of somatopy in imaging studies are often defined using distances measured between points in a simple co-ordinate system, without acknowledging that the surface of the cortex is a complex folded sheet. In addition, the PoG is not a functionally homogeneous region. For example, the Euclidean distance between the peak D2 and D5 voxels for subject BA is 16.61mm. This is comparable to previous estimates. The peak voxel of the cluster responding to D2 stimulation was located inferior and lateral to the peak voxel of the cluster responding to D5 stimulation. However, the neuroanatomical location of these voxels is more contentious. Although the most significant voxel in the D5 contrast is located on

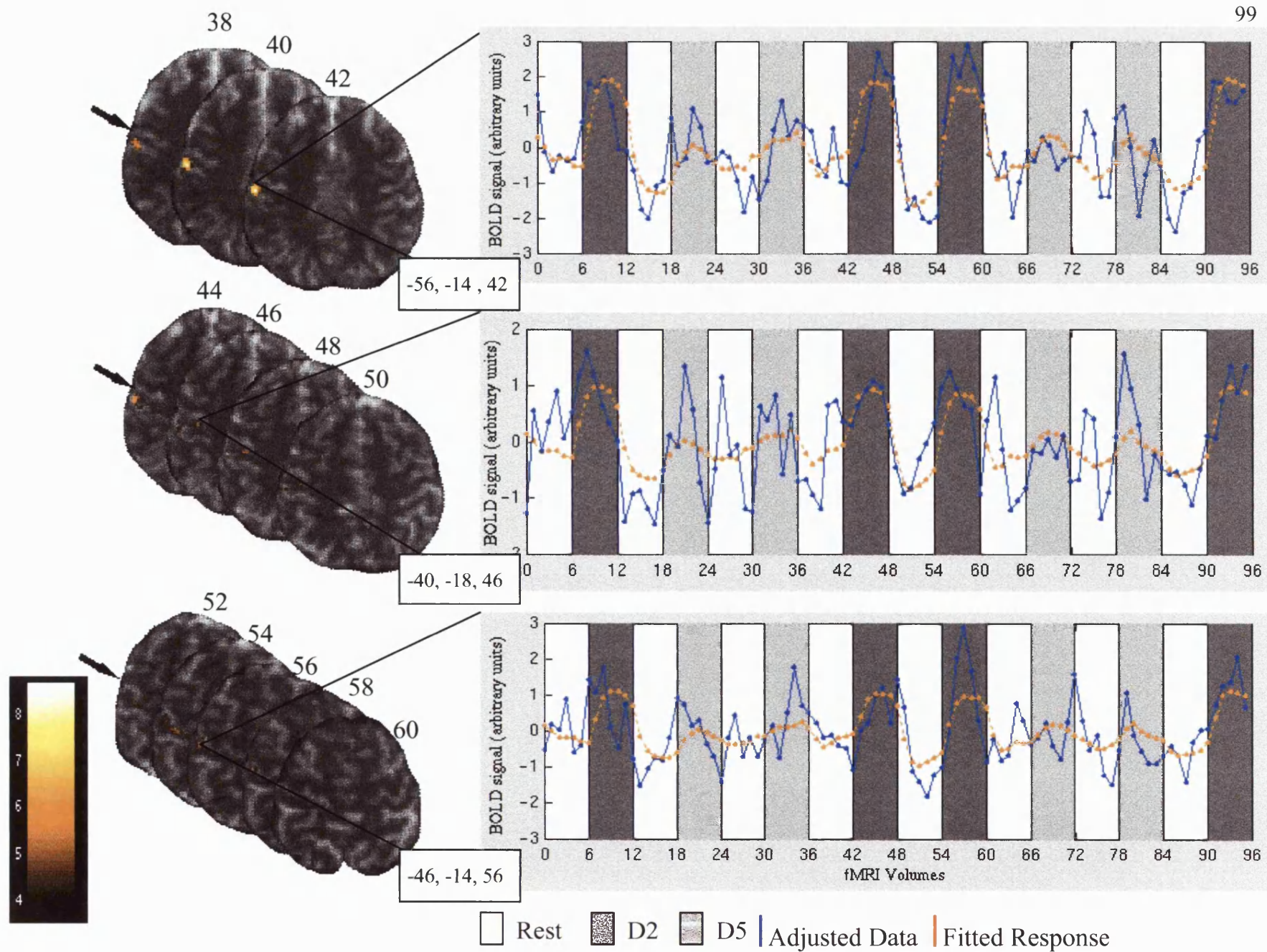
the posterior bank of the central sulcus, the D2 cluster (Figure 3.4. below) is located on the lateral convexity of the postcentral gyrus, extending into the postcentral sulcus. This distinction is important because the PoG and surrounds contain multiple cytoarchitectonically-defined areas that may reflect the underlying functional organisation of the cortex (Geyer et al., 1997,1999,2000; Moore et al., 2000). This issue becomes apparent when attempting to interpret the results from the D2 contrast (Figure 3.3) in subject BA. This contrast contains multiple, separate activated clusters around the postcentral gyrus. While non-human primate studies have revealed the existence of multiple, functionally segregated maps in the PoG, it does not make sense to ‘jump’ between maps when defining patterns of somatopy. For example, if posterior PoG clusters are activated in one contrast (likely to be BA1/2) and anterior PoG clusters activated in another (likely to be BA3b), nothing can be concluded about patterns of somatopy, which need to be defined *within-region*.

Individual stimulation of either digit produced bilateral opercular activation in one subject only. Of the remaining four subjects, bilateral opercular activation was observed during stimulation of one digit in three subjects (D2), who each displayed unilateral opercular activation during stimulation of the other digit (D5). The remaining subject did not display significant activation in the opercular region. In addition, the maxima in one subject (E.M.) were located inferior to the lateral sulcus in auditory cortical areas. This may be because the vibrators, when active, emitted a loud buzzing noise that subjects could occasionally hear over the noise of the scanner. Although subject E.M.’s contrasts also contain some active parietal voxels, it is difficult to unambiguously attribute these activations to ‘true’ parietal signal changes, as opposed to spread of signal from auditory areas inferior to the lateral sulcus. Vibrotactile stimulation has robustly activated bilateral ‘lateral sulcal’ areas in previous studies of this area (PET - Burton et al, 1993; Burton et al., 1997; fMRI - Francis et al., 2000).

Interestingly, no activation of the ipsilateral PoG was seen in any subjects. Previous studies (e.g Francis et al., 2000) have found activated foci in the ipsilateral PoG, but the functional significance of these activations is currently contentious. Indeed, evidence from the motor system suggests that one should

expect a *decrease* of activation in ipsilateral cortical areas when the same areas in the opposite hemisphere are stimulated. Activity was observed in areas outside the PoG and opercular areas, although these activations frequently did not survive correction for multiple comparisons over the entire image volume. Figure 3.4 below shows the field of view from subject BA during D2 stimulation as an example. Activation can be seen clustered around the contralateral PoG (Talarach Z co-ordinates 38-56) and bilaterally around the posterior parietal operculum (Talarach co-ordinates 22-28), which, in this subject, was more posterior than one would expect from previous reports of the possible location of human SII (e.g. Paulesu, 1997). Activation is also apparent around the left insular region (local maxima -58,2,14; $p < 0.12$ corrected) although this area does not survive correction.

Figure 3.3. (next page) Examples of peak voxel timeseries' from separate PoG clusters elicited during vibrotactile stimulation in subject BA. Each plot displays the adjusted data from the voxel (the raw data adjusted for effects of no interest in the design matrix, blue) and the fitted response (the model, red). Note that the most significant voxel (-56,-14,42) is not located on the posterior bank of the central sulcus but instead on the lateral convexity of the postcentral *sulcus*. While there is activity in the central sulcus (the clusters at -40,-18,56 and -46,-14,56), these are neither as large or significant. The numbers above each series are slices' Z-Coordinates in Talairach space.



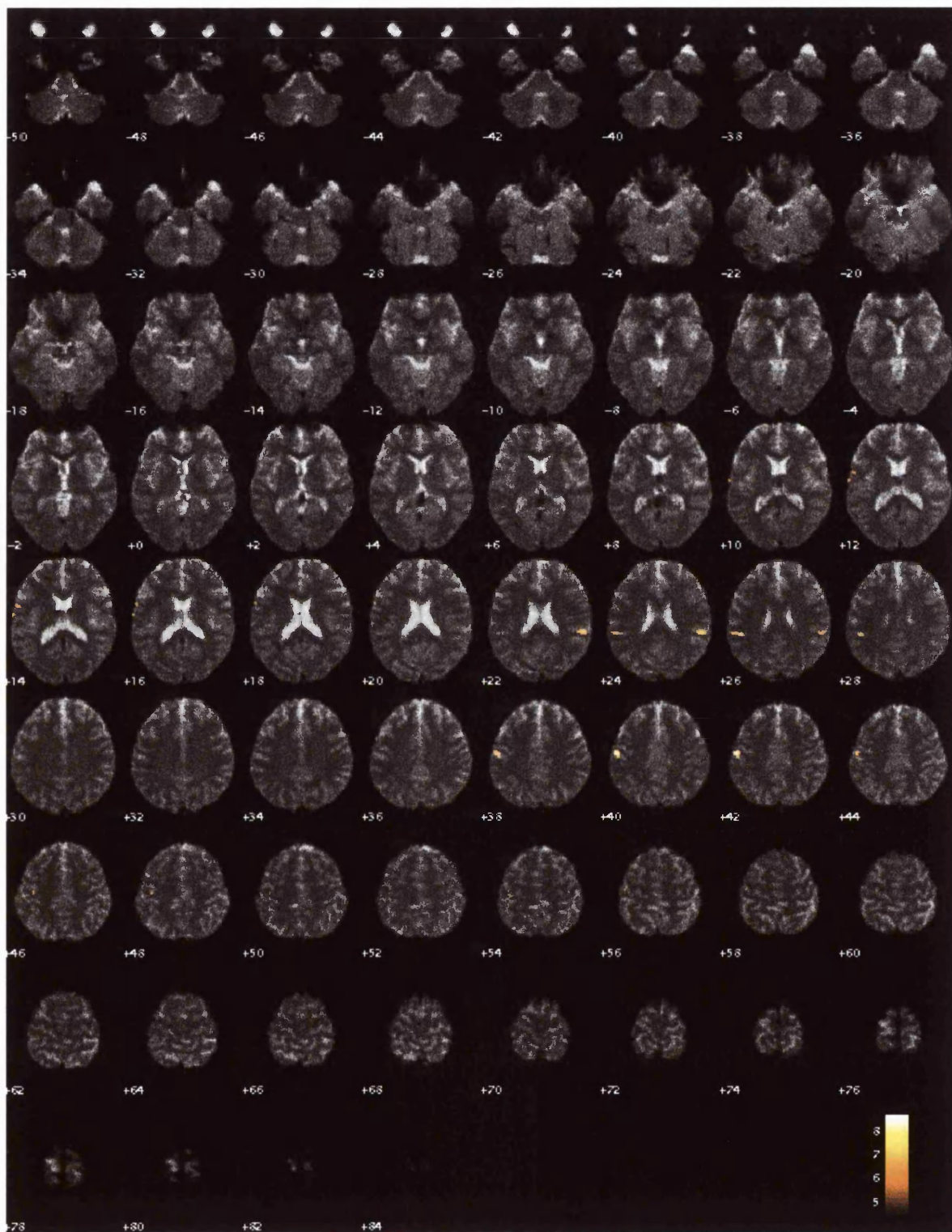


Figure 3.4. Main effect of D2 stimulation, subject BA. All voxels surviving the statistical threshold (see above) are overlaid on the subject's mean normalised functional EPI volume. The numbers on the bottom left of each slice are the slice's z co-ordinate after transformation into the space of Talairach and Tournoux (1988). The colour bar represents statistical significance, with higher t scores having a brighter colour.

3.2.4.2 *Group Results*

In addition to examining subject-specific contrasts for D2 and D5 digit stimulation, the significance of each contrast across all subjects was also tested. Although subject-specific interaction terms were included in the model used, the between-subject variance component was not used to calculate the significance of group effects. This kind of analysis is a fixed-effects analysis, employing only a single variance component. Strictly speaking, the results from this analysis cannot be generalised to the population that the subjects were sampled from, as fixed-effects analyses are extremely sensitive to the effects of outliers (some issues relating to fixed-effects inferences are explored in Chapter four). Nevertheless, it is often advantageous to pool data across subjects as it can increase the ratio of signal to noise. I was therefore interested to see if a somatopical pattern existed at a group level.

Figure 3.5. summarises the group results, concentrating on the axial planes where significant signal changes were most abundant. Although between-subject averaging has removed some subject-specific noise, the group results exhibit a problem of the type to which fixed-effects analyses are prone: a large effect in a single subject can exert a disproportionate effect. The auditory cortex activation observed in planes 10-14 only reaches group significance because of subject EM – the parameter estimates for this area are low in all other subjects. The pattern of somatopy observed is the reverse of what one would expect from Penfield's original maps in humans: the peak central sulcal area voxel for the mean D5 contrast lies below D2. As well as in the postcentral gyrus, the maps for D2 and D5 overlap frequently, for example in the right prefrontal cortex (planes 18-24).

The group results confirm that the pattern of activation to vibrotactile stimulation is consistent with results from other groups, showing activation of contralateral primary somatosensory cortex, bilateral opercular and insular areas, and some right frontal activation (e.g. the combined MEG/fMRI work of Korvenoja and colleagues, 1999). However, neither the group nor the individual results show consistent patterns of somatopy in primary somatosensory cortex. Given the stimulus used, it is also startling to observe that, in all subjects, the maxima of each contrast were located not on the posterior bank of the PoG (where Brodmann's area 3b, the 'true'

primary somatosensory cortex is located), but instead on the lateral convexity of the PoG. These findings were enough to suggest that it was prudent to examine the pattern of evoked activity using another somatosensory modality.

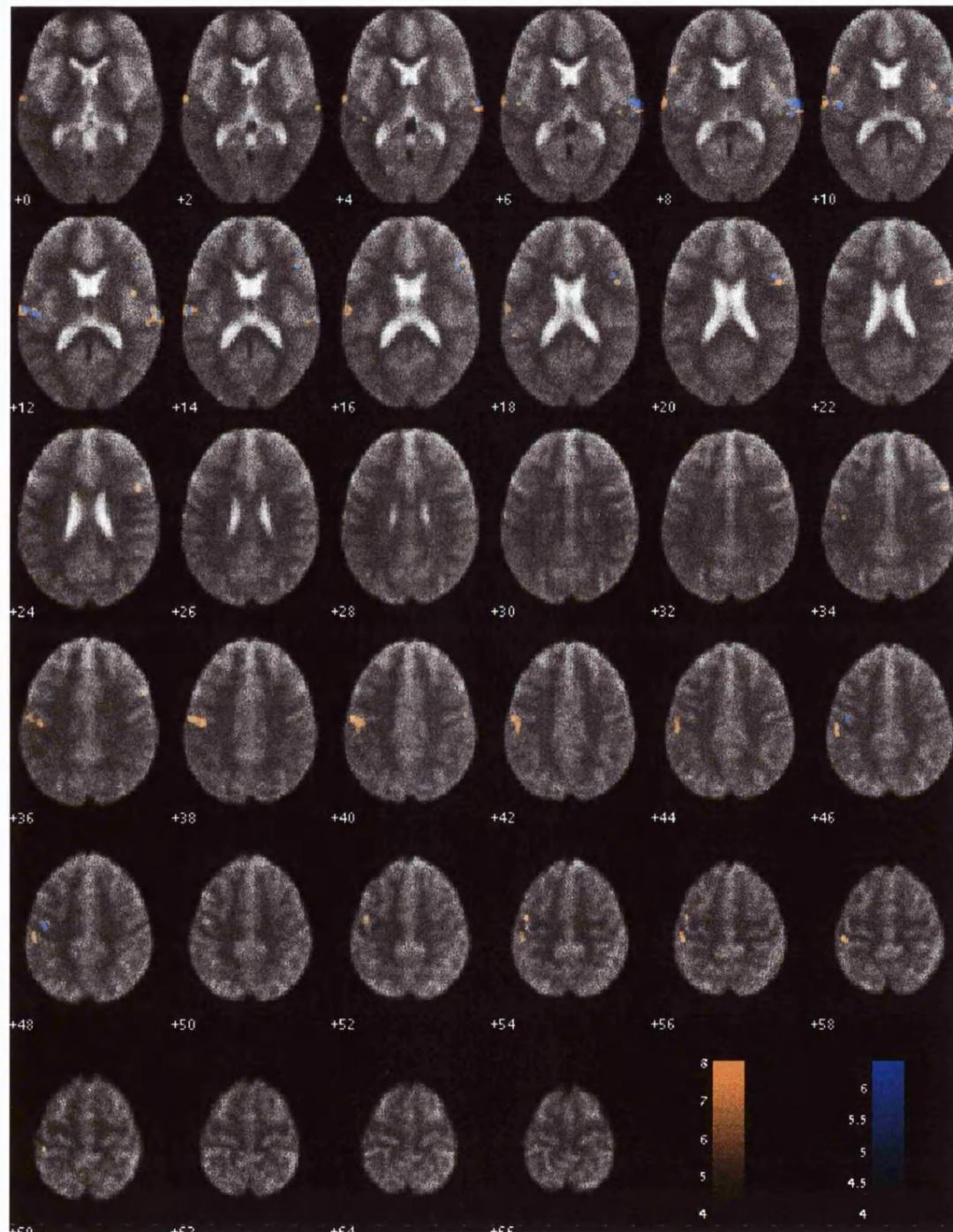


Figure 3.5. Group analysis of D2 and D5 stimulation, overlaid on the mean normalised group functional image (axial slices, 2mm thick). Voxels surviving the statistical threshold (as before) for D2 stimulation are shown in red, and D5 voxels in blue. Note that while separate clusters can be seen on the posterior bank of the central sulcus for both contrasts (D2 peak voxel $-44, -6, 54$; D5 peak voxel $-42, -12, 48$) they are in a non-Penfieldian configuration.

3.3 Stimulation of the digits using airpuffs in fMRI

My results using the vibrotactile stimulator demonstrated that somatosensory stimulation in the MR environment is feasible, and can produce statistically significant signal changes in somatosensory cortical areas. The stimulator suffered from two major flaws, however: i) the magnitude of stimulation was heavily dependent on the stimulator's position and orientation in the scanner; and ii) subjects reported being aware of slight resistive movements in their fingers to the stimulation. One of the primary concerns of delivering tactile stimulation is minimising any accompanying movement occurring with the same phase as the tactile stimulation. As some of the subjects from section 3.2 displayed motor cortex activation, the interpretation of these activations is ambiguous: is the cause subject movement, or afferent somatosensory activity being fed to the motor cortices as sensory feedback? To distinguish between these two possibilities, it is necessary to use a stimulation method that is mechanically coupled to the fingers. In addition, to explore digit somatopy in detail, a device that can stimulate more than two skin locations in a single scanning session is a necessity.

Airpuff stimulation has been used successfully in SEP and SEF studies as a more naturalistic source of stimulation than peripheral nerve stimulation. Brief airpuff stimulation is thought to primarily activate rapidly adapting low-threshold cutaneous afferents (Schieppati and Ducati, 1984; however, the stimulation intensities used in SEPs studies tend to be lower than the ones used in this thesis). While subjectively weaker in intensity, airpuffs do not seem to be less efficient than electrical stimuli at eliciting SEP responses. Whereas sensory nerve action potentials (SNAPs) recorded over the median nerve at the wrist have a smaller magnitude for airpuff than electrical stimulation, cortical SEP components are essentially similar for both forms of stimulation (reviewed in Hashimoto, 1999). The method has not been used often in neuroimaging, possibly because the majority of custom built airpuff stimulators (Wallois et al., 1997; Hashimoto, 1999) cannot be used in the MR environment without extensive modification. These potential problems can be overcome if the stimulator is custom-built for use during MRI. The aim of the current section was to build an MR-friendly airpuff stimulator that could stimulate

different skin locations independently, and to evaluate it by using it to examine the somatopy of the five digits in individual subjects in fMRI.

3.3.1 Methods – Stimulator Construction

A schematic representation of the stimulator is illustrated in Figure 3.6. All mechanical and electrical components of the stimulator were housed in the control room of the scanner.

3.3.1.1 *Stimulator Electronics and Valves*

The stimulator was designed to be able to stimulate twelve separate skin locations independently. In addition, the stimulator was constructed to integrate easily into the laboratory's current triggering setup to ensure that airpuffs could be timelocked to user-selected time intervals. A Domino 2 microcontroller (Micromint) with embedded BASIC interpreter was used to provide the independent I/O lines needed, and to interface between the airpuff valves and triggering signals from the scanner. The Domino's twelve output lines (5V stepped to 24V) were connected to twelve pneumatic valves (SMC Pneumatics; stock no. 234/5276, R&S, Northants), mounted on two six stage manifolds (SMC Pneumatics, stock no. 234-5771 as before). A cylinder of medical air (a mixture of 22% oxygen, 78% nitrogen) supplied the manifolds at an output pressure of 5 bar. The valves were connected to the stimulator's nozzles with polyurethane tubing (internal diameter 2.5mm).

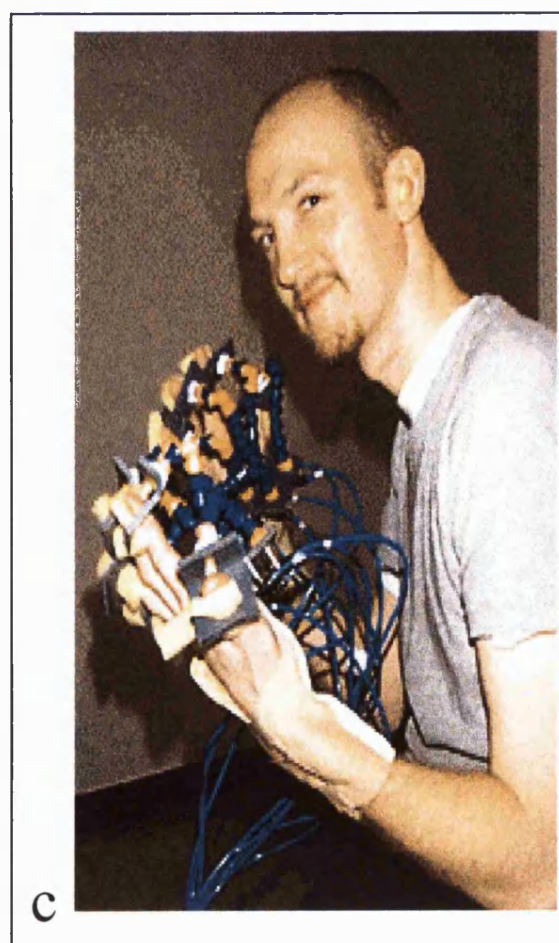
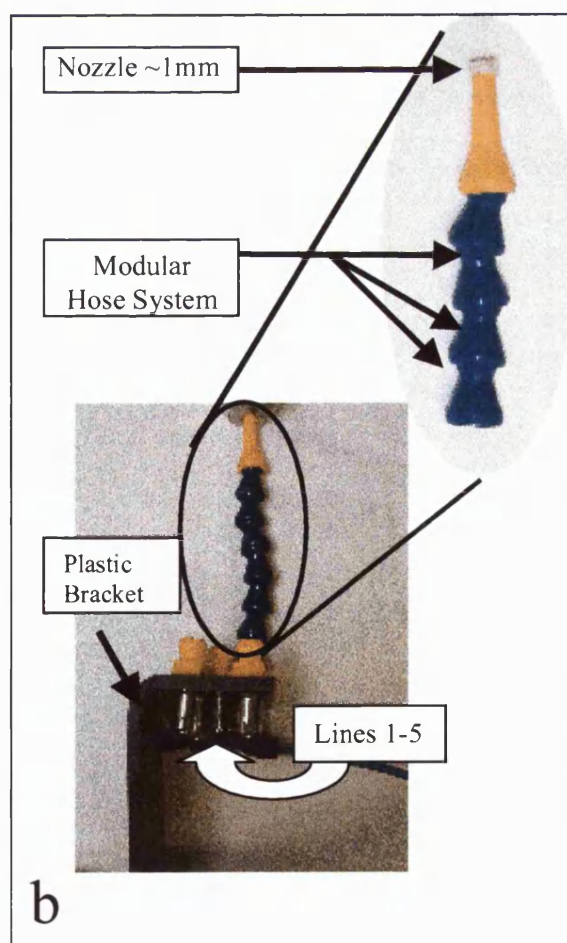
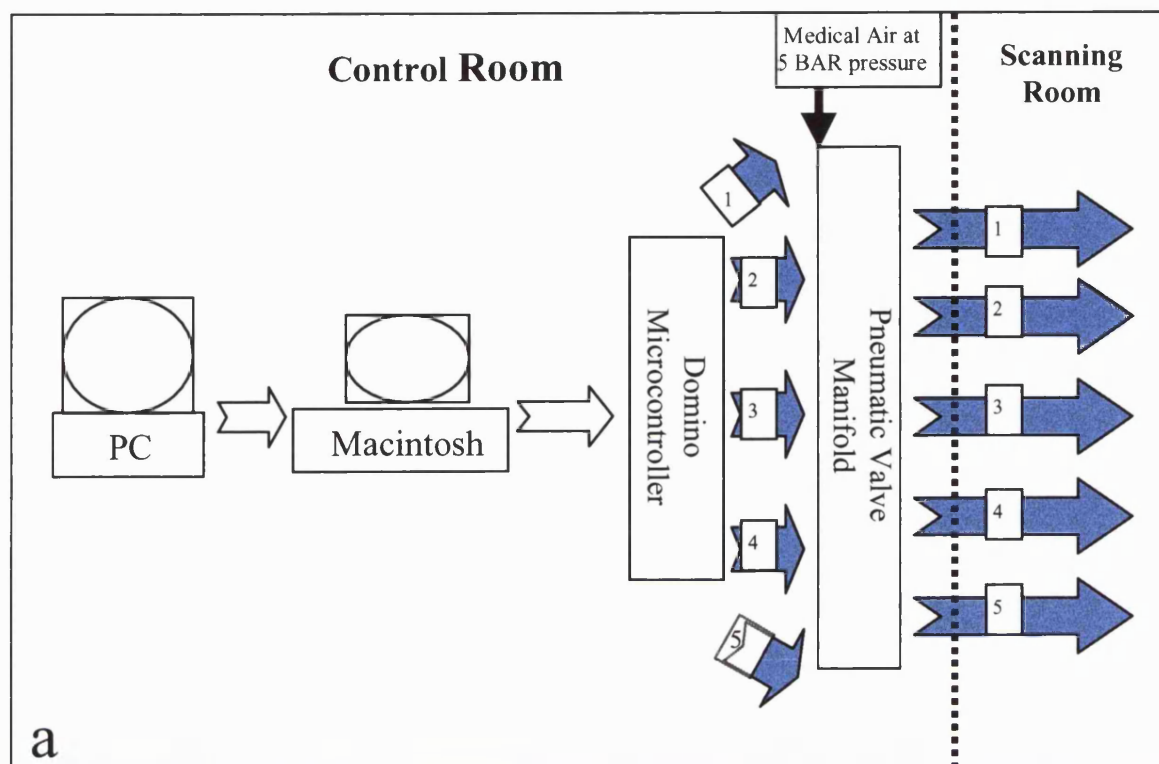
As described above, stimuli are triggered to occur at set times using a PC computer running PLSCNT software and a Macintosh computer running COGENT. To deliver airpuffs, COGENT was programmed to send ASCII characters to the Domino unit via a serial cable when triggered by PLSCNT. The identity of each character determined the duration and location of each airpuff. The high temporal resolution of the Domino's clock (5ms units) meant that airpuffs could be delivered at high-speed if required (see Chapter five for an application of this feature). This setup allowed for complete flexibility in the design of each experiment: the stimulator could easily deliver complex spatiotemporal stimulation patterns to a number of spatially distinct areas. By reprogramming the Macintosh's COGENT program and the simple BASIC program running on the Domino the order and duration of airpuffs could be changed quickly and simply.

3.3.1.2 Stimulator Nozzles

For the pilot experiments described in this chapter, the nozzles used were as depicted in Figure 3.6b below. The air lines were connected to nonferrous fittings mounted in a plastic bracket; the bracket fitted into a padded holder that was worn on the subject's wrist (Figure 3.6b and 3.6c). To allow maximum flexibility for subject comfort and hand size, I used a plastic modular hose system to link the nozzles to the plastic bracket (figure 3.6b; .25 inch diameter; R&S as before). The end diameter of each nozzle was 1mm.

To ensure that subjects' finger did not move during stimulation, each nozzle was coupled to a digit using a 90° plastic bracket that allowed subjects to position their hands comfortably. The setup was individually adjusted for each subject to maximise comfort during scanning.

Figure 3.6. (Next page). Diagrammatic representation of the airpuff stimulator. A) Schematic showing the setup of the stimulator during scanning (see section 3.3.1.1. for details). B) Close-up of an individual airpuff nozzle. The plastic bracket is attached to a splint worn on the subject's wrist during scanning. C) Author with airpuff stimulator setup to deliver ten lines of stimulation. Only five lines were used in the current experiment.



3.3.2 Methods – Experimental Setup and Scanning

3.3.2.1 *Subjects and Scanning Details*

Five right-handed males (mean age 28, age range 24-34) served as subjects. The local ethics committee approved the experimental procedure and all subjects signed a consent form before being scanned.

Functional data were acquired using echo-planar imaging (EPI) {TE=40ms; in plane matrix 64x64 pixels [19.2cm x 19.2cm] giving 3mmx3mm pixels; TR=4.1s}. 48 2.5mm thick slices with a .5mm inter-slice gap were obtained per volume measurement. 366 functional volumes were acquired per subject in a single experimental session. A T1-weighted high-resolution MRI of each subject (voxel size 1x1x1.5mm) was also acquired.

3.3.2.2 *Experimental Setup*

For the current experiment the airpuff stimulator was set up to use five lines, one for each finger of the subject's right hand. Each subject was familiarised with the equipment before entering the scanning room, and where possible the position of each nozzle above the digit pad was adjusted to ensure that subjects perceived all airpuffs to be of a similar intensity. During scanning, subjects lay supine on the scanner bed with their right hand lying comfortably over their torso, supported by a pillow. In the previous experiment subjects had reported that, with their eyes closed and with no explicit task demands, they occasionally found themselves losing concentration. To attempt to control for this in the present experiment, subjects lay with their eyes open and fixated a black cross on a white background backprojected onto a transparent screen by a video projector. Subjects were told to fixate on the cross throughout scanning and attend to the pattern of stimulation throughout.

In the current experiment each digit received 6 epochs of airpuff stimulation. Stimulation epochs (24s/6 volume scans in length) were alternated with periods of rest in a pseudorandomised design (stimulation epochs were randomised so that each subject received stimulation to digits 1-5 in a random order for six repeats of each digit in total; Figure 3.7. below). During stimulation epochs subjects received 5Hz airpuff stimulation to a single digit, which induced the greatest subjective perception of tactile stimulation in pilot studies.

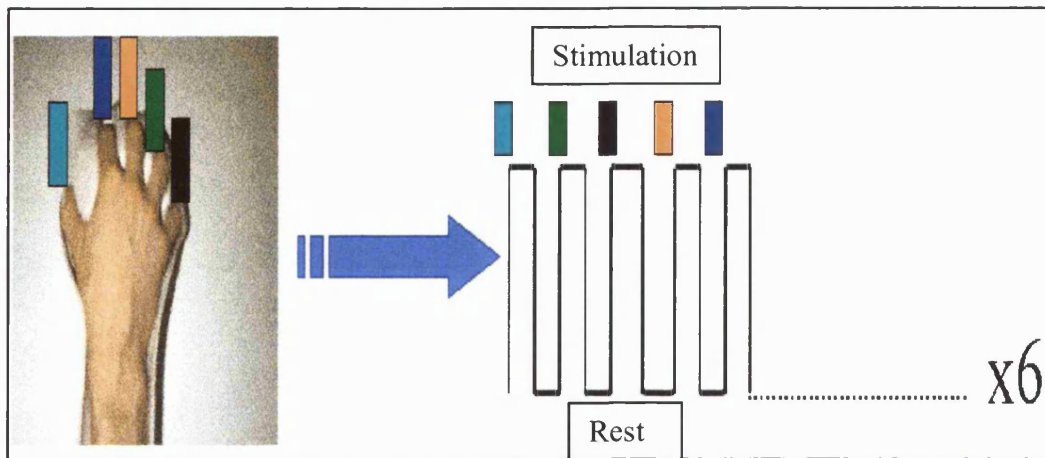


Figure 3.7. Example of one cycle of airpuff stimulation (each subject received six of these). Each finger received a 24 s block of 5 Hz airpuff stimulation alternating with 24 s of rest. The order of airpuff stimulation across fingers was pseudorandomised between cycles.

3.3.2.3 Image Preprocessing and Data Analysis

The data from this second experiment were analysed in a similar fashion to Sections 3.2.3.2 and 3.2.3.3 above. One obvious difference is the number of covariates in each model: as all five digits were stimulated in each subject in the present experiment, each single subject partition of the design matrix contained five stimulus regressors (one for the main effect of stimulation of each digit), and six movement parameters as before. As I was concerned about the signal:noise ratio of my previous experiment, I increased the number of scans (366 vs. 96). Due to this, the cut-off period for high-pass filtering was longer (512 s).

3.3.3 Results

3.3.3.1 Single Subject Results

The single subject results are summarised in Table 3.2 below. Contrary to expectations, I did not find ‘better’ somatopy or increased numbers of activated somatosensory areas using this paradigm. No subjects displayed a Penfieldian homunculus using the maxima from PoG clusters as a guide. Of the five subjects studied, two subjects displayed significant PoG foci for four digits, one subject for two digits, while the remaining subjects lacked significant foci.

Activation in opercular areas was similarly variable, with only two subjects having bilateral activation, both in a single digit (D1). Unilateral opercular activation was

observed in eight additional single digit contrasts. As in the previous experiment, activation around the region of the lateral sulcus often extended into inferior, auditory areas (*cf.* subject J.A. in table 3.2 below).

Those subjects that had significant activation in the region of the central sulcus often had multiple clusters spanning several PoG regions, with the lateral convexity or crown of the PoG being frequently activated (e.g. see Figure 3.8. below showing PoG activations for subject JA in detail). There was no obvious spatial pattern governing PoG activations across subjects.

	<u>Contralateral PoG</u>					<u>Contralateral PO</u>					<u>Ipsilateral PO</u>				
	X	Y	Z	k	T	X	Y	Z	k	T	X	Y	Z	k	T
CP D1	-	-	-	-	-	-62	-20	20	4	4.43	54	-24	22	40	7.00
D2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
D3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
D4	-	-	-	-	-	-	-	-	-	-	68	-28	22	3	4.51
D5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
EM D1	-56	-14	48	80	8.22	-60	-12	14	81	7.23	62	-6	12	16	5.80
D2	-52	-18	46	25	5.72	-	-	-	-	-	-	-	-	-	-
D3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
D4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
D5	-	-	-	-	-	-54	-12	14	12	5.00	-	-	-	-	-
JA D1	-62	-14	40	16	5.84	-50	-12	10	8	4.87	-	-	-	-	-
D2	-50	-14	50	8	4.76	-50	-14	10	88	7.41	-	-	-	-	-
D3	-62	-14	42	5	5.10	-52	-12	8	52	6.54	-	-	-	-	-
D4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
D5	-62	-14	42	3	4.89	-54	-12	8	13	4.91	-	-	-	-	-
JR D1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
D2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
D3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
D4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
D5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
DM D1	-62	-18	36	23	5.87	-	-	-	-	-	-	-	-	-	-
D2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
D3	-44	-32	52	61	6.46	-	-	-	-	-	-	-	-	-	-
D4	-44	-32	52	36	6.93	-	-	-	-	-	62	-22	20	26	5.84
D5	-60	-18	36	39	6.80	-	-	-	-	-	66	-20	20	12	4.92

Table 3.2. Local maxima within the contralateral postcentral gyrus (PoG), contralateral parietal operculum (PO) and ipsilateral parietal operculum for digit stimulation per subject. The Talairach coordinates of each voxel are listed along with the *t*-value for each subject. All local maxima reported are either significant at a $p < 0.05$ corrected for multiple comparisons over the entire image or corrected for a 32.4cm³ volume as suggested by the measurements of Kennedy and colleagues (1998) for the PoG and bilateral frontal and parietal opercula.

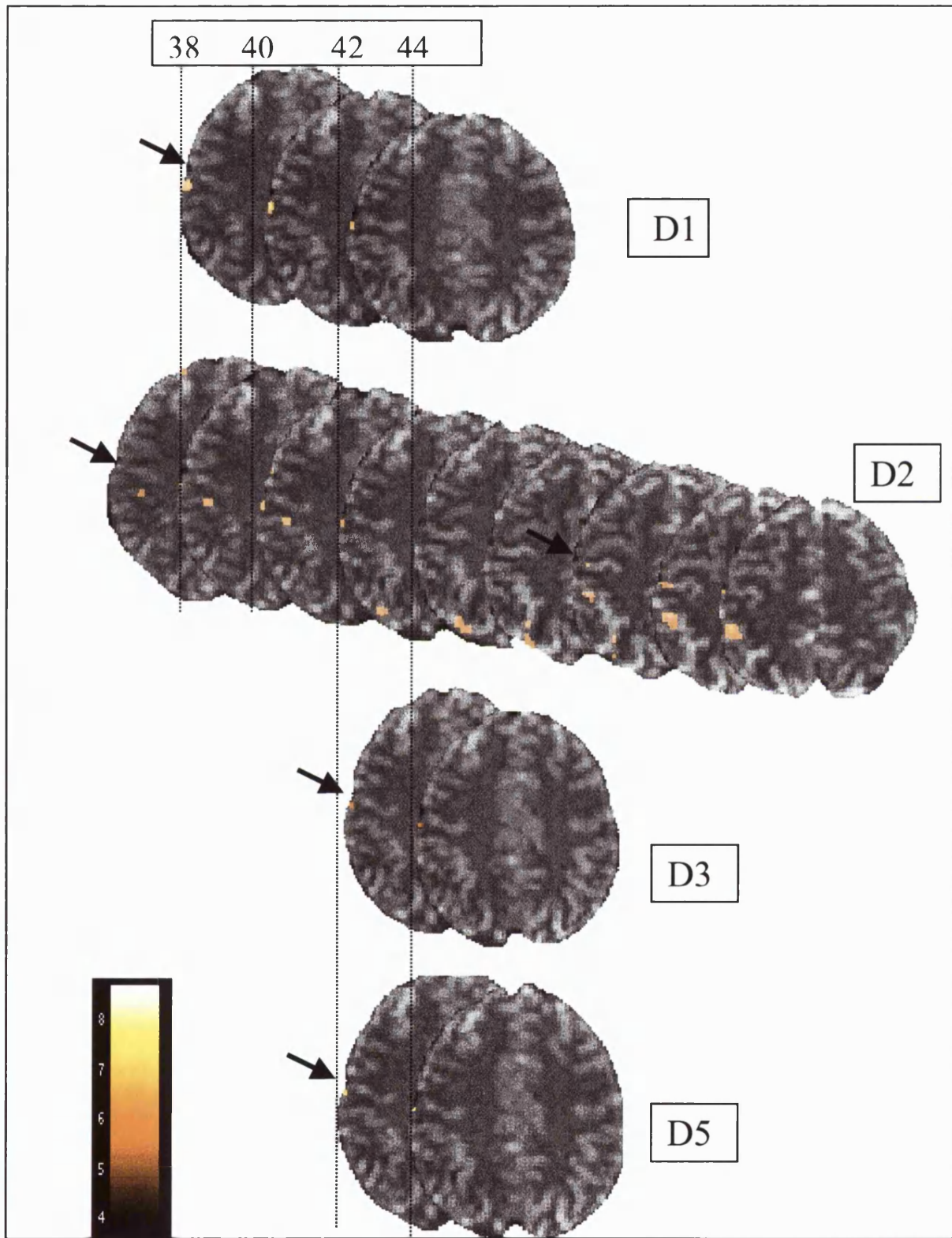


Figure 3.8. Main effects of single digit stimulation, subject JA. Voxels surviving the statistical threshold are overlaid on the subject's mean normalised functional EPI volume. Each series of axial slices is an independent contrast testing for the main effects of each digit. The numbers above each series are slices' Z-Coordinates in Talairach space. The arrow denotes the location of the central sulcus.

3.3.3.2 *Group Results*

Group contrasts were evaluated for each stimulated digit, to see if pooling signal between subjects had an appreciable effect on the significance of activations. Out of five contrasts evaluated (main effects of D1-D5 stimulation averaged over all five subjects), only contrasts examining the effects of D1 and D2 stimulation revealed significant signal increase around both the PoG and opercular areas (Figures 3.9 and 3.10). D5 stimulation produced bilateral opercular activation. The remaining two contrasts (D3 and D4) did not contain any significant voxels in the areas of interest. However, when the statistical threshold was decreased from $P < 0.00001$ to $P < 0.0001$, activation could be seen in the PoG and opercular regions. Minimal activation was seen in other areas.

In summary, while pooling results over subjects increases signal-to-noise ratio and can thus allow investigators to reject false positive activations with higher confidence, it is not the method of choice to use for the delineation of somatopy. This is especially true in the case of fixed effects models, where a single subject's activation can drive the mean group activation. This can 'smear' activation over the length of a gyrus (see Figure 3.9 below). Again, as with the results from experiment one, it is common to see multiple activation foci when examining these figures. However, as appealing as it may be, it may be premature to infer that these different regions represent different functional zones.

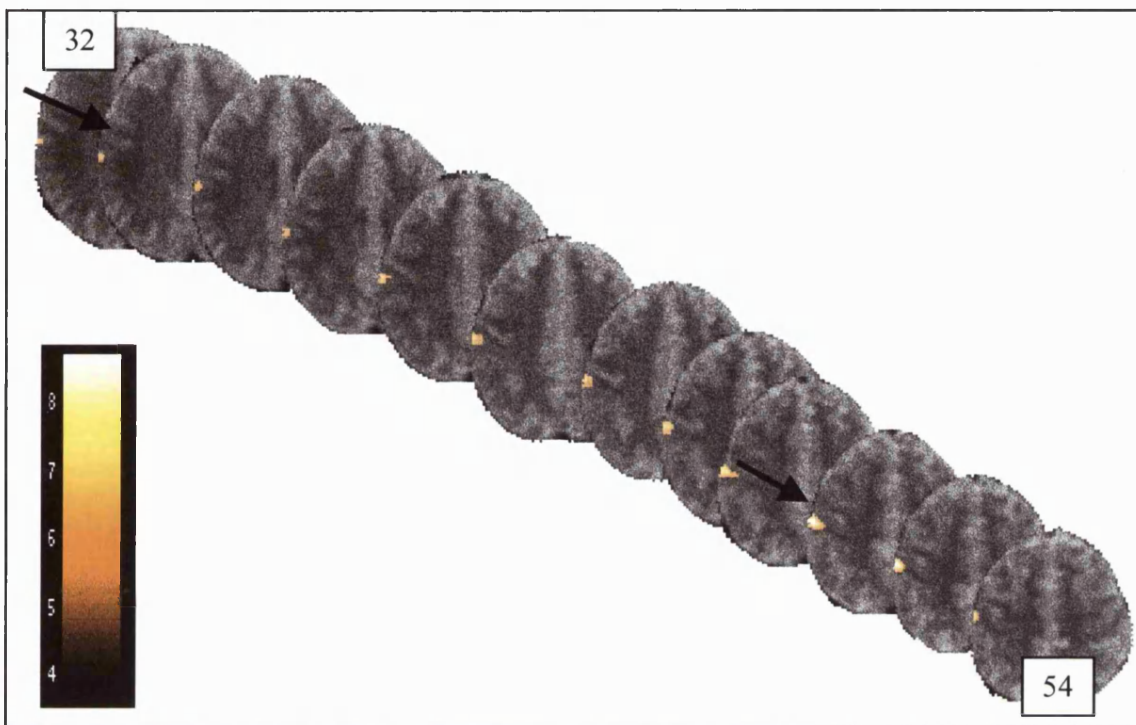


Figure 3.9. Group activation, thumb stimulation. The arrow indicates the central sulcus. An extended band of activation running down the lateral aspect of the PoG is instantly apparent. No activated voxels can be seen in the central sulcus. The colour bar represents t values, with higher t values being brighter. Numbers are Talairach Z co-ordinates. All slices are 2mm thick axial mean functional images.

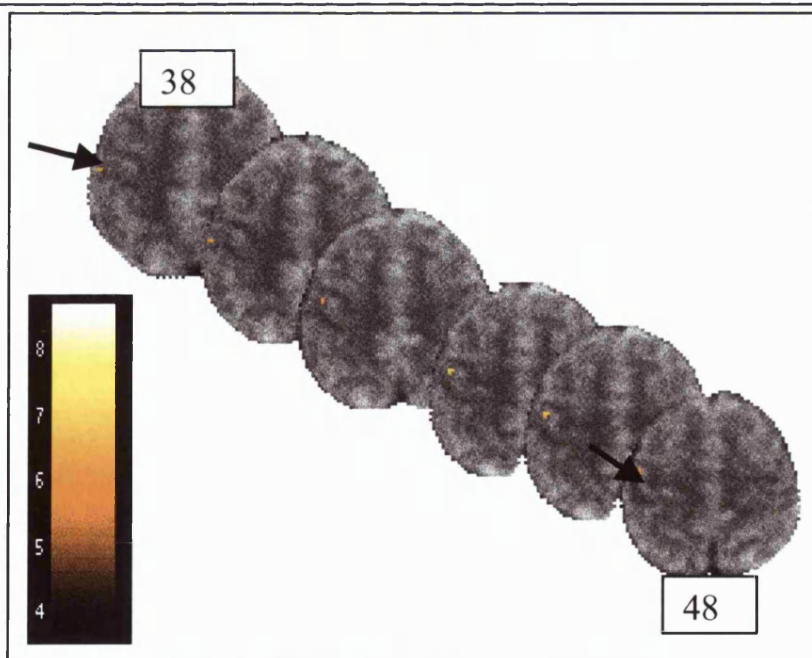


Figure 3.10. Group activation, index stimulation. Two separate clusters can be seen around the central sulcus: one in a similar position lateral position above on the convexity of the PoG, and the second lying on the posterior bank of the central sulcus. The colour bar and values are as in the above figure.

3.4 Discussion and Conclusions

The aims of the experiments within this chapter were twofold: i) to construct ‘MR-friendly’ tactile stimulators, and ii) to benchmark the stimulators by using them to investigate a well-known feature of somatosensory cortex – the gross mediolateral somatopy of the digits. As the initial aim of my experiments was to examine the reorganisation of this pattern of somatopy after experimental intervention or pathology, it was essential to confirm the ability of fMRI to characterise these patterns in normal humans. In addition, as subjects being scanned may be unable to comply with active tasks due to injury, all stimulation was passive, without explicit task demands.

The former aim was met – both vibrotactile and airpuff stimulators were designed and built. The second aim proved more problematic. Two major differences in the expected stimulation patterns were observed. On average, a mediolateral pattern of somatopy was not evident within primary somatosensory cortex either within or between subjects. In addition, the maximal area of signal change in contralateral somatosensory cortex, when observed, was often not located in the central sulcus, but instead on the lateral convexity of the PoG. This is significant. There are two possible explanations for this deficit. The first is methodological – some aspect of the scanning paradigm used may not have been optimised for the detection of signal in the PoG. This could conceivably be influenced by a number of factors: from the resolution of the functional data to the characteristics of the stimulator. The second explanation is more intriguing – perhaps, although the neurophysiology underlying the generation of the BOLD signal is spatially discrete, the resulting neurovascular change may not be (see Disbrow et al., 2000b for a discussion of this point). Other studies using somatosensory stimulation in fMRI have encountered similar difficulties (Kurth et al., 1998; out of twenty subjects scanned only five showed two cortical SI foci for D2 and D5 digit stimulation).

Brodmann (1909/1999) was one of the first to subdivide the postcentral gyrus of humans into four separate ‘strips’ or ‘zones’ lying from anterior to posterior (areas 3a, 3b, 1 and 2), based on cytoarchitectonic criteria. There is currently a wealth of

evidence from studies performed in non-human primates that these areas, in addition to being anatomically distinguishable, can be distinguished by their different physiological responsiveness (reviewed in Iwamura et al., 1998). Current evidence supports the idea that the human PoG is organised in a similar fashion, both anatomically (Geyer et al., 1997, 1999, 2000) and functionally (Moore et al., 2000). The non-unique mapping between cytoarchitectonic borders and gross anatomy (Geyer et al., 1997) renders the definitive identification of Brodmann areas from MRI scans contentious. However, relying on the probability maps generated by Geyer and colleagues (1999,2000), it is fair to say that BA3b is usually located on the posterior bank of the central sulcus. As one progresses further posteriorly, BA1 occupies the convexity of the PoG and the superior part of the anterior bank of the postcentral *sulcus*. Across both pilot experiments, this area was most likely to be active or, if more than one cluster was seen, have the most significant signal change

3.4.1. Stimulation, Scanning and Analysis Methodology

The stimulation methods used in this chapter are novel, but are typical of the methods employed by other groups to overcome the problem of somatosensory stimulation during fMRI. At the time of performing these studies I was unaware of any other attempts at digit stimulation in the MR environment employing vibration. Since then there have been a number of studies published using piezoelectric stimulators as a more advanced stimulation technique (e.g. Maldjian et al., 1999; Francis et al., 2000; Harrington et al., 2000). Similarly, although I am at present unaware of any custom-built airpuff stimulators for use in the MR environment, other studies (e.g. Puce et al., 1995) have used air jets that flow over the digits as a stimulation method. Early studies, such as Sakai and colleagues (1995) used von Frey hairs. Across all of these studies it is difficult to detect a consistent pattern between different stimulation methods and ‘successful’ and ‘unsuccessful’ delineations of somatopy.

Different magnet pulse sequences, voxel sizes and field strengths are other factors that may produce differences between studies. The increase in field strength from 1.5T to 4T, for example, is thought to differentially weight T2* signal with a greater proportion of intravascular spins (as opposed to signal in

larger vessels). In addition, it is possible to image the so-called ‘initial dip’ or negative BOLD response with higher field strengths. It has been asserted that this effect allows researchers to visualise neuroanatomical features (e.g. ocular dominance columns; Menon and Goodyear, 1999) with greater resolution than initially thought possible. However, the resolution used in the experiments in this chapter should be sufficient to detect digit specific signal changes. It has been estimated that the cortical territory devoted to each finger in human BA3b and BA1 should be on the order of 5mm^2 , which should be large enough to detect using 3mm isotropic voxels. In addition, the results of this chapter do not seem to be adequately explained by citing ‘partial volume’ type effects caused by a greater proportion of ‘nonactivated tissue’ to ‘activated tissue’ within each voxel. Although there is certainly a lack of activated voxels in experiment two, the results of experiment one are characterised by differences in the spatial pattern of activated voxels rather than a lack of activated voxels *per se*.

Other researchers have been more successful in activating the posterior bank of the PoG (BA3b, accepting the caveats on location outlined above), however. Francis and colleagues (2000) were able to produce Penfieldian somatotopic patterns at 3T using a piezoelectric simulator applied to digits of the right hand. Kurth et al (2000) illustrate particularly impressive activation patterns in multiple regions along the course of the PoG, including ‘BA3b’. Yet even some of these authors found that their highest signal changes lay not within the anterior bank of the PoG, but instead on the crown of the gyrus (Ralph Kurth, personal communication). In addition, even when taking into account the greater sensitivity afforded them by a 3T magnet and a separate headcoil, Francis and colleagues (2000) found that the most consistently activated area was *not* ‘area 3b’, but ‘area 1’, similar to the results of the current studies.

Finally, different ways of analysing data will almost certainly lead to differences in results. The most commonly used analysis method currently employed in somatosensory studies is correlation. Usually, a delayed boxcar function (to account for the temporal lag of the hrf) is used as the stimulus waveform, and voxels whose timeseries pass a pre-determined coefficient threshold are selected. This is exactly similar to a case where the GLM has only one covariate of interest.

However, when there are a number of different covariates in the design matrix, each contrast must take into account the effects of the other contrasts in the matrix. Therefore, if there is a high degree of covariate correlation, attempting to fit covariates onebyone will be affected by the shared variance that can be explained by them and the other covariates. In both the experiments in this chapter, however, there was not a strong correlation between covariates, and so this seems an unlikely explanation. It is certainly true that researchers rarely have access to the same materials across laboratories. Yet converging evidence has come from different researchers in different labs using quite different MR hardware, experimental paradigms, and analysis techniques. It is unlikely, therefore, that current results can be explained due to these reasons.

3.4.2 Experimental Design and Task Constraints

If methodological differences do not seem to adequately to the different results found by neuroimaging studies of SI, what other variables may be responsible? In both of the experiments presented in this chapter subjects did not have any explicit task demands. While they were told to concentrate on the pattern of stimulation, they did not have to transform this information in any way in order to guide behavior. Similarly, the dimensions of the stimulus did not change across the experiment, although different skin locations were stimulated in both studies. Could habituation or attenuation of BOLD signal be responsible for the lack of signal in some subjects? Early PET work (Roland, 1981) demonstrated increases in rCBF of around 25% in the region of the PoG when subjects were instructed to detect threshold stimulation of von Frey hairs, but no stimuli were delivered. Later studies of somatosensory attention have been more equivocal. These results deserve closer inspection. Following on from Roland's findings Meyer and colleagues (1991) demonstrated a 13% change in rCBF over the sensorimotor cortex when comparing attention to vibrotactile stimulation with a distraction task (mental arithmetic). There was no statistically significant difference comparing the attention to vibrotactile stimulation condition with just vibrotactile stimulation. Similarly, Hamalainen and colleagues (2000) compared attention to monofilament stimulation with monofilament stimulation plus a distractor task. Johansen-Berg and colleagues (2000) showed attentional modulation when contrasting the

differential use of either visual or somatosensory information simultaneously presented in a unimodal detection task.. Burton and colleagues (1999) found similar results using a sophisticated tactile attention paradigm in PET. No foci of activation in either SI *or* SII were detected when comparing baseline (eyes closed) to passive tactile stimulation with randomly chosen responses. Attention effects were largest in SII in this study (similar to the MEG study of Mima and colleagues, 1998).

Thus this evidence makes it difficult to conclude that uncontrolled attentional modulation could have played a major role in the present results. In the studies quoted above attentional effects were found most consistently when contrasting attention to a somatosensory stimulus (usually to perform some kind of behavioural task) with an *active* distractor paradigm. The results of Meyer and colleagues (1991) showed no significant difference between passive vibrotactile stimulation and attention to vibrotactile stimulation. This suggests that attentional modulation in simple stimulation studies is most marked when the attention is modulated both *towards* and *away* from the stimulus used.

While conscious, overt attentional modulation may not have occurred in the current studies, unconscious habituation or attenuation may have occurred. Many researchers have made the point (e.g. Gibson, 1983) that successful sensory and perceptual systems should be tuned to transients, discontinuities, or dynamically changing stimuli to maximise information transfer from environment to organism. Tonic stimuli, or stimuli that do not change over time carry no new information over repeated presentations to the organism, and so it may not be efficient from an information-processing perspective to devote scarce neural resources to these stimuli. This phenomenon can be found in other sensory systems – for example, the phenomenon of ‘Troxler fading’ in the visual system that occurs when low contrast stimuli are fixated for a protracted period of time. In my experiments, the parameters of stimulation in both studies were chosen to attempt to reduce these effects. In experiment one, short ‘bursts’ of high-frequency vibrotactile stimulation were separated by brief rest periods. In both experiments, stimulation was always phasic and not merely tonic. Stimulus presentations, however, were predictable,

and thus it is difficult to categorically rule out changes in subject's attention throughout the experiment.

In addition to 'higher-order' mechanisms of attentional modulation, receptors and first and second-order spinal neurons will habituate to constant stimulation. This may be due either to biophysical sensitisation mechanisms, or the preferential tuning of receptors to transient stimulus events and not tonic ones (whereas it is accepted that RA and SA receptors exist in the somatosensory system, even SA receptors will show transient responses to brief stimuli). These mechanisms exist in the somatosensory system, as in all primate sensory systems, but they are unlikely to have had a major effect on the current studies since as before, if these mechanisms exerted such a prominent effect on cortical somatosensory activity they would have affected other studies using similar stimulation parameters (e.g. Francis et al., 2000).

3.4.3 Postcentral Gyrus Cytoarchitecture, Localising Activation Foci and Receptive Field Properties

Moore and colleagues (2000) noted three basic patterns of activation foci in tactile neuroimaging experiments: moving stimuli/gratings elicited dual peaks in anterior and posterior PoG; electrical stimulation produced dual peaks in anterior PoG (but see Kurth et al., 2000 for contrasting findings); and vibrotactile/roughness discrimination tasks activated posterior PoG. The distinction between anterior and posterior PoG is important, because there is an anterior-posterior gradient of receptive field complexity within the PoG corresponding to the four cytoarchitectonic areas first defined by Brodmann – areas 1,2,3a and 3b. In monkeys these areas each contain a representation of the periphery corresponding to input from one or more receptor subtypes (Merzenich et al., 1978; Kaas et al., 1979; Huffman and Krubitzer, 2000). As mentioned previously, structure and function are thus invariably twinned within the PoG.

In humans, these areas have been extensively characterised by Geyer and colleagues (1997, 1999, and 2000). While there is no easy relationship between microarchitecture and macroanatomy, the construction of probability maps by this group allows tentative conclusions to be made based on the location of activation foci within the PoG. As noted by the above authors (2000): 'Despite considerable

interindividual variability, a clear focus is obvious for each area...the focus of area 3b [lies] in the rostral bank of the PoG (or posterior bank of the central sulcus), and the focus of area 1 on the crown of the PoG'. The majority of activation foci in the present studies were located on the lateral convexity or 'crown' of the PoG. From the work of Geyer and colleagues, this area is more likely to be BA1 than BA3b. BA3b has been called 'SI proper' in humans because it contains a high-resolution map of the periphery and is primarily driven by both slowly adapting (SA) and rapidly adapting (RA) cutaneous mechanoreceptors (Sur et al., 1981). BA1 instead contains neurons that have complex and larger receptive field properties (reviewed in Kaas, 1983; Iwamura, 1998). Activation of one area over the other may therefore reflect the different cell populations in these areas. While there are certainly differences in the response properties of neurons in BA1 and BA3b, evidence suggests (Iwamura et al., 1993) that on average both areas have similar *absolute* numbers of cells tuned to cutaneous stimulation. In addition, the stimuli used in this chapter are likely to preferentially activate RA-I and RA-II type receptors (vibrotactile) and RA-I receptors (airpuff). In other words, it is unlikely that the stimuli used would be selective enough to consistently activate one PoG region over another.

The consistent activation of lateral PoG is therefore somewhat puzzling. If we accept that this region is BA1, it is unlikely that BA3b would not also be activated. However, this logic assumes that the dynamics of an 'area' follows similar spatiotemporal dynamics to the simple rfs of the neurons within it. Multiple simultaneous recording from sites within the somatosensory cortex (e.g. Nicolelis et al., 1995) reveals that within-area neuronal dynamics code for stimulus properties in a complex fashion that is not apparent from individual r.f.s or single-cell responses. In other words, while it is useful to know something about the differential response properties of cells across different cortical areas, it is important to note that these results may say as much about the recording method initially used to sample these responses (i.e. using multiunit recording techniques in anaesthetised non-human primates) as the actual *in vivo* dynamics of the network.

The spatial ‘mismatch’ in my data may also reflect subtle limitations of the spatial concordance between brain and vein. While researchers have been successful in delineating with high resolution the organisation of the visual cortex using fMRI, the visual cortex is densely vascularised, and thus quite different to other areas (Marinković et al., 1995). A recent study combining electrophysiological and fMRI-derived maps of the somatosensory cortex in the same monkeys showed a 55% overlap between maps (Disbrow et al., 2000b). Perhaps the ‘BA1’ signal may in fact be ‘BA3b’ signal that is expressed maximally at a distance from the site, due to flow/activation spatial mismatches? While this is certainly possible, without high-resolution magnetic resonance angiograms (MRAs) of the central sulcal region this cannot be confirmed. Combining MRAs and fMRI data in motor paradigms has previously demonstrated that BOLD signal in distal veins can contribute to the observed BOLD signal (Kansaku et al., 1998). This possibility has been acknowledged since some of the earliest fMRI SI mapping studies (e.g. Sakai et al., 1995). However, Sakai and colleagues collected MRAs of subjects, and did not find a strong spatial relationship between veins and activated areas to simple somatosensory stimulation. It is possible, though, that the resolution of most MRA procedures is not sufficient to detect small diameter vessels in which BOLD effects downstream of active areas are located.

Finally, it is important to remember that the detection of multiple clusters is not *de facto* proof of multiple, separate neuronal populations. The resolution of the functional data exerts a strong influence on the ability to categorically claim that two neighbouring blobs are truly different neuronal ‘fields’. Smoothing, whether imposed implicitly (voxel size) or explicitly (post-processing) affects the ability of investigators to construct maps of cortical responsiveness that mimic the work performed by neurophysiologists in mapping cortical areas. This may be caused by the relatively poor signal to noise ratio of fMRI compared to neurophysiological methods. Claiming that two clusters are ‘separate’ when they both respond to the same stimulus is a contentious conclusion. Similarly, changes in the extent of an activated cluster can be driven exclusively by an increase in the peak activation of the cluster, rather than a true expansion *per se* (e.g. Weiskoff et al., 1998). Because of these reasons I chose not to perform any statistical inference relating to the sizes

of different clusters (one additional problem is not knowing the null distribution of cluster sizes such that one can then evaluate the significance of size changes; J.B. Poline, personal communication). However, this is not to deny the utility of some ‘voxel-counting’ methods, as long as the caveats surrounding their use are clearly stated.

3.5. Conclusions

3.5.1 The Sensory-Motor Paradox Revisited

The experiments presented in this chapter demonstrate that the ‘sensory-motor’ paradox, at least as originally defined by Ingvar, can be regarded as dead and buried. Using two novel stimulation methods it was possible to elicit significant signal changes in the PoG of subjects. However, the ghost of Ingvar’s paradox remains. The spatial pattern of activations was not what one might expect from current knowledge of somatosensory neurophysiology. Similarly, a number of false negative results are assumed to have occurred in the second paradigm, as a number of subjects did not have statistically significant activation foci in their PoG, despite being able to perceive stimulation.

fMRI studies of SI somatopy often produce results that are at odds with similar studies performed using other modalities (e.g. MEG – Nakamura et al., 1998) and different species (Kaas, 1983; Iwamura et al., 1998). One distinct possibility is that the variability in results between subjects may be due to hitherto-unappreciated variability in the fMRI response between different scanning sessions. While one study showed reproducible patterns of activation between sessions in the same subjects (Francis et al., 2000), it remains to be seen if these results are similarly stable over a larger number of scanning sessions.

Another possibility is that, although the stimuli used in the current chapter should have activated primary somatosensory areas, they may not have been tuned sufficiently to maximise signal while not recruiting subthreshold ‘surround’ regions that may blur the delineation of classic receptive fields (*cf* Moore et al., 1999). In other words, while it is important to ensure that perceptible stimuli are used in studies, suprathreshold signals at the primary somatosensory cortex may recruit nominally silent receptive field surrounds. It is

often forgotten, furthermore, that Penfield's original map was an attempt to summarise a large and variable set of data. Thus the clear demarcations between neighbouring cortical representations (i.e. hand and face) seen on popular reproductions of the homunculus should be regarded as indicative of *mean tendencies* in Penfield's data. The non-physiological levels of current used by Penfield and Boldrey were commented on by one of their contemporaries: '...application of a stimulating current to tissue of such histological complexity cannot be expected to give the same results as the arrival of definitely grouped corticopetal nerve impulses' (Bard, 1938). This effect may smear activation over the cortical surface, making it more difficult to effectively delineate 'core' areas maximally tuned to a particular stimulus. There may therefore be an optimal stimulus for either maximising signal within SI (this stimulus would recruit surround areas) or delineating somatopy within SI (this would minimally recruit surrounds, leaving well segregated 'core' areas. The questions of session stability and stimulus tuning are explored in the next two chapters.

4 Variability in fMRI: The Generality of Single Session Results

4.1 The Generality of Experimental Data

The results of all scientific experiments, however well controlled, are influenced by a collection of variables that are usefully grouped together under the heading *context*. Abelson (1995) defines context as 'Everything about the experiment beyond the critical manipulation of the treatment – research team, time, place, subjects, and ancillary aspects of the procedure and materials – becomes context'. 'Context' differs between scientific disciplines; I will focus exclusively on its influence on experiments in experimental psychology, and by extension, neuroimaging.

Context can be illustrated by the following example. A researcher wishes to use neuroimaging to investigate differences between Parkinsonian patients and normal controls while performing a simple movement task. Unfortunately for the researcher, the Parkinsonian patient population is based at another neuroimaging institute. For pragmatic reasons, the researcher is forced to assemble her own control group and scan them using her local MRI scanner, and analyse the data *en masse* once data from the other population have been collected. Once completed, the researcher publishes her results as an illustration of the differences between Parkinsonian patients and normal subjects.

This (rather contrived) example usefully illustrates some of the problems faced in attempting to derive general laws and principles from a limited number of manipulations and subjects. When studying human subjects one usually cannot obtain experimental results from every member of the groups (hypothetical or otherwise) being studied. It is therefore necessary to make a compromise: a *sample* of the group (or population) must be taken. To protect against bias, samples should be *random* - theoretically, every member of the population must have an equal chance of being included in the sample. In addition, samples should

be *independent* – the selection of one unit from the population should have no influence on the selection of other units.

This is not the case in the above example: logistical problems mean that the researcher has to take whatever Parkinsonian patients she has access to. The opposite of this process would be access to a large number of Parkinsonian patients who are all equally motivated and can come into the lab at any time. To a lesser extent, the normal population that the researcher is using is usually well motivated right-handed Caucasians who respond to financial reward - typically university undergraduates.¹ Another problematic issue arising from the Parkinsonian example is the comparison of experimental results from two different research establishments. Differences may therefore arise from different researchers being involved in scanning the subjects (the ‘experimenter effect’; *cf.* Hicks et al., 1970).

In addition, because neuroimaging is a relatively new science, the slightly different hardware used at both institutes may produce systematic differences where none exist (known in electrical engineering as ‘loading the circuit’). This phenomenon is not unknown in experimental psychology. At the beginning of the century, many psychologists were interested in studying the Féré effect (what is now known as the galvanic skin response [GSR]). However, a number of different factors affect the magnitude of the GSR: electrode type, the concentration of salt used, and the level of stimulating current can all produce effects that are not related to the psychological factors being studied (Plutchik, 1974). Studies that demonstrate a difference in GSR must therefore ensure that the differences cannot be explained by mere differences in data acquisition methods. In neuroimaging there are a similar number of experimental variables that may lead to systematic differences between studies. While the relative contributions of each of these effects to variability can be assessed over time, this requires considerable effort.

¹ This point is often made by neuroscientists working in the field of animal experimentation: cognitive neuroscience purports to study human behaviour but can only generalise to college students. Such examples of ‘*j’accuse*’ are somewhat undermined by said researchers’ own reliance on inbred strains of experimental animal who often bear little resemblance to the species found in the wild.

As demonstrated in Chapter three, when evaluating the effectiveness of a particular form of somatosensory stimulation it is often useful to know how much variation one would expect *by chance* (or context). In other words, while there may indeed be a ‘mean’ somatotopical map, its intrinsic variability may mean that several measurements are necessary to properly characterise it. However, although exceptions exist, it is unusual for a subject to be scanned on more than one occasion and, more often than not, a single fMRI session is assumed to give an accurate representation of a subject’s functional neuroanatomy. If there is high variability in the spatial expression of the evoked neurovascular response or the neuronal response, a single session has little descriptive power.

There are therefore obvious problems with the ‘one subject, one session’ approach to neuroimaging experiments. One session is only a single, discrete ‘snapshot’ of the subject’s brain, and may not epitomise responses to the sensorimotor or cognitive challenge employed. Indeed, differences between sessions are inevitable: for example, the BOLD response is an indirect and semi-qualitative measure of neuronal activity, and the relationship between BOLD contrast and cerebral oxygen metabolism is influenced by a number of physiological factors (e.g. for review see Ogawa *et al.*, 1998). Furthermore, single session results may be influenced by slight variations in the hardware characteristics of the MR scanner, which are not systematic across sessions (e.g. the shim performed to homogenise the B_0 field of the scanner; Howseman *et al.*, 1998). Any differences in subject position within the headcoil on separate scanning sessions may also result in greater variability in voxel signal change due to partial volume effects. In addition to the above, nonspecific physiological effects such as the level of arousal may further influence the neurovascular response to the activation task in question.

These effects are hard to control and may substantially influence single session results, such that the experiment may ultimately say as much about the context under which the data were acquired as the effects of the experimental manipulation itself. Although few researchers would expect a *precise* replication

of the results if an experiment were repeated, it is currently unclear how generalisable single session results are with fMRI.

This influence of session context on the effects of an experimental manipulation constitutes a *session by condition* interaction. Although a number of studies have examined the reproducibility of fMRI across a small number of sessions (Cohen *et al.*, 1999; Noll *et al.*, 1997; Rombouts *et al.*, 1998; Tegeler *et al.*, 1999; Yetkin *et al.*, 1996), the small sample size of these studies limits their conclusions. My primary aim in this chapter is to examine how well a single session *typifies* a subject's responses, using simple activation paradigms. Just as the significance of within-session experimental effects are assessed by sampling a number of scans for each condition, to assess *between-session* differences one must sample multiple sessions. If a single session is to be a good exemplar of a subject's functional neuroanatomy, session by condition interactions must be minimal. Although the experiments in this chapter were primarily concerned with the stability of the BOLD response in the somatosensory cortices over multiple stimulus presentations, I did not use a somatosensory task as one of my activation paradigms. I instead chose to examine multiple, simple activation paradigms that could be easily implemented in the scanning environment.

4.2 Populations, Inference and Multi-Level Modeling

Neuroimaging data naturally have a *hierarchical* or *clustered* structure. Scans are sampled from single subjects, and single subjects are sampled from a putative population. The data are clustered because we expect scans from a single subject to be more alike at a basic level than scans taken at random from different subjects. Hierarchical data analysis treats data as consisting of *units* grouped at different levels. In this chapter, the data have a two-level structure: *scans* are level-one units collected from different *sessions*, which are level-two units. This kind of nomenclature is similar to that used to categorise variation in data sets by examining different combinations of experimental factors consisting of a number of levels (Searle *et al.*, 1992).

If there are a possibly infinite number of levels in data (e.g. levels tend to be

infinitely divisible) then the levels used represent a limited subset of all possible levels. For example, in drug studies it is possible to choose from an infinite number of drug concentrations to give to subjects. The levels chosen reflect the experimenter's questions. If the experimenter is interested in generalising *exclusively* across the chosen levels of the factor (five drug concentrations, for example), then the model is called a *fixed effects* model. This is because the experimental effects are attributable to a finite set of levels of a factor that occurs in the data. They are there because the experimenter has chosen them as worthy of study.

On the other hand, if the data represent a sample from a possibly infinite population that the experimenter is interested in generalising and extending inference to, the model is a *random effects* model (typically in neuroimaging the term 'random effects' refers to linear models with two levels or *components* of variance, [Searle et al., 1992]). How does this affect the generality of single session results? If activation effects do indeed vary substantially between sessions, to generalise the results to the subject an experiment needs to utilise multiple sessions and assess the data accounting for both within- and between-session variability. Typically, these two levels of variability are not addressed, even if multiple sessions are acquired; the experimental effects of interest are assessed using statistical models that use within-session error variance (residual scan/scan variability) as the only component of variance. Although sessions by condition interactions are often modeled, the variability of the interaction effects does not enter into the inference – only the mean effect across sessions is computed. These models have been the norm in neuroimaging analysis, and assess only the average experimental effect across the observed sessions – in other words, they are examples of fixed effects models. They do not take account of the variability of responses between sessions, and therefore cannot be used to draw conclusions about a subject's typical response. For example, a spuriously large activation in one voxel during only one session may be large enough to dominate that voxel's average responses across sessions. In the case of a single session

collected from a single subject, the experiment is reduced to a case study. Conclusions regarding the subject's typical response can only be made under the implicit assumption that inter-session variability of response would be negligible were the experimental session repeated. As discussed above, this is highly unlikely.

If session by condition interactions are substantial, random effects models are required, so that the effects of each session on the BOLD response are treated as a random variable. This reflects the fact that a single session is considered as a sample from the population of all possible sessions from the subject, and so significance can be computed, accounting for both between and within session variance. Random effects analyses have previously been employed to account for between-subject variability, or *subject by condition interactions* in fMRI studies (Holmes *et al.*, 1998; Henson *et al.*, 1999a; Henson *et al.*, 1999b).

As the results of a random effect analysis permits inference about the population from which the samples were drawn, the N of observations is now the number of sessions. As the number of sessions is quite small, these analyses tend to have low power (with a high chance of type II errors). An analysis of this type, however, is essential for the correct level of inference if sessions by condition interactions are considerable. In the present study I examined the reproducibility of the BOLD response in a *single* subject over multiple sessions for simple motor, cognitive and visual paradigms. First results from each session analysed in isolation are presented, as if from a single session experiment using only within-session variance to compute significance. Finally the entire multi-session data set is analysed twice using different variance component models. The first is a *fixed effects* analysis, the second a simple *random effects* analysis.

4.3 Methods – Experimental Setup and Scanning

4.3.1 Subject and Scanning Details

The subject was a healthy 23 year old right-handed male. The data were acquired on a Siemens MAGNETOM Vision (Siemens, Erlangen, Germany) at 2T. Each BOLD-EPI volume scan consisted of 48 transverse slices (inplane

matrix 64x64; voxel size 3x3x3mm; TE=40ms; TR=4.1s). A T1-weighted high-resolution MRI of the subject (1 x 1 x 1.5mm resolution) was acquired to facilitate anatomical localisation of the functional data.

4.3.2 Experimental Setup

As the experiment was designed to examine the generality of a single session, each session was conducted as if it were the first time the subject had been examined: in effect, as if only one session was to be obtained. This was done to control for obvious and artefactual between-session differences whilst ensuring that sources of typical between-session variability (scanner hardware and subject physiology) would be sampled in an unbiased manner. The following precautions were taken: the same operators always controlled the scanner; ambient light and sound levels were similar between sessions; and spoken instructions to the subject were always exactly the same. Day-to-day quality control measurements of scanner characteristics were not acquired. It was impossible to control for the fact that the subject was always aware that he had performed the task before in the scanner, only under slightly different circumstances. I refer to this effect as the '*Groundhog Day*' effect.

Thirty-three individual sessions were acquired from the subject over a period of two months, collected at 12pm and 6pm. Each scanning session consisted of one run of each of a motor, cognitive and visual paradigm, presented in random order. Session paradigms were designed to reduce the effects of variable task performance. For example, the subject was familiarised with both the random number generation and finger-tapping task before performing them in the scanner, in an attempt to eliminate performance effects. In addition, the rates at which both tasks were performed were chosen to ensure that subject performance would be stable across sessions. These decisions were informed by studies that used similar paradigms (motor paradigm - Blinkenberg *et al.*, 1996; cognitive paradigm - Jahanshahi *et al.*, manuscript submitted), demonstrating that the rate at which the subject tapped his finger, and the degree of randomness of the sequence generated were both stable over time. It is worth noting, however, that an empirical

demonstration of these would have been desirable.

4.3.2.1 *Motor Paradigm*

The subject tapped his right index finger, paced by an auditory tone (1.5Hz). The subject's hand was restrained within a custom-built thermoplastic splint, which ensured that the amplitude of the finger movement was consistent both across and within sessions. Each activation epoch was alternated with a rest epoch, in which the pacing tone was delivered to control for auditory activation. Thirteen blocks were collected per session (seven rest and six active). Each block was 24s/6 scans long, making 78 scans total for each session. The subject maintained fixation on a cross that was backprojected onto a transparent screen by a LCD video projector as in previous experiments. The projector was similarly employed to deliver visual instructions to the subject before each block (either 'Move' or 'Rest').

4.3.2.2 *Cognitive Paradigm*

The subject generated random numbers from 1-9, paced by an auditory tone (.66Hz). In the rest condition the subject counted from 1 to 9, similarly paced by the auditory tone. The subject fixated in a similar fashion to before. Thirteen epochs were collected in total (seven rest and six active). Again, block length was 6 scans, and 78 volumes were collected in each session.

4.3.2.3 *Visual Paradigm*

A reversing black and white checkerboard flickering at 8Hz (Fox and Raichle, 1985) was presented to the subject. The subject focused on a central fixation spot that was constant across both activation (reversing checkerboard stimulation) and rest (fixation spot only) blocks. Six epochs were acquired in total (three activation and three rest). Blocks were 6 scans long, and 36 scans in total were acquired in each session.

4.3.3 **Image Preprocessing**

Data preprocessing was carried out using SPM99 (Wellcome Department of Cognitive Neurology, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>). All functional volumes, independent of session or paradigm, were realigned to the

first volume acquired (Friston *et al.*, 1995) and a mean realigned volume created. Sessions containing obvious movement artifacts were discarded at this stage: three motor sessions, two visual sessions and three cognitive sessions were excluded in this manner. The subject's T1-weighted structural scan was co-registered to the mean functional volume, and the mean volume used to determine the parameters applied to all volumes during spatial normalisation and resampling (Ashburner *et al.*, 1997; Ashburner and Friston, 1999) to a standard template (Evans *et al.*, 1993). As the volume of brain sampled in each study was affected by the position of the subject within the scanner's field of view, we found that the extreme superior and inferior portions of the subject's brain were sparsely sampled. To address this, voxels not sampled in *every* session were eliminated during normalisation. All functional volumes were then smoothed with a 6mm FWHM Gaussian kernel. Global changes in fMRI response from scan to scan were removed by proportionally scaling each scan to have a common global mean voxel value.

4.3.4 Data Analysis

Statistical analysis was carried out using the general linear framework described by Worsley & Friston (1995). As the analyses presented in this chapter are more elaborate than previous chapters, it is necessary to revisit the implementation of the general linear model (GLM) in SPM.

The sessions for each paradigm were modeled with a simple linear model for the data at each voxel:

$$Y_{ij} = \gamma_i + \alpha_i f(j) + \sum_{k=1}^K \beta_{ik} g_k(j) + \varepsilon_{ij} \quad (1)$$

Here Y_{ij} denotes the value of the voxel of scan j ($j = 1, \dots, J$) of session i ($i = 1, \dots, I$). γ_i is the mean (block) effect for session i . $f(j)$ is a reference waveform, a function of the scan index within session that has the same form for all sessions. This is simply one possible expansion of eqn.7 from chapter 2. As in previous analyses, a simple "convolved box-car" reference waveform [CBC] was

used as $f(j)$, consisting of a box-car function of zero's and one's representing the experimental timecourse, convolved with the expected hemodynamic response function (HRF). The parameter α_i is the amplitude of the CBC response for session i . Differences in the session response amplitudes α_i constitute session by condition interactions. The additional reference functions $g_k(j)$ are a set of discrete cosine basis functions, effecting a simple “high pass” filter, as described by Holmes *et al* (1997), with cut-off (specified by K) set at twice the experimental period. Unlike previous analyses, the high-pass filter was explicitly included in the design matrix. Under the assumption that this model fits, any residual errors (ϵ_{ij}) will have zero mean and exhibit only short term auto-correlation within session. In the following I shall refer to the CBC amplitudes α_i simply as the response for session i .

4.3.4.1 Individual Session Analyses.

Each session was first analyzed as a single fMRI session (as though it were the only session acquired) using a ‘standard’ SPM analysis. The ‘Groundhog Day’ effects aside, this enables a comparison of how the results of a single session experiment can vary. It also illustrates why drawing conclusions about a subject from a single session can be dangerous.

The model used is that of Eqn. 1 evaluating a single session (i) at a time. The residual errors are assumed to be Normally distributed with variance $\sigma_{i(\epsilon)}^2$, estimated individually for each session. The design matrix for each session is illustrated in figure 1A. A t -statistic assessing the null hypothesis of zero response ($\alpha_i = 0$) was constructed for each voxel, giving an SPM{t} for each session indicating the significance of the response for each session. For display, each session specific SPM{t} was transformed to an equivalent SPM{Z} by probability integral transform. This was effected by replacing each t -value with the standard Normal ordinate with the same upper tail probability. Temporal autocorrelation was dealt with using the method of Worsley and Friston (1995), by temporally smoothing the session time series with a Gaussian kernel of 6s FWHM.

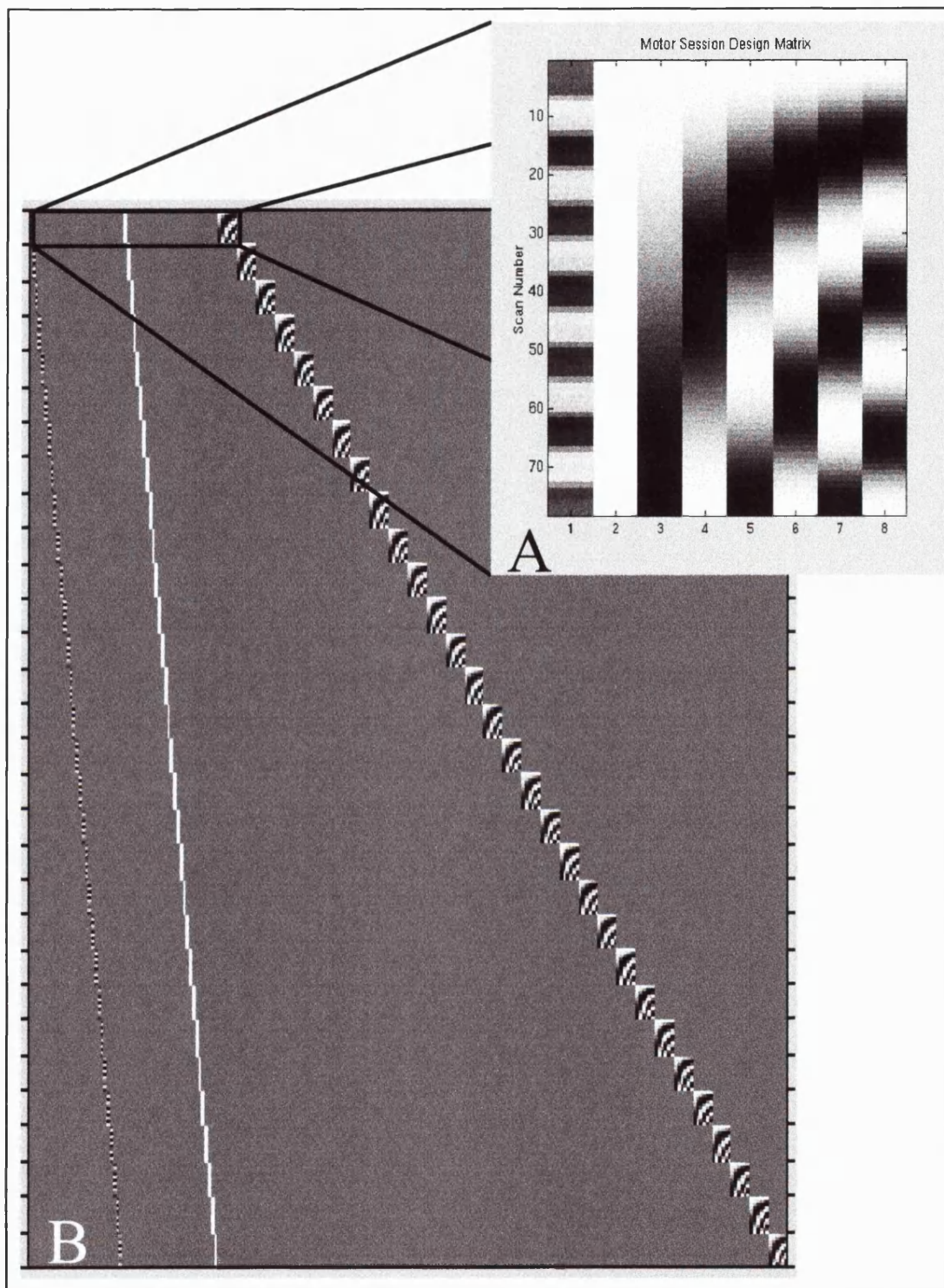


Figure 4.1. Design matrices used in analysis. *A* is a single session design matrix with the regressor of interest (the CBC, column 1), the session mean effect (γ_i , column 2) and the set of discrete cosine basis functions used to effect high-pass filtering (columns 3-8). *B* is a multi-session design matrix, constructed from n single session design matrices, where n is the number of sessions analysed at the multi-session level. The design matrix in *A* was used for single session analyses, whereas *B* was used for both fixed and random effects multisession analyses

4.3.4.2 Multiple Session Analyses - Session by Condition Interactions

To assess whether there were significant session by condition interactions, the model of Eqn. 1 for all I sessions (design matrix shown in figure 1B) was contrasted with a reduced model where the response was identical for all sessions ($\alpha_i = \alpha'$, $i = 1, \dots, I$). Again, it is assumed that residual variance is identical across sessions, such that the residuals are normally distributed with zero mean and variance σ_ϵ^2 . The additional variance modeled by the full model (including session by condition interactions) was compared with the residual variance using an extra sum-of-squares F -test (Draper and Smith, 1981), modified to account for temporally auto-correlated residuals using the method of Worsley and Friston (1995). The resulting $\text{SPM}\{F\}$ identifies voxels that display significant session by condition interactions.

4.3.4.3 Multiple Session Analyses – Fixed Effects Model

If there are substantial differences in response from session to session a single session experiment is inadequate if one wishes to examine a subject's response to experimental stimuli in general, and so a multiple session experiment is necessitated. Given a multiple session data set, modeled with Eqn.1 (design matrix shown in figure 1B), a fixed effects analysis proceeds by assuming that the session specific responses α_i themselves are of interest – in other words, these discrete levels of the factor are those over which we wish to extend inference. The residual errors ϵ_{ij} are assumed normally distributed with zero mean, and constant variance σ_ϵ^2 . Evidence of a response across sessions can be tested by examining

$\bar{\alpha}$, the average of the I session specific responses $\bar{\alpha} = \sum_{i=1}^I \alpha_i$. Again, short term

temporal auto-correlation in the errors were handled using the method of Worsley and Friston (1995), temporally smoothing each session time series with a Gaussian kernel of 6s FWHM. However, since the session specific responses are considered fixed, only one component of variance is accounted for (the residual error variance σ_ϵ^2), and inference from the resulting $\text{SPM}\{t\}$ is limited to the

average response *for the observed sessions*. As such, this analysis is sensitive to large effects in a small number of sessions.

4.3.4.4 Multiple Session Analyses - Random Effects Model.

To extend inference beyond the sessions acquired, a different approach is needed. The sessions acquired are treated as a sample of all possible sessions, each of which with its own response α_i . Thus, the α_i of Eqn.1 is treated as a *random effect*. In other words, the response amplitudes α_i for the sessions under consideration are merely one sample from the (hypothetical) distribution of response amplitudes for a session chosen at random. A simple second level (between-session) model would be:

$$\alpha_i = \alpha + \varepsilon_i \quad (2)$$

where the α_i are from Eqn.1 (the within-session model), and the between-session errors ε_i have zero mean, variance σ_α^2 , and can be considered independent. Thus, the random effects model has two components of variance, between-session, σ_α^2 , and within-session (residual), σ_ε^2 . Using this model inference can be extended to α , the underlying average response across all *possible* sessions.

In general, analysis of such random effects models can be difficult (Searle & Casella, 1992). However, the simple models considered here are balanced (the models for each session are exactly the same), and separable (the only common parameter across sessions is the intra-session (residual) variance σ_ε^2 , assumed constant for all sessions). This permits a simple “summary statistic” approach (Frison & Pocock, 1992). Such an approach was first described for neuroimaging data by Worsley *et al.* (1992), and its importance subsequently highlighted by Holmes *et al.* (1998) who describe the implementation (in SPM) used here. In essence, the model of Eqn.1 is fitted to yield estimates $\hat{\alpha}_i$ of the response amplitude α_i at each voxel for each session. The variance of the estimated response amplitudes $\hat{\alpha}_i$ across sessions incorporates both within (σ_ε^2) and between-session variability (σ_α^2) in the appropriate proportions to assess the significance of the overall subject activation effect α (Frison & Pocock, 1992).

Thus, each session data set is summarised by a single *contrast* image whose voxel values are the fitted response amplitudes. These contrast images can then be assessed at the inter-session level for a significant average effect, with inference extending to the subject in general (under similar experimental conditions) rather than just the particular sessions acquired.

To conduct a parametric analysis, a specific form must be used for the between-session errors ε_i . In the absence of any evidence (yet) to suggest otherwise, consider a simple Normal model:

$$\alpha_i = \alpha + \varepsilon_i, \varepsilon_i \sim N(0, \sigma_\alpha^2) \quad (3)$$

My approach here is pragmatic: nothing is known about ε_i 's distribution. The assumption of Normality allows random effects analyses to be introduced simply and logically as an extension of the parametric statistical tests used by SPM. The validity of this assumption will be explored in the Discussion.

With the models of Eqn.1 and Eqn.3, the random effects analysis can be effected as a simple one-sample *t*-test on the contrast images, yielding an $\text{SPM}\{t\}$.

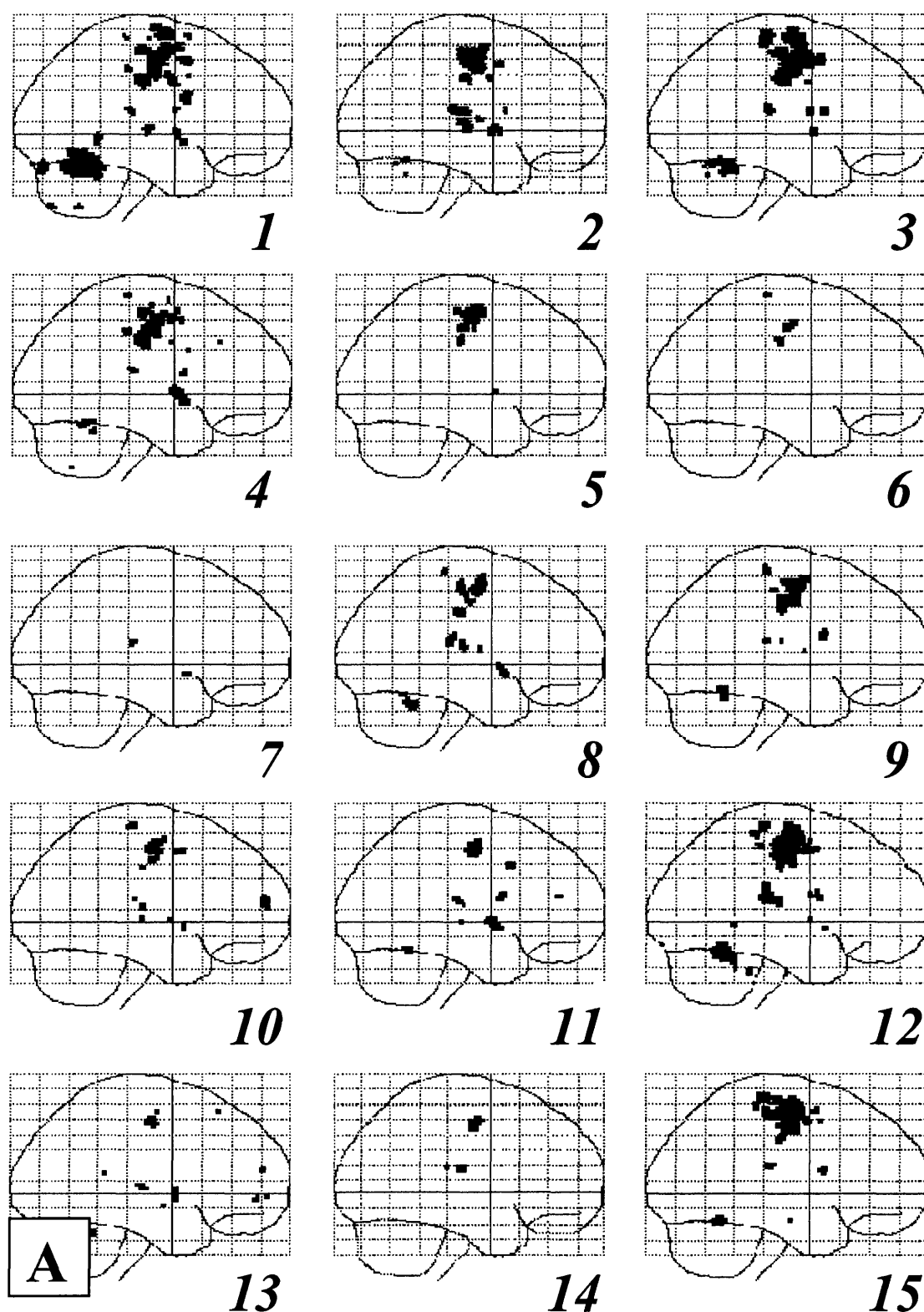
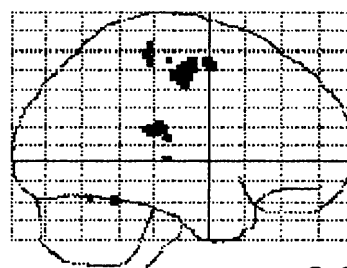
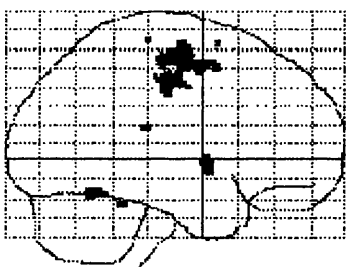
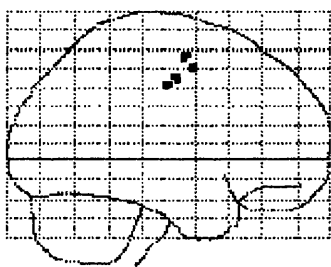
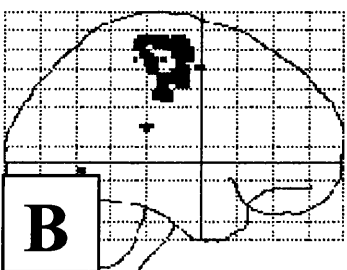
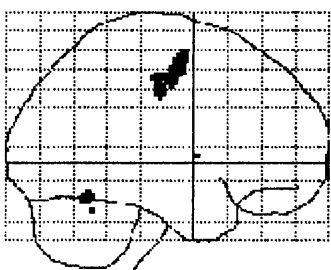
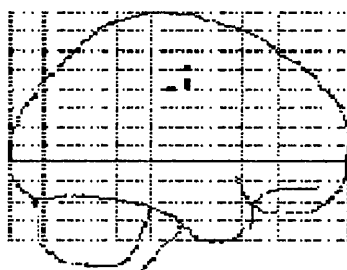


Figure 4.2. A and B. Single session sagittal Maximum Intensity Projections (MIPs) for the motor paradigm. The number of each session is displayed below it. Although thirty-three sessions were collected, only thirty are shown here (sessions 17 23 and 24 were rejected due to movement artifacts). All results are thresholded at $p < 0.05$ corrected for multiple comparisons unless otherwise stated.

**16****18****19****20****21****22****25****26****27****28****29****30****31****32****33**

4.4 Results

4.4.1 Individual session results

Figures 4.2, 4.3 and 4.4 show sagittal maximum intensity projections (MIPs) per session for the motor, cognitive and visual tasks, respectively. Each SPM{Z} MIP shows voxels that survive a threshold of $p < 0.05$, corrected for multiple comparisons. It is immediately obvious that the pattern of activated voxels varies widely between repeated single sessions in our subject. While a grossly homogeneous pattern is evident across single session MIPs of the same paradigm, the spatial distribution of voxels in each MIP is highly variable. Even though striking similarity is evident between certain data sets (e.g. visual sessions 10 and 12, figure 4.4), a large number of sessions from all three paradigms display *no* significantly activated voxels (e.g. visual sessions 4 and 30). The differences are best exemplified by comparing the SPM{Z} of motor session 1 (figure 4.2), which contains 1076 voxels above threshold, and motor session 33, which contains only 5. Results from the cognitive paradigm (figure 4.3) are broadly similar: while the spatial distribution of voxels between MIPs is more comparable than in the motor and visual paradigms, a large number of sessions contain no significantly activated voxels at the chosen threshold.

MIPs are binary statistical images, in which voxels are classified as ‘active’ or ‘inactive’ according to accepted but arbitrary statistical thresholds (for discussions of this issue, see Poline *et al.*, 1996; Genovese *et al.*, 1997; Noll *et al.*, 1997; Cohen and DuBois, 1999; Tegeler *et al.*, 1999). In any of the MIPs of figures 4.2, 4.3 and 4.4, a voxel i could have very different α_i ’s between sessions, yet still pass the threshold and appear to be consistently activated.

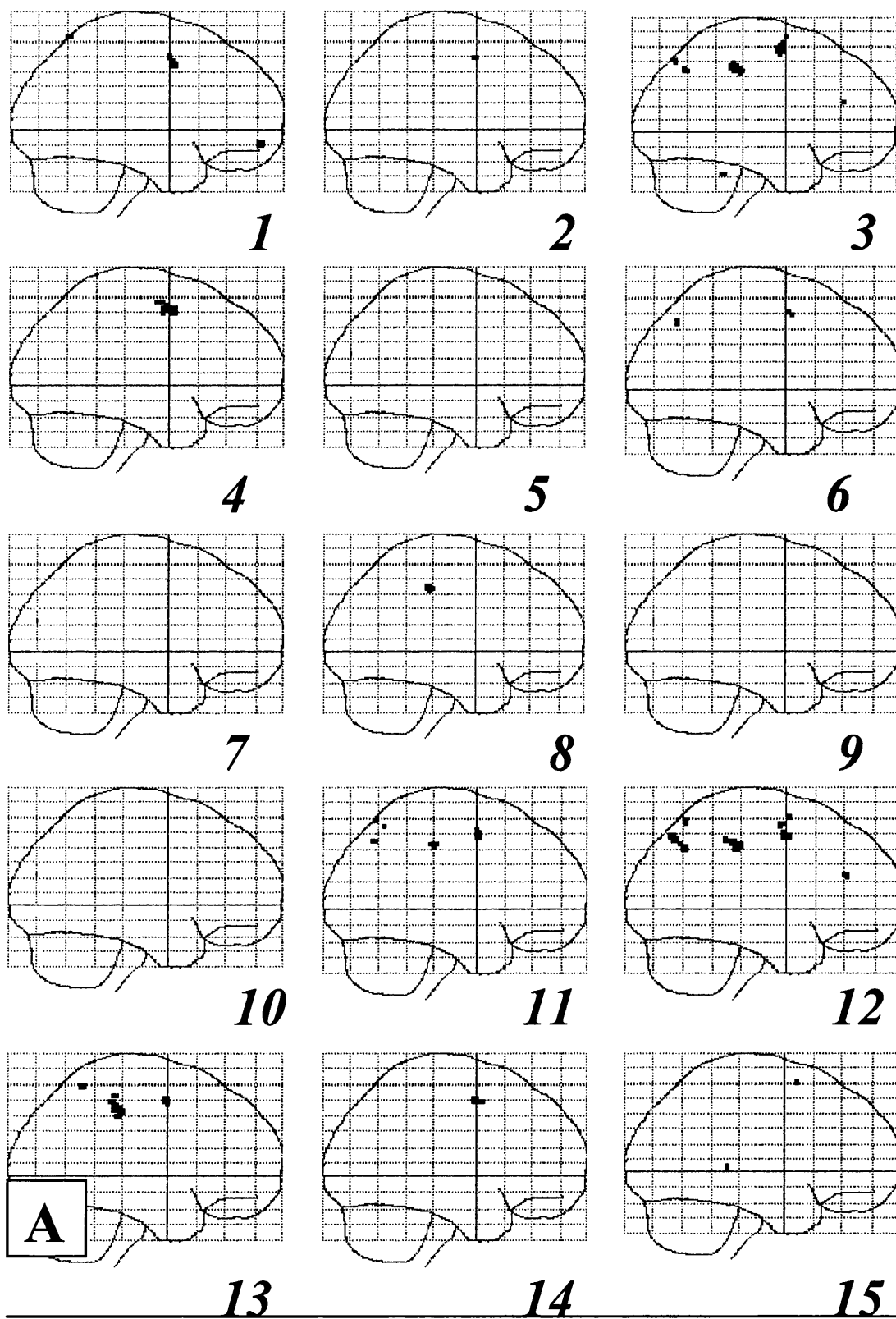
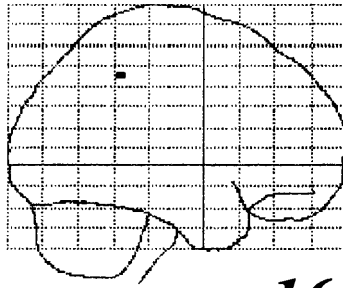
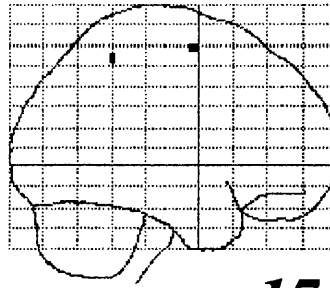
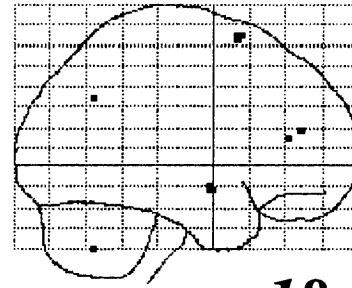
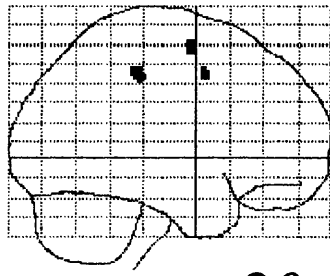
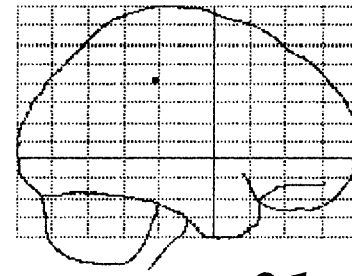
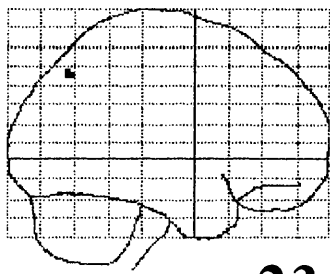
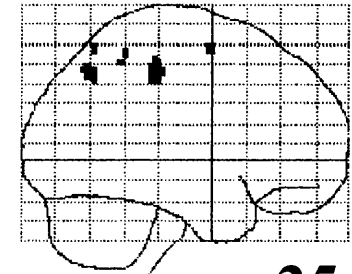
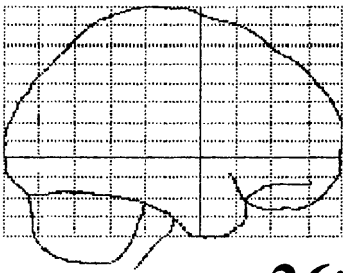
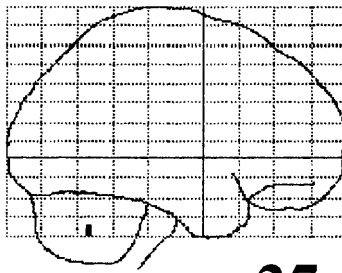
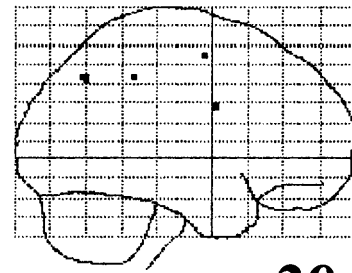
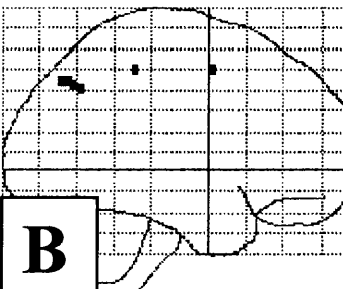
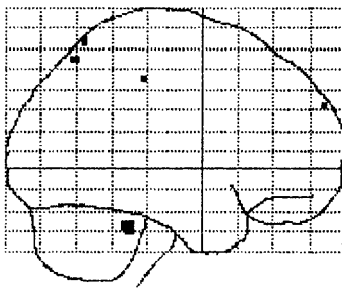
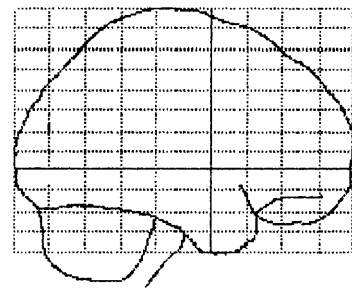


Figure 4.3 A & B. Single session sagittal MIPs for the cognitive paradigm. Similar to figure 4.2, although thirty-three sessions were collected, only thirty are displayed. Sessions marked with ‘*’ contain no significant voxels.

**16****17****18****19****20****21****22****23****25****26*****27****29****B****31****32****33***

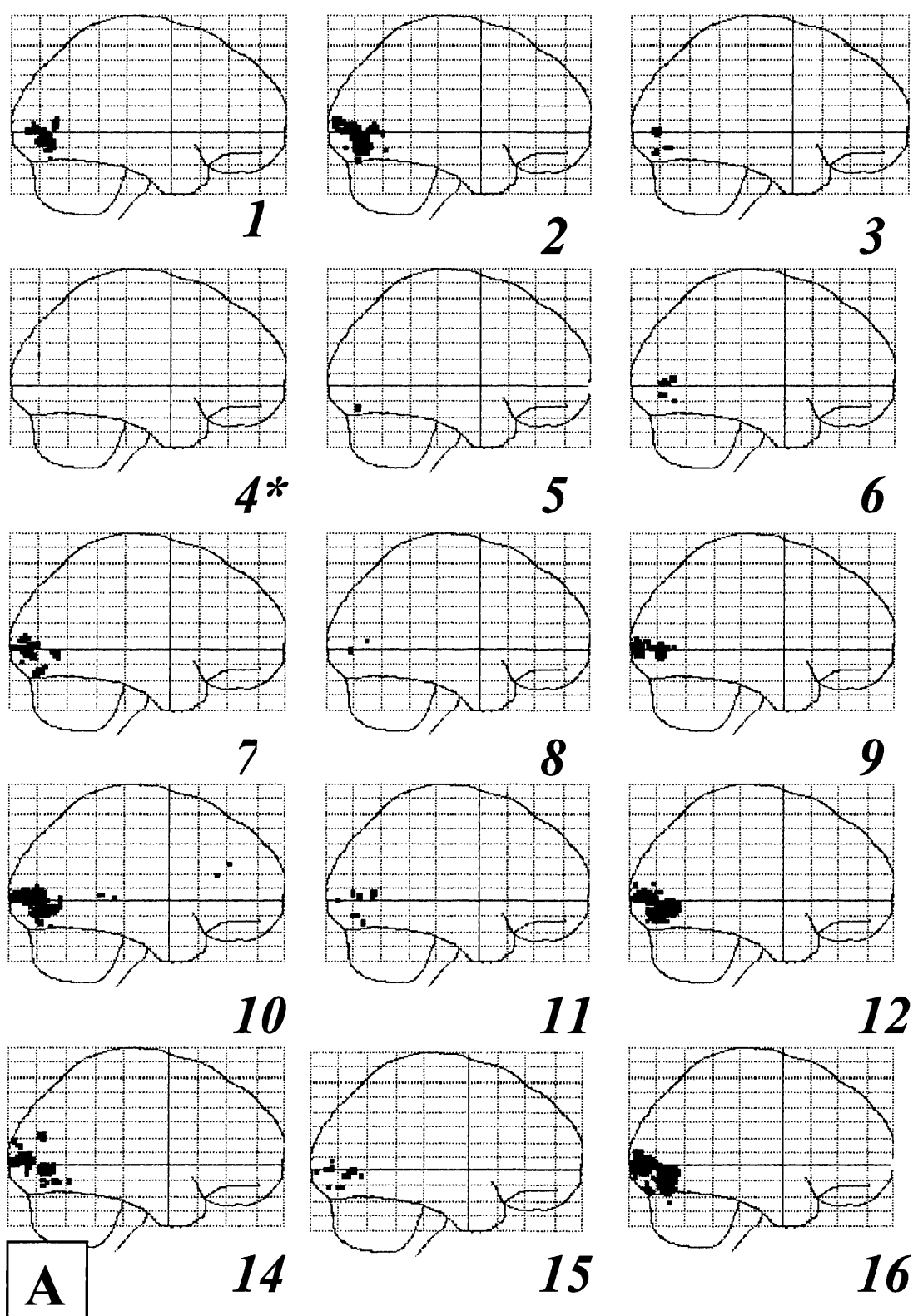
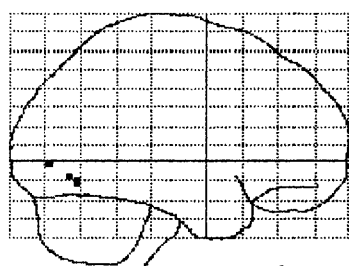
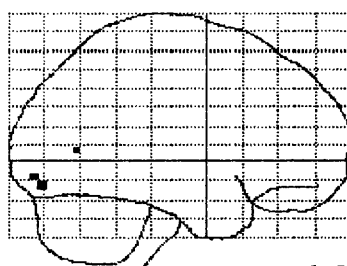
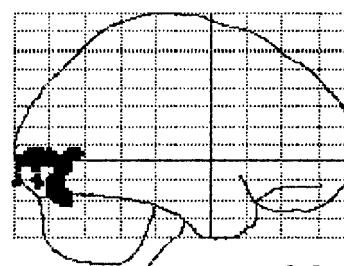
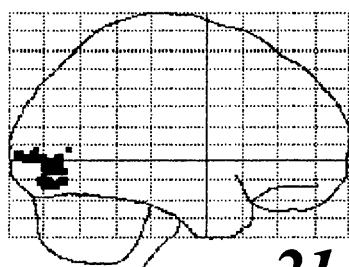
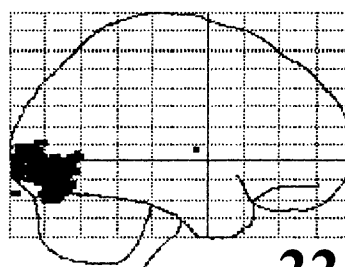
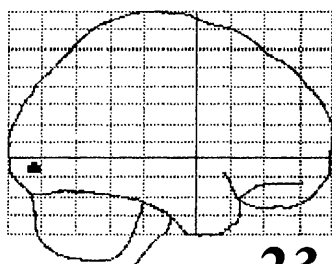
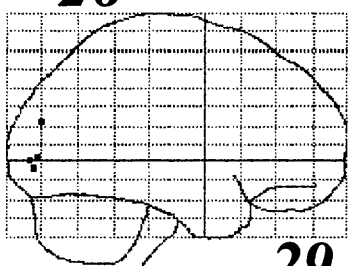
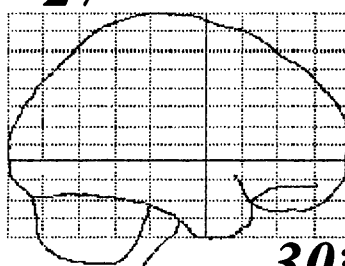
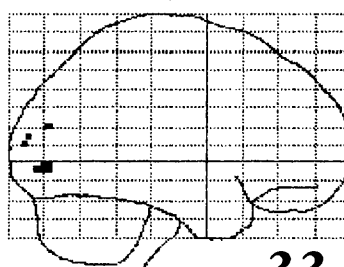


Figure 4.4 A & B. Single session sagittal MIPs for the visual paradigm. As with figures 4.2 and 4.3, only thirty-one sessions are displayed. Sessions marked with ‘*’ contain no significant voxels.

**17****18****19****21****22****23****24****25****26****27****28****29****30*****B****31****32****33**

4.4.2 Multiple Session Analyses

Figures 4.5, 4.6 and 4.7 show the results of the motor, cognitive and visual multiple session analyses, respectively. As noted above, merely examining thresholded statistical maps is perhaps not the best way to examine similarities between sessions. The use of the extra-sum-of-squares (ESS) F -test enables voxels with *statistically significant* variability across all sessions to be identified (figs. 4.5b, 4.6b and 4.7b). If a single session typifies the subject's response, there should be few sessions by condition interactions, and thus the $\text{SPM}\{F\}$ maps from each analysis should display relatively few voxels. By specifically examining the variability of session by condition interactions, the analysis is implicitly limited to voxels that are activated on at least one session by the task. Noise that has a truly random expression over time is unlikely to be modelled sufficiently well by each session's regressor of interest: however, task- correlated noise, such as movement still presents a problem.

4.4.2.1 $\text{ESS}\{F\}$ Analyses (*session by condition interactions*)

Figures 4.5b, 4.6b and 4.7b show the results of each multisession ESS- F test. These SPMs were thresholded at $p < 0.05$ corrected as for the fixed effects $\text{SPM}\{Z\}$ s, reflecting the lack of any *a priori* hypotheses concerning the location of greater variability. An important point to note at this stage is that the ESS F test is free of any constraints about the direction of activation effects observed. As such, although the main concern of this chapter was to examine the variability of activation effects, each $\text{SPM}\{F\}$ also contains voxels with highly variable *deactivations*. In the interests of brevity, these results will not be discussed here.

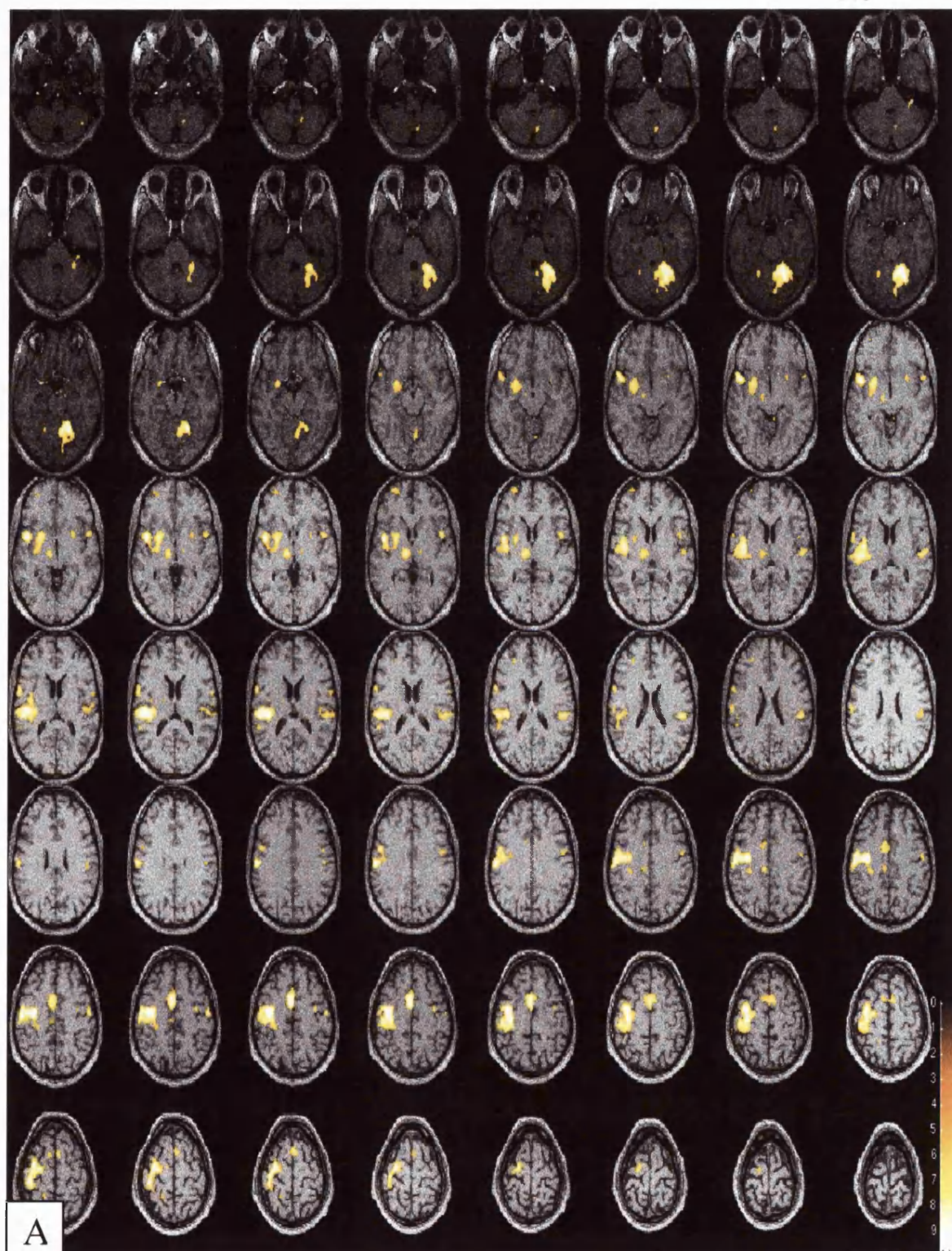
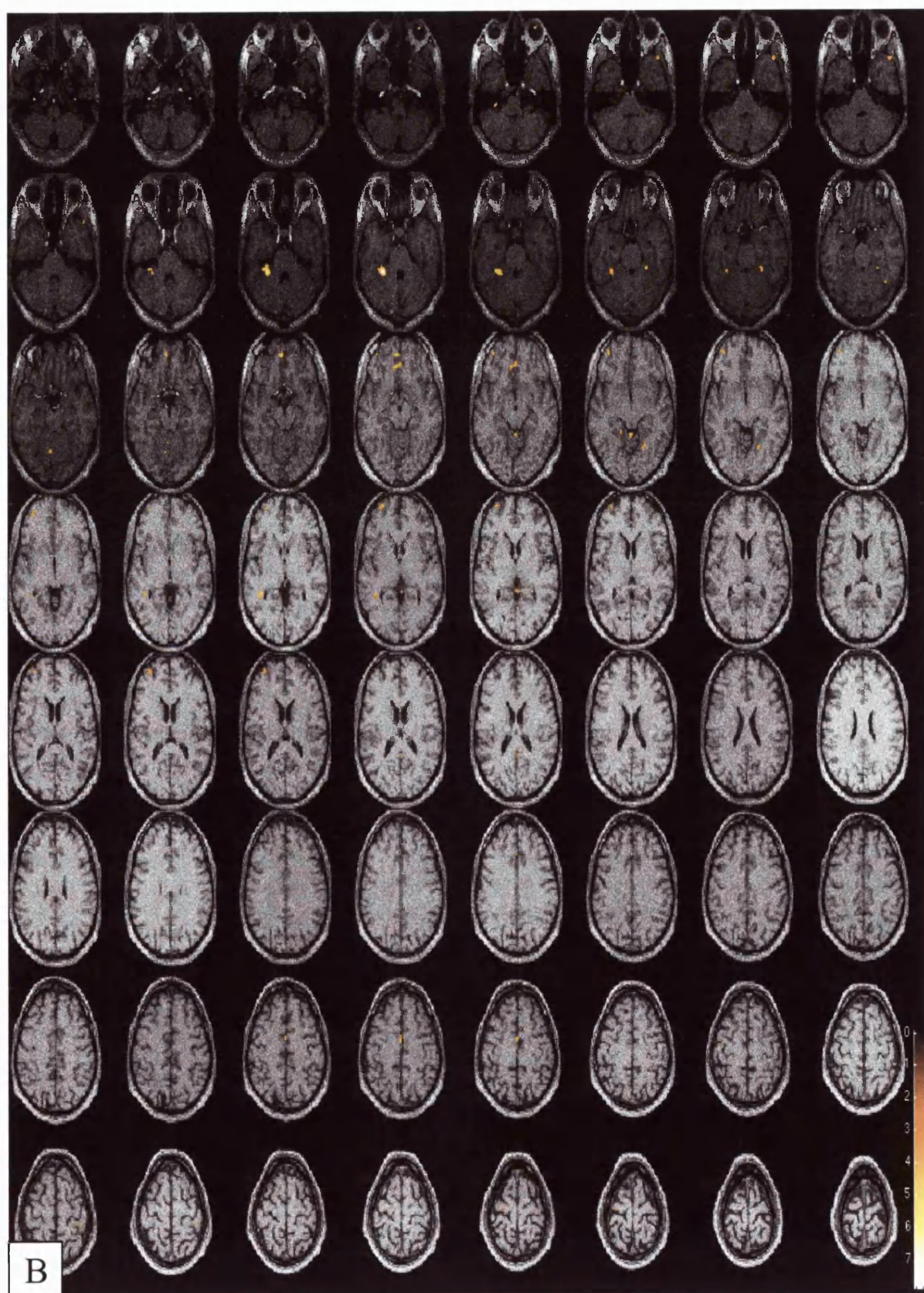
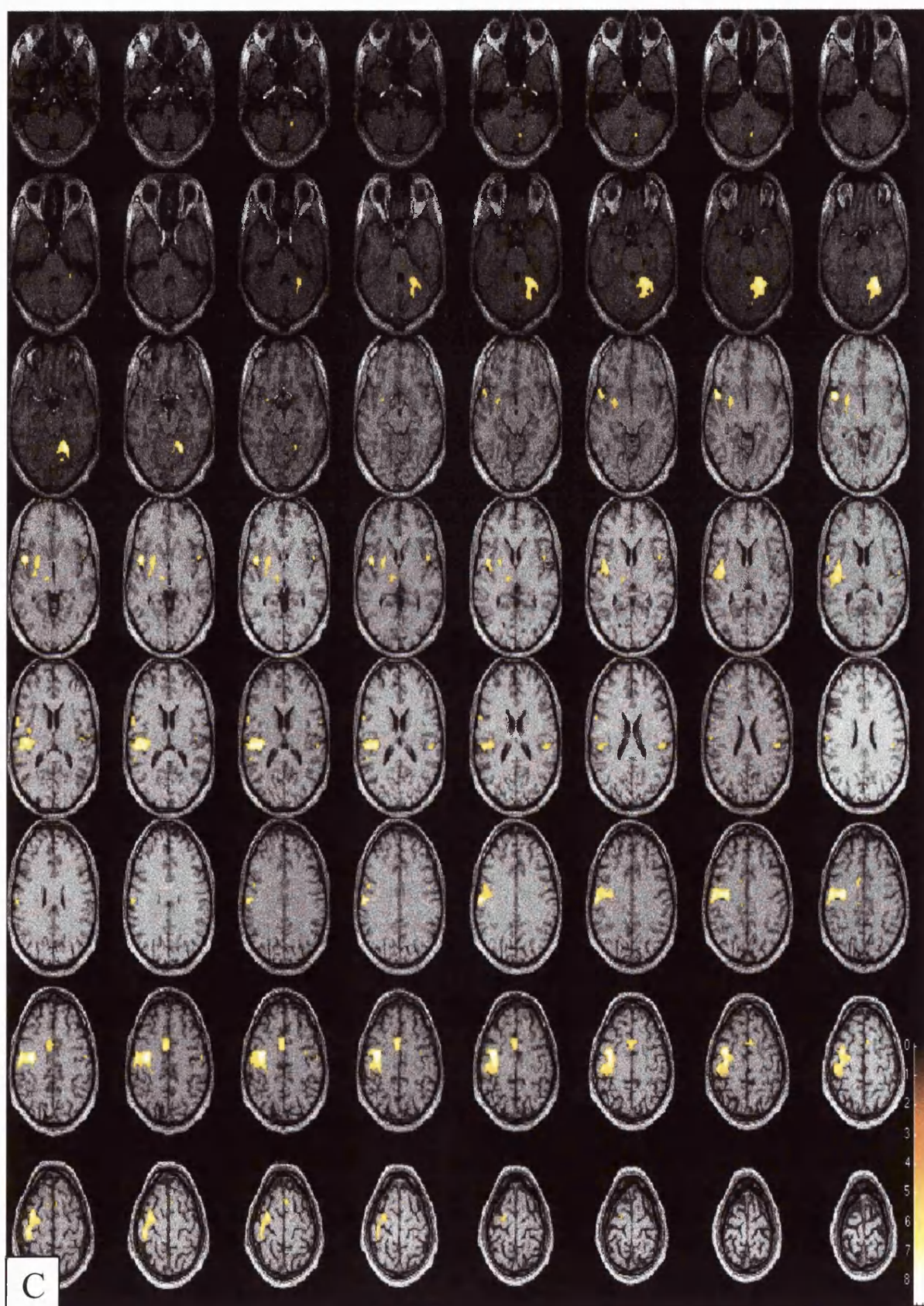


Figure 4.5 A, B & C. Multisession analyses of the motor paradigm, analysed using a fixed effects model (4.5a), extra-sum of squares F test (4.5b), and a random effects model (4.5c). Voxels surviving the statistical threshold are displayed on a coregistered structural scan of the subject to aid the identification of activated areas. Each transverse slice is 2mm thick. The colour bar represents statistical significance, with higher Z and F scores having a brighter colour.





Somewhat surprisingly, each fixed effects SPM{ Z } did not display a high degree of overlap with its corresponding SPM{ F }. This seems logical: voxels that display high variability across all sessions should be less likely to have a significant mean effect across sessions. However, it is possible that a voxel could display high variability, yet still, on average, pass an arbitrarily-defined statistical threshold. The area displaying the highest degree of variability in signal intensity between sessions in the motor paradigm (Figure 4.5b) is located within the white matter of the temporal lobe (-28, -42, -28, $F=7.88$) – an area which does not appear on the fixed effect SPM{ Z } map (figure 5a). A similar area is observed in the cognitive paradigm's SPM{ F } (-38, -40, 6, $F = 7.40$; figure 4.6b); again, this area is not present on the fixed effects SPM{ Z } (figure 4.6a). There was some overlap between voxels which displayed significant variability in each SPM{ F } and the corresponding fixed effects SPM{ Z }: for example, posterior SMA (-2, -8, 52; $F=4.67$), ipsilateral cerebellum (26, -38, -22; $F=5.68$), and contralateral precentral gyrus (-26, -18, 70; $F=4.66$). These voxels were typically located at the edge of a larger cluster of activated voxels. The variability seen may reflect subtle differences in the areal extent of activations at the periphery of large clusters – an effect that may be more prevalent in areas in which the spatial pattern of activation is indicative of underlying intra-areal organisation (e.g. M1 and S1), due to the preponderance of horizontal layer II/III fibres in these areas.

4.4.2.2 Fixed Effects Analyses

The fixed effects analyses of all three tasks (figures 4.5a, 4.6a and 4.7a) displayed areas of activation concordant with previous studies employing a similar task. A number of fMRI studies have used finger-tapping as a stereotypical motor task (e.g. Rao et al., 1993), and we found similar results (Table 1), including contralateral SM1 (Talairach co-ord. -38, -10, 52; Z score=9.77), the ipsilateral anterior lobe of the cerebellum (20, -54, -18; $Z=9.50$), the SMA (-2, -2, 52; $Z=9.39$), contralateral thalamus (-12, -18, 2; $Z=8.84$) and ipsilateral premotor cortex (38, -8, 50; $Z=8.80$). It is notable that the SPM{ Z } also contains areas not previously reported during simple externally paced finger-

tapping paradigm, such as the right inferior parietal lobule (50,-28,24; $Z=8.54$). This is not surprising, as a single α_i of sufficient magnitude may be adequate for any voxel to pass the average significance threshold over sessions and so appear on the multisession fixed effects SPM $\{Z\}$. If the fixed effects SPM $\{Z\}$ is viewed in isolation, it is impossible to know if these are ‘true’ activated voxels which have not been reported in previous studies due to a lack of sensitivity, or areas which display a significantly large activation effect to appear in the multisession fixed effects maps, yet are not consistently activated across sessions.

Similar patterns of results were observed upon inspection of the multisession fixed effects SPM $\{Z\}$ s from the cognitive and visual paradigms (figs. 4.6a and 4.7a.). Although less is known about the functional neuroanatomy of paced random number generation, the results were similar to a recent study (Jahanshahi *et al.*, manuscript submitted). In common with Jahanshahi and colleagues, activation was found in the anterior cingulate cortex, but discrepancies were also apparent e.g. the finding of bilateral calcarine cortex (12, -78, 8, $Z=6.45$ and -6, -72, 20, $Z=5.80$) and left SMA activation (-2,18,50, $Z=8.30$) in the current study. Similarly, the visual paradigm activated striate and extrastriate areas around the calcarine sulcus (Figure 4.7a, Appendix - table 3) including bilateral V1 (14, -86, 2, $Z=9.72$ and -8, -82, 0, $Z=9.57$) in common with studies employing a comparable stimulus (e.g. Kwong *et al.*, 1992). However, as with the other paradigms, a number of areas not previously implicated in the functional neuroanatomy of this task were activated (e.g. the right SMA: 2,2,64, $Z=5.50$).

Clearly, these effects beg closer scrutiny. To examine repeated trials of the same activation paradigm within a particular subject, it is necessary to define *variability* within the same subject. While the fixed effects SPM $\{Z\}$ s identify where voxels are active on average across the observed sessions, they do not permit further generalisation.

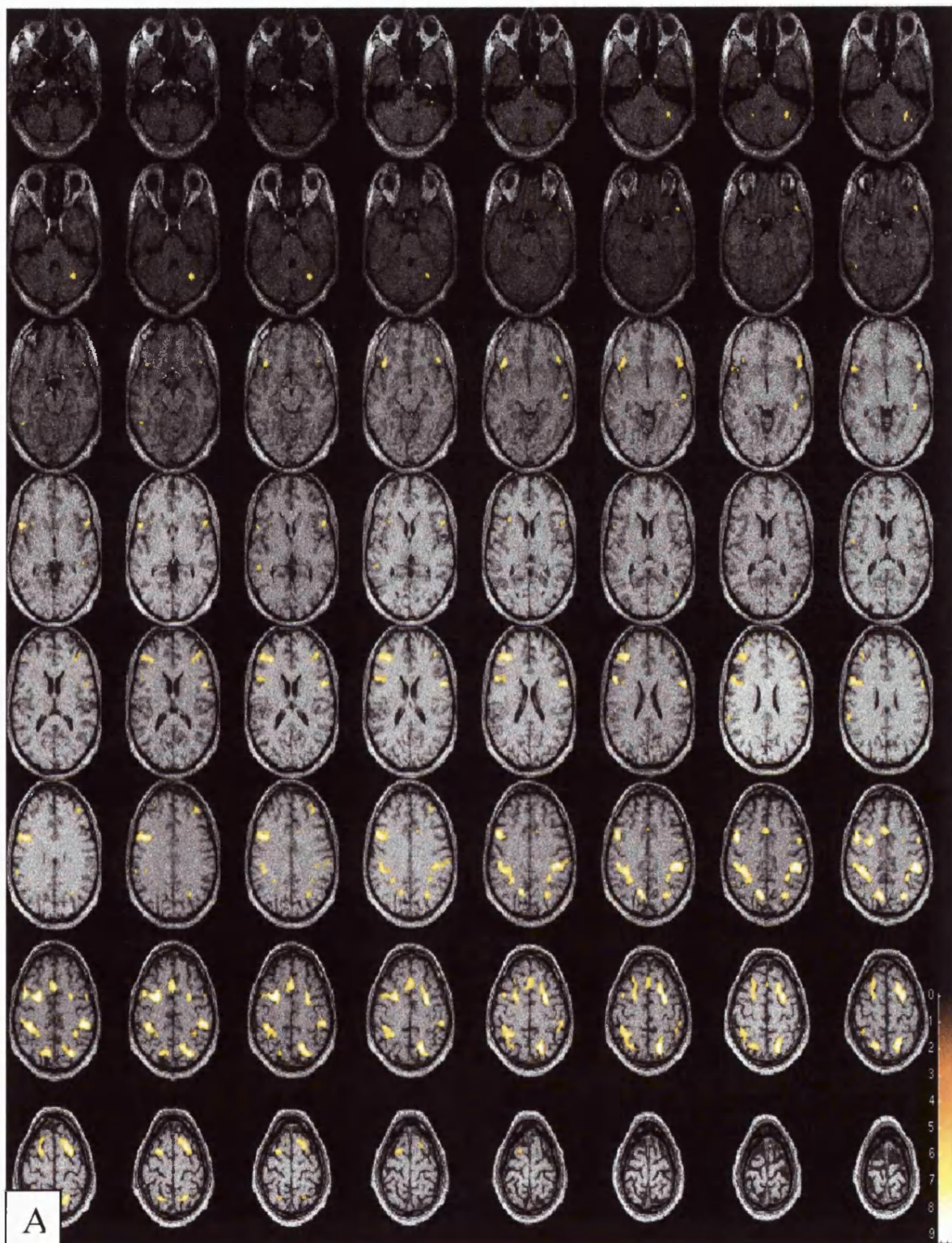
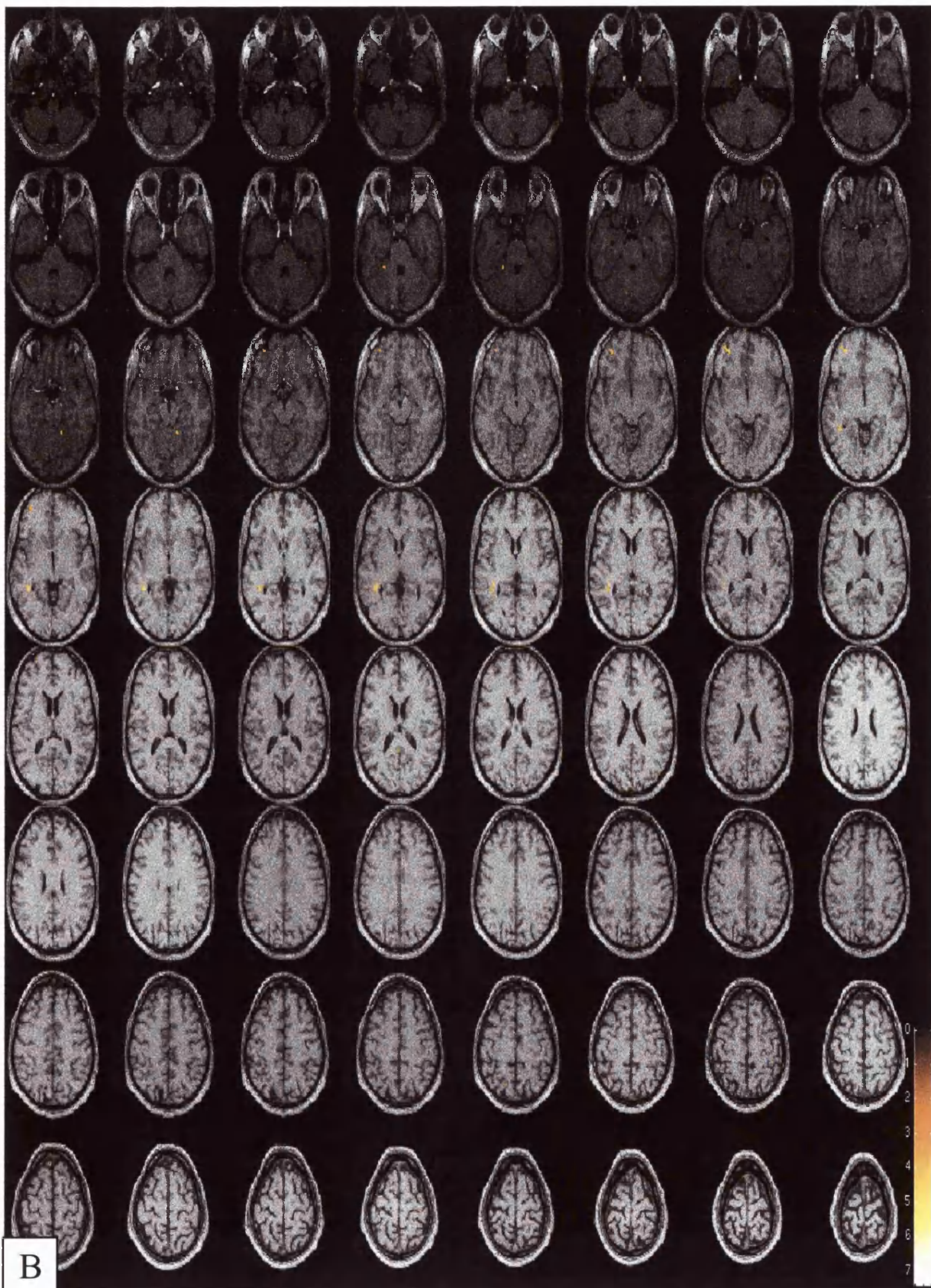
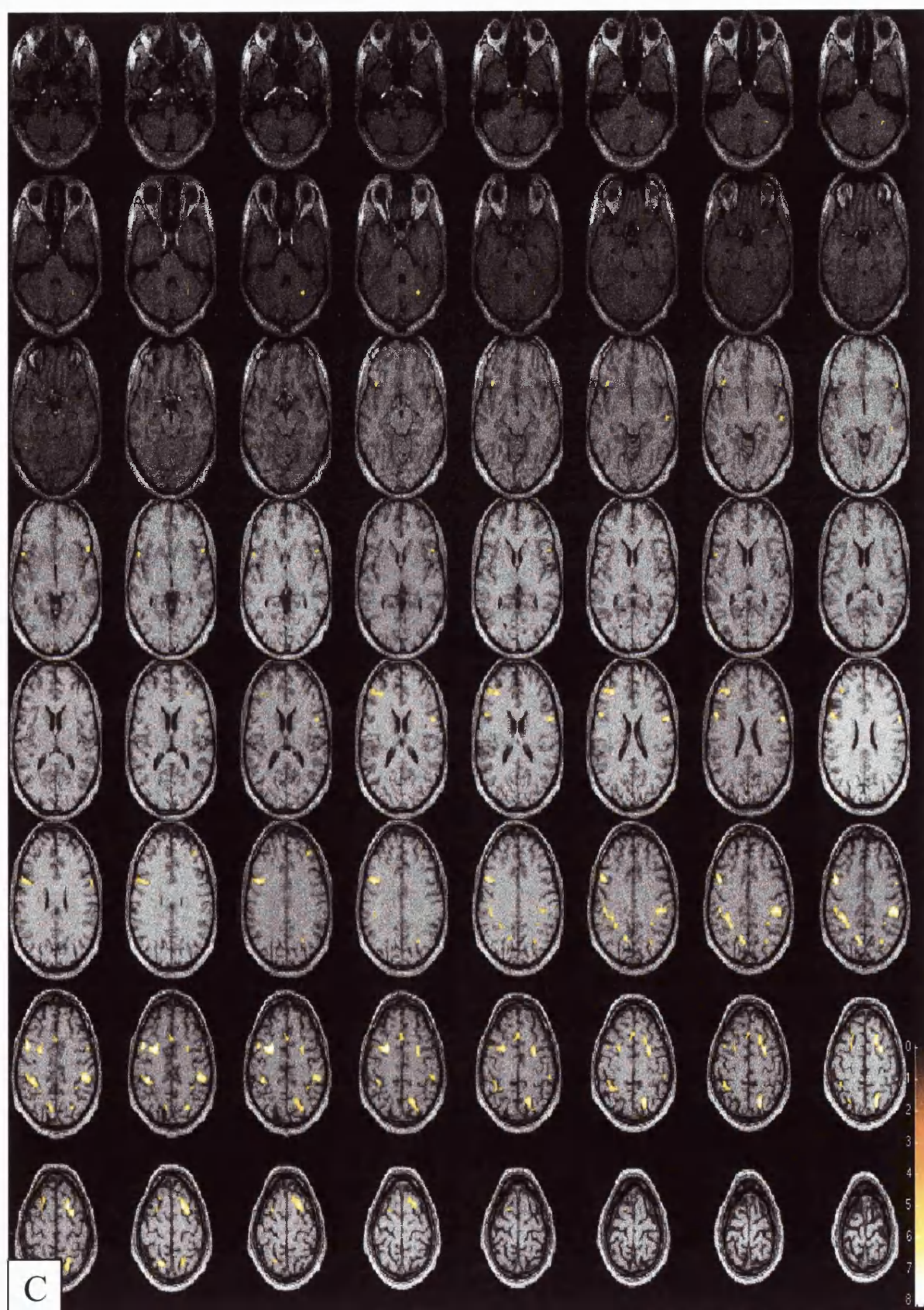


Figure 4.6 A, B & C. Multisession analyses of the cognitive paradigm, analysed using a fixed effects model (4.6a), extra-sum of squares F test (4.6b), and a random effects model (4.6c). Voxels surviving the statistical threshold are displayed on a coregistered structural scan of the subject to aid the identification of activated areas. Each transverse slice is 2mm thick. The colour bar represents statistical significance, with higher Z and F scores having a brighter colour.





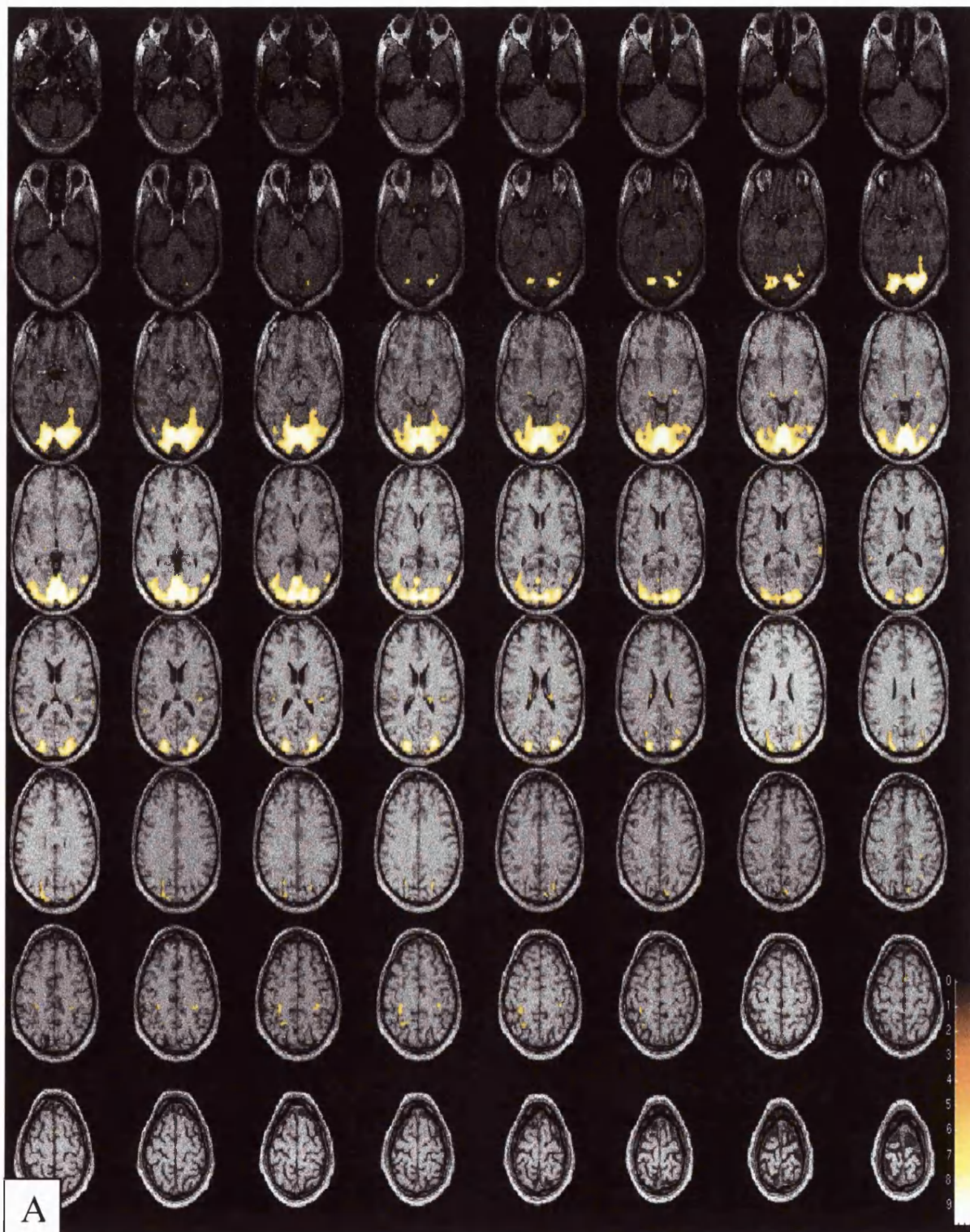
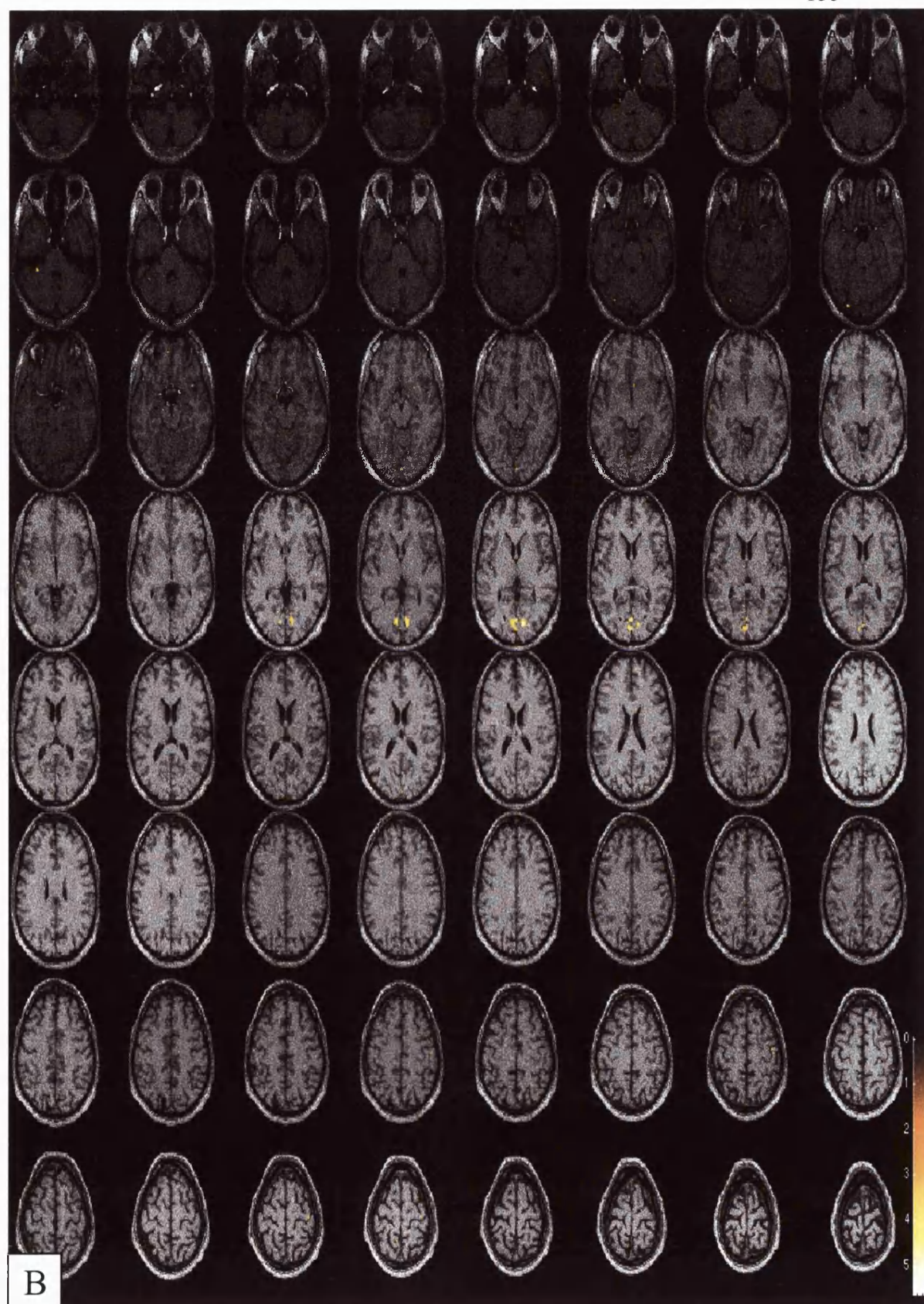
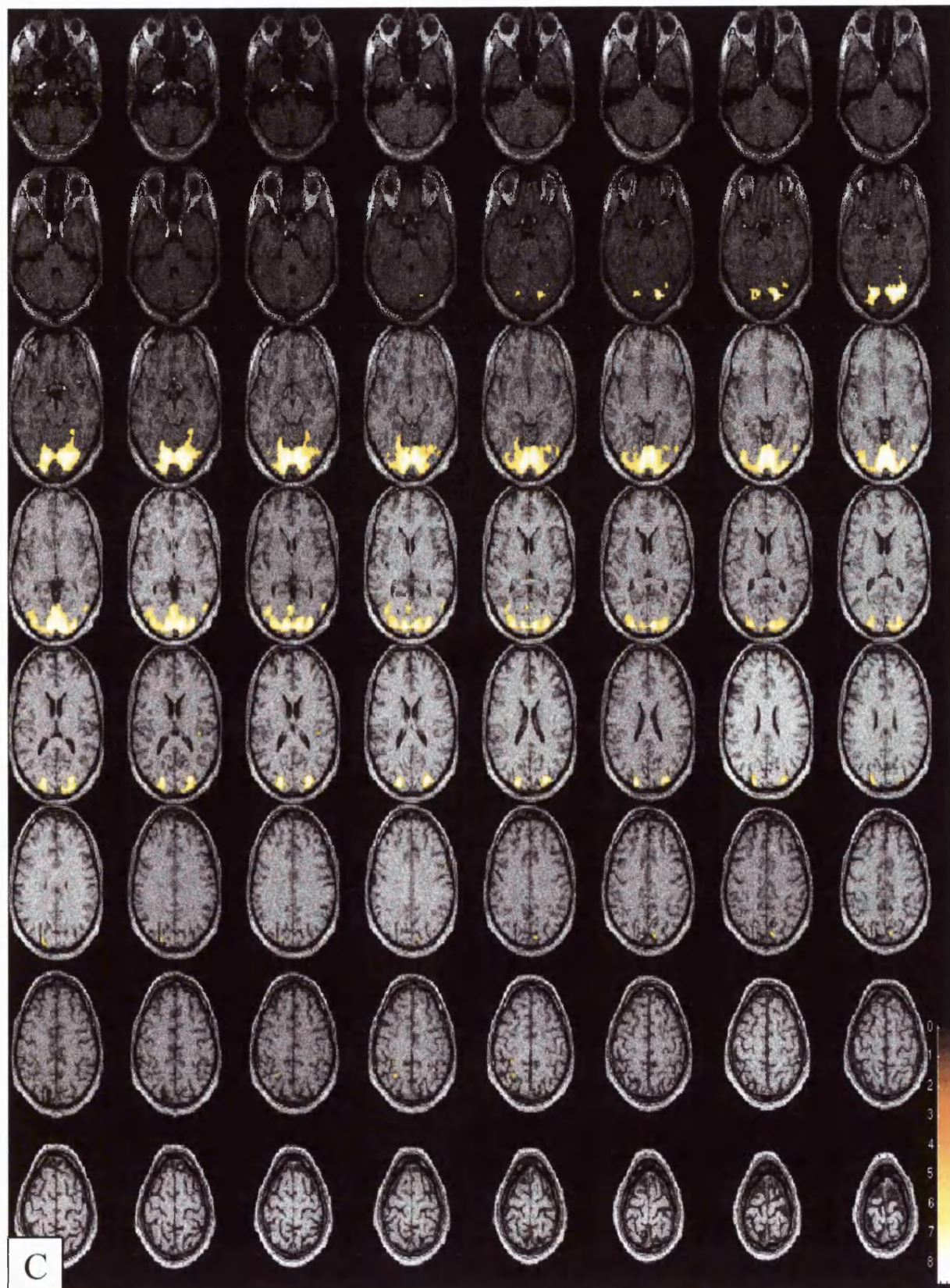


Figure 4.7 A, B, & C. Multisession analyses of the visual paradigm, analysed using a fixed effects model (4.7a), extra-sum of squares F test (4.7b), and a random effects model (4.7c). Voxels surviving the statistical threshold are displayed on a coregistered structural scan of the subject to aid the identification of activated areas. Each transverse slice is 2mm thick. The colour bar represents statistical significance, with higher Z and F scores having a brighter colour.





4.4.2.3 Random Effects Analyses

Figures 4.5c, 4.6c and 4.7c show random effects analyses of each multisession data set. These $\text{SPM}\{Z\}$ s have been weighted by both between-session and within-session variances of each data set. Upon visual inspection, the random effects $\text{SPM}\{Z\}$ s resemble a ‘cleaned up’ version of the fixed effects $\text{SPM}\{Z\}$ s, and each paradigm’s pattern of results is now more concordant with previous studies. There are still, however, areas within the fixed effects $\text{SPM}\{Z\}$ that one would not expect, *a priori*, to be involved in the functional neuroanatomy of each task (Appendix - Tables 1a, 2a and 3a). For example, the motor random effects $\text{SPM}\{Z\}$ (figure 4.5c) displays prominent bilateral auditory cortex activation (-42, -28, 18, $Z=8.14$ and 48, -18, 14, $Z=6.16$). This was not expected, as pacing tones were played during both rest and activation epochs during each motor session. This result may reflect attentional modulation of auditory areas (Woodruff *et al.*, 1996; Grady *et al.*, 1997), as the tones’ salience was different between the rest and activation conditions. Whatever the neurobiological explanation for this result, it is sufficient to acknowledge that this pattern of activation was not predicted. If only a single session from the subject had been acquired it would be impossible to comment further on these activations. Even a multisession fixed effects would not have helped: it would be difficult to identify if the activation was driven by a small number of sessions only, or was indeed a true activation. The majority of voxels present in both the fixed effects $\text{SPM}\{Z\}$ and the interaction $\text{SPM}\{F\}$ do not appear in the random effects $\text{SPM}\{Z\}$ s. Properly accounting for between-session variance means that these voxels no longer survive a threshold of $p<0.05$, corrected for multiple comparisons. This demonstrates that combining multiple sampling of sessions with a statistical model with more than one component of variance correctly accounts for session by condition interactions.

Figures 4.8 and 4.9 show voxels that typify different patterns of behaviour across sessions, using the motor paradigm as an example. Figures 4.8a and 4.9a show a voxel in posterior SMA (-2, -8, -52) which survives a threshold of $p<0.05$,

corrected for multiple comparisons, in the multisession fixed effects analysis. However, this voxel also displays significant session by condition interactions (as seen by its appearance on the ESS F map), and thus fails to survive correction when a random effects model is used. This voxel is an excellent example of variability in ‘active’ voxels. When one examines its parameter estimates by session (Figure 4.9a), it is striking how stable it appears over some sessions (for example, sessions 15 to 18), and yet how variable its behaviour is over all sessions. The histogram of parameter estimates in Figure 4.9a shows that although only one session has a parameter estimate of greater than 1.5, this can still weight the average activation effect over all sessions.

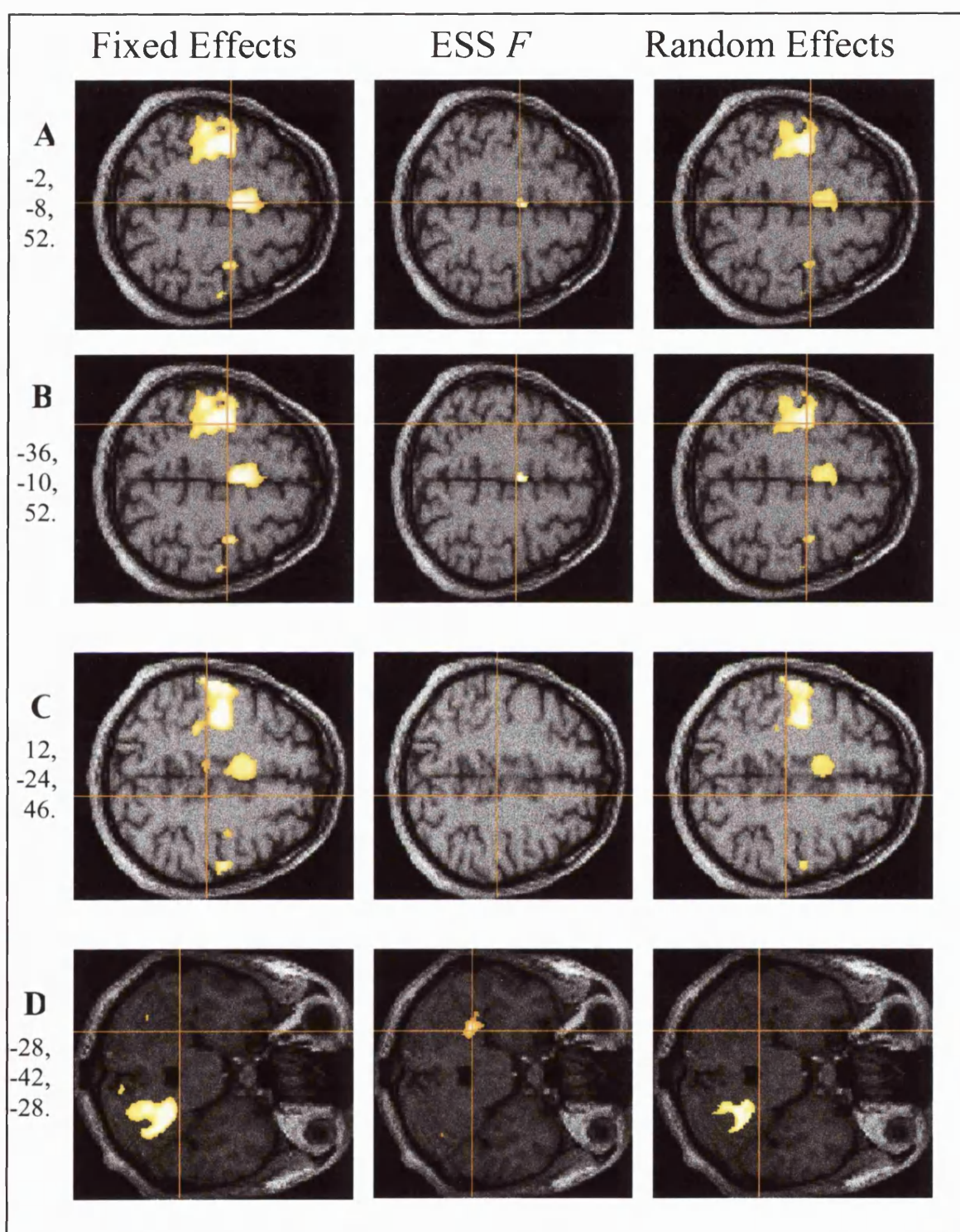


Figure 4.8. Examples of voxels from the multisession motor analyses that typify different kinds of statistical significance. Voxel A is significant at a fixed effects level, but variable enough to not appear in a random effects analysis. Voxel B is significant at both a fixed and random effects level, and does not display significant session by condition interaction terms (it does not appear in the ESS F). Voxel C is significant at a fixed effects level, and is not significantly variable across sessions, but does not possess a random effects level of significance. Voxel D has significance at neither fixed or random effects level, but is significantly variable between sessions to appear in the ESS F .

When the variability of responses over sessions is addressed in the random effects analysis, the voxel loses significance. The voxel in left primary motor cortex (-36, -10, 52) displayed in Figures 4.8b and 4.9b typifies voxels that survive statistical thresholds in both fixed and random effects analyses. This voxel shows remarkably similar parameter estimates over all sessions (Figure 4.9b). The voxel in Figures 4.8c and 4.9c is one that, although not significantly variable (not shown on the $ESS\{F\}$ map in Figure 4.8c), does not survive correction when a random effects model is used.

Voxels within each $SPM\{F\}$ can be thought of as belonging to various classes: those which are not activated by each paradigm, but display high variability of their parameter estimates (Figures 4.8d and 4.9d); ‘true’ active or deactivated voxels, surviving both fixed and random effects definitions of variability (Figures 4.8b and 4.9b), voxels which are significant at a fixed effects level but are significantly variable and do not survive correction for between-session variance (Figures 4.8a and 4.9a); and voxels which, while not surviving a random effects analysis, are not significantly variable as defined by the $ESS\{F\}$ map (Figures 4.8c and 4.9c).

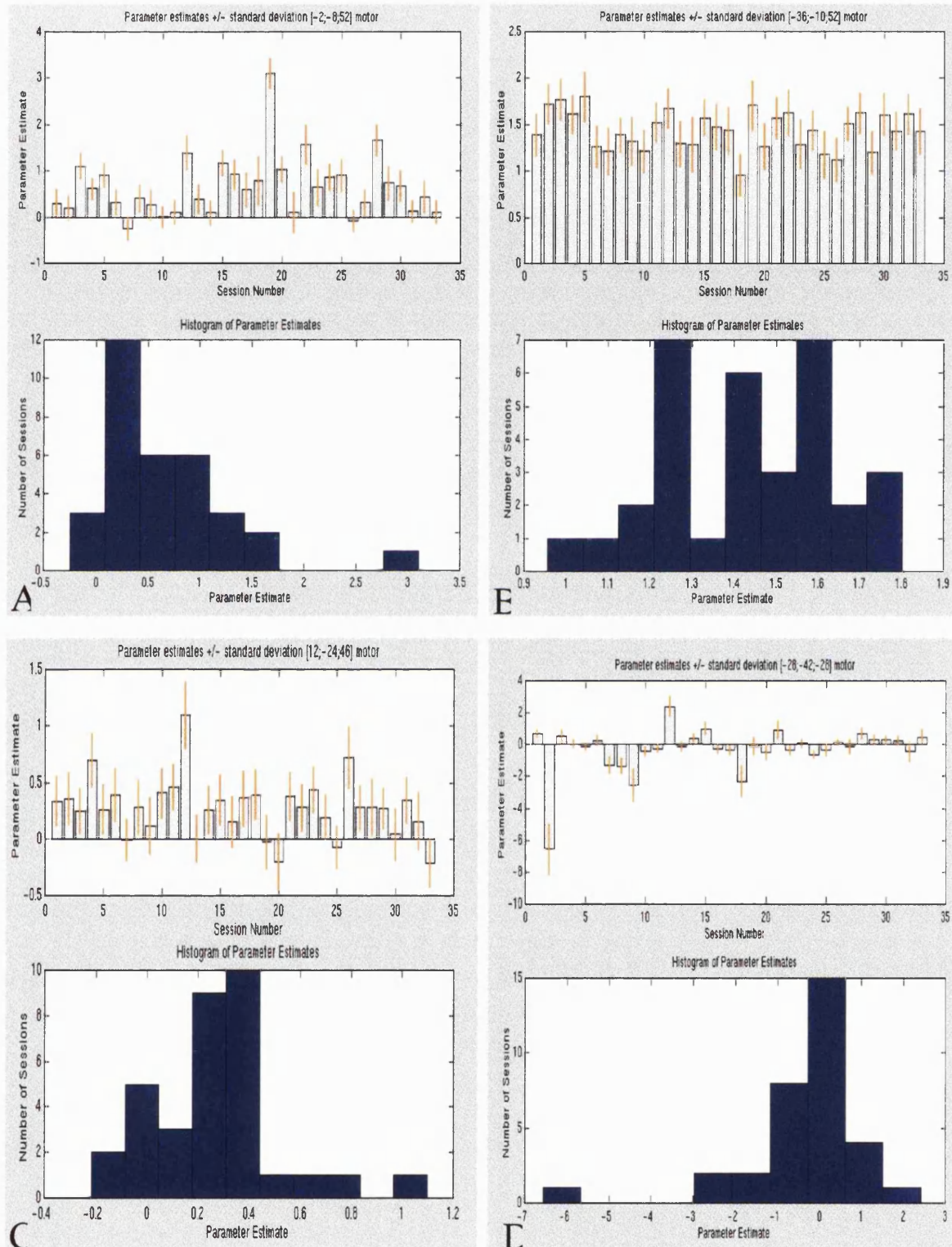


Figure 4.9. Session by session plots of the parameter estimates (α_i) and their standard deviations (red bars) of voxels from figure 4.8 (A-D). The histograms below each plot show the spread of values of α across all sessions.

4.5 Discussion

The generality of any experimental result is an issue which confronts all researchers, independent of experimental discipline (Abelson, 1995). Contextual effects may contaminate the results of any isolated experiment, and fMRI is no exception. As fMRI is an ideal experimental technique to examine questions that require serial scanning sessions, there have been a number of previous studies that sought to examine the reproducibility of fMRI data. Researchers have examined similar activation paradigms across laboratories (Casey *et al.*, 1998), imaging modalities (Ojemann *et al.*, 1998), and sessions (Le *et al.*, 1997; Noll *et al.*, 1997; Rombouts *et al.*, 1998; Cohen *et al.*, 1999). These studies sought to characterise the reproducibility of fMRI data, and so tried to ensure that each session was carried out similarly to those preceding it.

Examining the reproducibility of fMRI data is an important question. The question being asked in the current study was however subtly different: how well does a single session data set from a single subject typify the subject's response across multiple sessions, using a variety of activation paradigms? By examining the variability in the magnitude of activation effects across a large number of sessions, I accepted that each session would be different. Indeed, it was exactly this between session variability that was of interest – *exact* replications of experimental results are unlikely.

Significant session by condition interactions occurred in each of the multisession data sets examined, as illustrated by the respective ESS SPM{ F }s. The results are evidence of the influence of session context on the results of individual sessions, and show the potential danger of drawing general conclusions from individual sessions analysed in isolation when nothing is known about reproducibility. If one samples more sessions, each successive session acquired facilitates a better estimation of between session variance, thereby increasing power to detect the underlying response.

4.5.1 Differences in the Generality of Different Activation Paradigms

Different activation paradigms were used to ensure that the results of the study

would not be limited to a single class of activation task. The majority of work examining repeatability in fMRI has employed simple visual or motor paradigms, though there has been limited use of ‘higher’ cognitive activation paradigms (Yetkin *et al.*, 1996; Noll *et al.*, 1997; Casey *et al.*, 1998). My initial expectations were that the visual task would prove to have the fewest session by condition interactions and the cognitive task the most. While the number or magnitude of voxels in each paradigm’s $SPM\{F\}$ were not explicitly compared, it was surprising to note that the visual $SPM\{F\}$ appeared to have prominent bilateral areas of high variability in primary visual cortex (figure 7b), while the cognitive $SPM\{F\}$ contained few voxels which overlapped with areas activated consistently by the activation task itself. As mentioned above, the visual activations were located in areas not activated on average by the task itself, but lay in close proximity to primary visual cortex. Slight differences in visual field coverage by our visual stimulus may have caused these effects, producing a variable rim around a core of visual cortex that was consistently stimulated across sessions. A further possibility is that these results reflect the high concentration of venules in the microvasculature of visual cortex (Marinkovic *et al.*, 1995), which may cause higher variability in its response to afferent stimulation.

4.5.2 Sources of Session by Condition Interactions

Identifying the sources of intersession variance is important. For example, it is possible that spatial pre-processing may affect intersession variance quite independently of underlying physical or physiological variability. The realignment procedure used (Ashburner *et al.*, 1997) seeks to minimise the sum-of-squares (SoS) differences between successive volumes and a reference (here, the first volume in the time-series). Since each paradigm induces intensity changes in voxels (i.e. it ‘activates’ them), volumes acquired during the ‘on’ period of each paradigm will contain focal intensity differences from volumes acquired during ‘rest’. As a successful realignment between two volumes relies on the volumes used being similar rigid bodies, differing only in their alignment in space, the paradigm-induced intensity changes will affect the efficacy of

alignment and may ultimately raise intersession (and perhaps *intrasession*) variance. In addition, similar effects in voxels lying at a tissue boundary (voxels in the walls of the ventricles, for example) may result from simple repositioning of the subject between sessions, causing session-specific partial volume effects.

Examples such as the above make it difficult to conclude if the variability observed is attributable to differences in: i) the scanning environment (e.g. position of subject within headcoil); or ii) preprocessing (misalignment). For this reason I did not attempt to assess systematically the relative magnitudes of different sources of variance on session reproducibility, as in some previous studies (e.g. Noll et al., 1997). I can be more confident that session by condition interactions that could be attributable to performance differences were minimised, given the efforts employed to ensure that the subject was scanned using tasks that should not improve upon repetition. Each successive scanning session was treated as though it was the first time that the subject had been scanned, to examine the potential influence of session context on a single session experiment (acknowledging that the ‘Groundhog Day’ effect may exert unknown influences on variability). It could be argued that systematic differences in the subject’s performance across sessions may have resulted in the session by condition interactions observed, as the repeated execution of any active task or protocol of sensory stimulation may result in habituation or learning effects (e.g. Karni et al., 1995). Activation tasks were chosen to minimise this possibility. The subject was pretrained on the motor task, and the task frequency was chosen to lie within a range previously demonstrated by Blinkenberg and colleagues (1996) to have a low error rate (between 1 and 2Hz). Similarly, a stable rate of number generation was chosen for the cognitive task (informed by the results of Jahanshahi *et al.*, manuscript submitted). Although subject performance on this task was not recorded (primarily because of the motion it would produce), performance at random number generation remains stable over a number of repetitions (Evans *et al.*, 1980). Furthermore, a preliminary MANCOVA analysis of the motor data set

examining the effects of session revealed no systematic expression of the experimental variance over subsequent sessions (data not shown). Although learning effects may exhibit complex temporal dynamics, the distribution of parameter estimates over sessions suggests random variation (Figure 8) around a 'true' mean parameter estimate. However, without independent measures of task performance, it is difficult to entirely rule out between-session habituation or learning-related changes in activation.

4.5.3 Stability of fMRI Results across Sessions - Consequences for Longitudinal Studies

As noted previously, fMRI is ideally suited to the examination of learning or recovery of function studies. These studies are typically predicated on the assumption that the experimental effects will be large enough to ensure their detection when compared to nonspecific between-session effects. Because of the considerable time that must typically be devoted to such studies, it would be useful to have some idea of the relative magnitudes of each effect before beginning. The current study does not really address the issue of signal to noise in longitudinal fMRI studies. As *any* difference between sessions is a session by condition interaction, any study which purports to focus on session by condition interactions produced by the experimental manipulation must ensure that nonspecific session by condition interactions can be efficiently controlled (for a discussion of these issues, see Petersson *et al.*, 1999). The three tasks examined were designed to exhibit limited session by condition interactions in subject performance. As such, current results cannot be used to address the validity of longitudinal fMRI studies. It is worthwhile noting, however, that the stability of these results suggests that longitudinal studies that produce unambiguous results should be feasible.

4.5.4 Use of Thresholded Statistical Maps to Analyse Session Generality

Typically, the results of neuroimaging experiments are displayed using binarised statistical maps. In this fashion, voxels that pass a predetermined

statistical threshold are classified as ‘active’, and other voxels as ‘inactive’. Although the utility and clarity of the results motivate this approach, much of the richness of functional neuroimaging data sets is removed. Attempts to examine the test-retest reliability of fMRI using measures such as ‘voxel-counting’ on thresholded maps therefore suffer from two problems: an essentially arbitrarily-defined statistical threshold, and the loss of complexity which accompanies any method that has to classify voxels as either ‘active’ or ‘inactive’. Most previous studies examining reproducibility have adopted this approach while tacitly acknowledging its limitations (Tegeler et al., 1999; Noll et al., 1997). My data sets were characterised by examining between-session variance in activations, and not by merely examining which voxels passed an arbitrarily set threshold on successive sessions. The differences between the two approaches are apparent when one compares the results of the single session analyses (figures 2,3 and 4) with the later multi-session analyses (figures 5,6 and 7). Generally a failure to detect activation within a single session may say more about the sensitivity of the experiment than about the presence of an experimental effect (Poline *et al.*, 1996). Certain areas may therefore appear more variable than they truly are if voxel-counting methods are employed.

4.5.5 Effects of Sample Size on the Analysis of Generality

The results demonstrate the need for a large sample size when examining how well a single fMRI session exemplifies a subject’s responses. The plots of parameter estimates by session in figure 9 show that voxels in which significant session by condition interactions were found over all sessions appear surprisingly stable when examined over a small number of sessions (for example, sessions 27-29 in figure 9c are almost identical). This effect has been termed ‘the law of small numbers’ (Tversky *et al.*, 1971) – the tendency to ascribe a lack of variability to small sample groups (see Grabowski et al, 1996 for a discussion of the power of small sample designs in PET). My use of a large number of sessions allowed a fuller characterisation of variability that may have been missed by previous studies that used five repeated sessions (at most) on the same subject.

Furthermore, the sessions were collected over a longer time period than most other studies (two months).

However, it is equally valid to argue that the present larger sample size contributes to the sensitivity of the analysis to reasonably small session effects. If the sample size is large enough a statistically significant difference will always be found – this is merely an example of the fallacy of statistical inference. This is a valid criticism, but I believe that an analysis of 30 sessions is an appropriate sample size for the purposes of this study. The existence of significantly variable voxels necessitates the use of a random effects model to allow the experimenter to truly generalise their results to the subject.

4.5.6 Levels of Inference Arising from Fixed and Random Effects Models

Worsley and colleagues (1992) first suggested the use of a ‘summary statistic’ approach to the analysis of functional neuroimaging data. However, the implementation used in the current study is that of Holmes and Friston (1998), who suggested random effects analyses for balanced designs in neuroimaging employing a general linear framework to allow for the between subject variance component in multi-subject designs. As discussed previously, the random effects analysis confers generality, but with a concomitant loss of sensitivity due to the inevitably low degrees of freedom. It was assumed that the ε_i were Normally distributed, and this assumption was incorporated into all random-effects level models. However, by examining figure 9 it is clear that the ε_i do not necessarily conform to this distribution. If the voxel in figure 9a is examined it is clear that this voxel has a skewed-right distribution. Indeed, if one asks a simpler question of the voxel in figure 9a (how often is $\alpha > 0$) and uses a simple sign test, the probability of getting 31/33 positive α 's is $< 7 \times 10^{-8}$. Yet this voxel does not pass the random effects analysis used here.

This is only a single voxel. However, it casts doubts on assumptions of Normality for the ε_i , and it is clear that further investigation is needed into the distribution of between-session variance. The development of random-effects models that do not require prior assumptions of the distribution of residuals may

be needed to address this issue. The use of random effects models in the analysis of fMRI data is a recent addition to the canon of neuroimaging analysis methods. It is established practice in experimental psychology to treat subjects as random factors. In fact, a growing number of experimental psychologists now argue that even *stimuli* should be treated as random factors (reviewed in Siemer, 1997), so that experimental results can be generalised to the population of stimuli.

These concerns are valid ones. Yet it is wise to learn from previous debates concerning these topics. Although he was primarily concerned with the generalisability of experimental stimuli, Clark's (1973) initial proposal that multilevel modeling should be used more frequently highlighted an obvious problem. *Treating* a sample as random does not mean it has actually been *selected* randomly from a population. Although I could argue that by using a random effects analysis in the study, it is possible to generalise the results to the subject as a putative population, there has been a very limited sampling of the subject's responses. All scanning sessions were collected over a two-month period, and session times were selected in a biased manner: near midday and near 6pm in the evening. It is not elegant, however, to have to state that 'the results generalise to the population of possible sessions sampled from the subject over a period of two months, using the resources available in the laboratory'. In practice, these caveats are usually accepted. Indeed, the use of random effects models to ensure the correct level of inference in multisubject fMRI analyses rarely addresses the other sources of systematic variation in the population that investigators are generalising to (usually male, Caucasian right-handers who respond to advertisements and financial reward). However, adopting a random effects model does afford some protection against inappropriate generalisation of results, as noted by Clark and colleagues (1976) in the reply to their critics.

Although I have shown that with an appropriate statistical model and a large sample of sessions it is possible to obtain robust results, a number of issues remain unanswered. In particular, I would hesitate before generalising the current results to other centres, subjects, or activation paradigms, as between-session

variance may vary greatly depending on the context under which it is studied.

4.6 Conclusions

In this chapter I have described the results of an experiment designed to examine intersession variance in fMRI during the performance of simple visual, motor and cognitive tasks by a single subject. A number of interesting points are raised by the data.

First, analysing the data session by session it is evident that binarised statistical maps, though convenient, are not a useful tool for the evaluation of intersession variability. When examining each multisession dataset, by paradigm, evidence of significant session by condition interactions was found. This result demonstrates that session context effects have a significant effect on fMRI data, and illustrates that a single session should be considered merely as a single sample of a subject's responses to the experimental intervention employed. As a large number of sessions across all paradigms were studied, I then compared the differences between analysing these data using either fixed- or random-effects linear models, the latter being a recent addition to neuroimaging analysis. Although random effects analyses are certainly useful as they allow inference about experimental effects to be extended to the population which the sessions were sampled from, the current random effects model used may be invalid. The assumption of Normally distributed inter-session residuals was not supported by close examination of some of the data, and thus future work is required before random effects models can be used to their full potential. Finally, I acknowledge that identifying the source and magnitude of the different sources of intersession variance in fMRI is crucial. The ability to differentiate between variability caused by the neurovascular signals that fMRI measures, and variability introduced by the means of measurement and analysis of these signals, is essential.

How do these results illuminate those of Chapter Three? While being of methodological interest in their own right, they illustrate that due care must be taken before fMRI will be able to fulfill its promise as a technique sensitive enough to use in longitudinal studies of human brain function. More importantly

from my own perspective, they usefully demonstrate that all studies, even those with simple hypotheses, must acknowledge the intrinsic variability in the fMRI response – whatever its ultimate origin. However, even with the variability demonstrated here, many studies have produced robust and repeatable results using fMRI to study cognitive paradigms. In the next chapter I explore if optimising both the stimulus equipment and stimulus protocols may lead to a better delineation of somatotopical detail.

5 – An Examination of Stimulus-Response Functions In Somatosensory Cortex

5.1 Stimulus-Response Dynamics in the Somatosensory System

In Chapter three, I suggested that a possible reason for the lack of robust BOLD signal increases in primary somatosensory cortex (SI) during simple somatosensory stimulation may have been that the stimuli used were not optimally *tuned* to excite SI. ‘Tuning’ is a principle common to all sensory systems: for example, the rods and cones of the human eye are ‘tuned’ to detect electromagnetic energy of a particular wavelength. Similarly, Merkel receptors in the human hand are ‘tuned’ to detect the application of forces to the skin surface. From a signal-processing perspective, these sensory receptors act as filters: only stimuli that pass through the filter are processed centrally by the nervous system. This concept can be extended to include the relative responsiveness of neurons within the CNS: for example, it is appropriate to classify V4 neurons as ‘tuned’ to detect light of particular wavelengths (Zeki, 1980). Thus, if a neuroimaging experiment is designed primarily as a ‘probe’ of the responsiveness of a particular cortical area, the known neurophysiological profile of the area should influence the choice of stimuli.

The experiments described in Chapter three were designed to map the somatotopical layout of the digits of a single hand. Stimuli were chosen to maximise the likelihood of seeing BOLD signal change without consideration of the relationship between the magnitude of a particular stimulus dimension and activation magnitude. Thus the stimuli were treated as a means to an end: they allowed me to attempt to map the somatotopical layout of the body surface within SI, with a view to eventually examining experimental alterations of this topography. The dimensions of the stimuli used to elicit BOLD signal change within SI (e.g. vibrotactile frequency, airpuff intensity) were regarded as subordinate to their ability to activate SI. However, as the results of Chapter 3 demonstrated, this initial challenge proved more complex than first imagined. Few studies have investigated the responses of human somatosensory cortex to a systematically varied input function in fMRI (although see Kampe et al., 2000 for human data and Gyngell et al., 1996 for animal data). I therefore chose to examine in more detail the stimulus-response characteristics of the somatosensory system to simple repetitive airpuff stimulation.

5.1.1 Neural Coding and Sensory ‘Tuning’

The lack of either robust BOLD signal changes or recognisable patterns of somatopy in SI may have been caused by the inability of previous stimuli to maximally excite SI. Sensory receptors are not digital filters that simply switch ‘on’ in response to a preferred form of stimulation – while they may be tuned to a particular quality of stimulation, they will typically respond to similar stimuli, albeit with lesser efficacy (Fig.5.1).

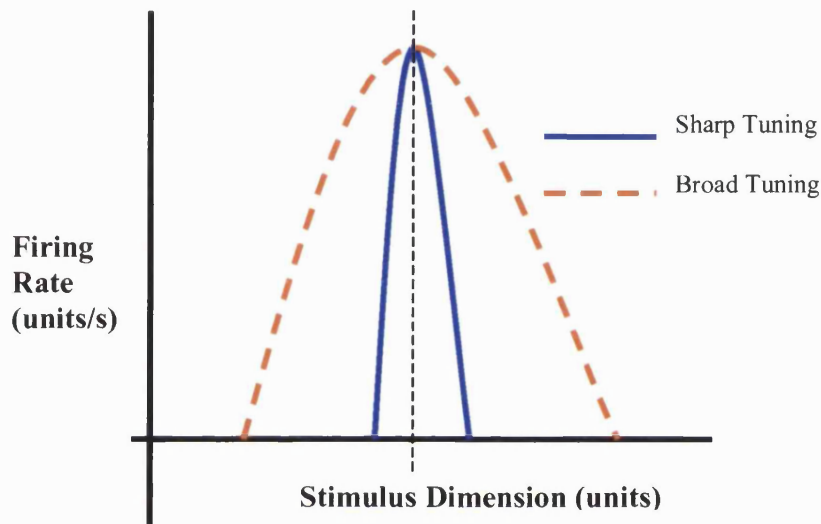


Figure 5.1. Schematic representation of tuning on sensory systems. Different cells display different degrees of selectivity. The graph shows two idealised plots of responses from neurons over different values of a stimulus. While both curves show a maximal response for a particular value, their responses are graduated such that values around the preferred stimulus value will also elicit an increase in firing. Depending on the properties of the neuron, there may be a small range of values around the optimal value that the neuron will fire to (*sharp tuning*), or the cell may respond to a broad range of values (*broad tuning*).

So, while receptors and cortical neurons may respond in a categorical fashion when presented with different classes of stimuli (e.g V4 cells show minimal responses to movement, and strong responses to colour differences), they will also invariably display graduated responsiveness to sub-dimensions of these stimulus classes (i.e. V4 cells show selectivity to specific wavelengths of light). Since neurons typically signal stimulus preference via an increase in firing rate (which is linked to neuronal metabolism), the greatest BOLD signal change should be elicited in SI when presenting stimuli that the cells are maximally tuned to detect. Logically, then, efficient mapping stimuli should be those that produce the highest firing rates in SI. However, in SI at least, it may be possible to rank the ‘best’ stimuli according to two, possibly orthogonal criteria: whether the stimuli produce the greatest signal change, or

whether the stimuli provide the best delineation of the underlying somatopy. This represents a further challenge for non-invasive investigations of map topography.

5.1.2 Convergent and Divergent Connectivity in the Somatosensory System

The situation outlined above can be explained by the physiological and anatomical processes underlying map structure in somatosensory cortex (Dykes and Ruest, 1986). Before incoming afferent information reaches the primary somatosensory cortex in humans, it must synapse in the spinal cord, brainstem nuclei, and the somatosensory thalamus. As discussed in Chapter One, there is no strict 'labelled-line' code for afferent somatosensory information – at each synapse information from adjacent ascending fibres can be combined, and the extensive divergence of ascending somatosensory projections results in a 'funnelling' effect, becoming most pronounced in the thalamus. For example, the terminal arborization of a single lemniscal fibre can branch in close proximity with up to two hundred thalamic neurons in monkeys (Jones, 1983). These aggregations of cells are known as *lamellae*. In the monkey, it is estimated that adjacent thalamic cells can project to cortical cells separated by up to 1.5mm. This divergence was posited as a possible mechanism to explain the topographic map expansions in SI seen after peripheral injury (Wall, 1977; Merzenich et al., 1984), and was initially thought to represent a 'hard limit' for the extent of map changes. However, while adjacent thalamic cells project to areas separated by only 1.5mm (in monkey cortex), the distance covered by thalamic cells *belonging to the same lamella* can project to points that are separated by a number of millimetres. Thalamocortical projections to SI do not therefore form an exact isomorph of the peripheral receptor sheet – overlaps exist (Rausell and Jones, 1995).

The functional significance of this divergence can be seen after central injury: it has been estimated that upward of 35% of the ventroposterior lateral nucleus, including a substantial portion of the cells projecting to a single digit representation, can be destroyed before any change in the digit's representation in area 3b can be detected (Jones et al., 1997). In other words, the pattern of divergence makes it unlikely that limited central lesions will produce 'silent zones' within the cortex that are not responsive to peripheral stimulation. A similar pattern of divergence is present in single

thalamocortical axons: projections to layer IV of macaque primary somatosensory cortex display similarly extensive arborizations (axons with arbores extending up to 2.5/3mm in cortex have been described; Garraghty and Sur, 1990).

5.1.3 SI Maps: Subthreshold Influences

However, in addition to the diffuse pattern of connectivity suggested by analysis of projection neurons to SI, there is a growing body of evidence to suggest that intracortical circuitry may also contribute to this arrangement (Lund et al., 1993). Under physiologically 'normal' conditions approximately 20% of racoon SI cells in which excitatory postsynaptic potentials (EPSPs) can be elicited by stimulation of a single digit *also* display EPSPs to stimulation of adjacent digits (Smits et al., 1991). Experiments involving pharmacological manipulation of GABAergic transmission in SI support this view: Dykes and Ruest (1986) found that iontophoretic infusion of bicuculline (a GABA antagonist) caused expansion of SI receptive fields in the cat. Alloway and Burton (1991) found similar results in primates. Thus the classical receptive fields of cortical neurons in primary sensory areas as mapped under anaesthesia are merely one possible configuration of a dynamic, context-specific map.

These findings do not mean that there are *no* constraints on the representations of peripheral representations in SI. Some studies have suggested that hard anatomical boundaries exist that act to limit neuronal representations from changing their size greatly under normal physiological conditions (e.g. Hickmott and Merzenich, 1998). However, these mechanisms still have the potential to obscure 'natural' map boundaries in SI when studied using neuroimaging techniques. For example, stimuli of a particular form may cause responses outside the 'classical' receptive field to be expressed. In the owl monkey, neurons within MT/V5 respond to complex stimuli across a region that may be up to 50/100 times the size of the classical receptive field (Allman et al., 1985). While V5 is a 'higher' sensory area, it contains an orderly retinotopic map of visual space, and thus any attempts to form a map of visual space within V5 would be suboptimal if stimuli of the kind used by Allman were employed. It is therefore important to carefully choose stimuli for mapping experiments.

5.1.4 Stimulus Rate and Neuroimaging Studies

It is possible to characterise tactile stimuli according to a number of different dimensions (e.g. intensity/predictability/location/roughness), and thus qualify the relationship between BOLD signal in SI and variations along each of these dimensions. I chose to examine the frequency- or rate-dependence of SI signal to airpuff stimulation. Although ‘rate’ and ‘frequency’ are essentially interchangeable terms, it is important to distinguish between them as it is typical in somatosensory neurophysiological/psychophysical studies to use ‘frequency-dependence’ in the context of experiments that use sinusoidal stimuli applied by vibrotactile devices (e.g. Bowlanowski et al., 1988).

When using naturalistic somatosensory stimuli, it is rarely possible to specify stimulus attributes to the fine degree permitted by median nerve stimulation. A more simplistic but more realistic way to characterise these stimuli is in terms of the rate at which they are delivered. This concept of the ‘delivery rate’ of a stimulus is similar to that used in parametric neuroimaging experiments (e.g. Fox and Raichle, 1985; Grafton et al., 1992; VanMeter et al., 1995; Price et al., 1996). A clear relationship between increasing the rate of finger movement and the maximum BOLD signal has previously been demonstrated (Rao et al., 1996; Schlaug et al., 1996), and in PET a linear increase of rCBF and median nerve stimulation frequency between 0-4Hz was demonstrated by Ibanez and colleagues (1995), with a subsequent plateau effect at frequencies between 4-20Hz. There has, to date, been only one systematic investigation of the frequency dependence of the BOLD signal measured with fMRI (Kampe et al., 2000). The results of this study bear out the concerns voiced above – stimulating the median nerve, the authors found that increasing stimulus frequency resulted in a linear increase in BOLD signal, but with an accompanying increase in the number of activated voxels. Therefore, increasing the rate of stimuli too much may act to obscure patterns of somatopy in SI.

If the spatial organisation of activity in topographically mapped areas is thought to be a useful metric of information processing (and there is ample evidence to suggest that map structure in SI is not merely an epiphenomenon of cortical development; e.g. Kaas, 1997), the stimuli used in mapping experiments must be carefully chosen. If the stimulus maximally excites neurons within SI, cells outside the ‘classical’ receptive fields may also be

excited. As SI digit representations are organised along a strip of cortex, any recruitment/lateral inhibition of surrounding neurons will result in a ‘smearing’ of the BOLD signal, and a loss of functional resolution. Similarly, if the stimulus only minimally excites SI, the BOLD signal change may be too small to permit reliable detection. Thus, for mapping purposes, the ‘best’ stimulus is one that excites SI enough to produce detectable changes in SI, yet produces minimal lateral spread to neighbouring representations. Sheth and colleagues (1998) have explored similar issues using optical imaging in rat barrel cortex.

5.2 Construction and Calibration of Airpuff Stimulator - Mark II

For the current experiment I chose to randomly deliver different rates of airpuff stimulation to a single finger at a time. Five separate scanning sessions were therefore required to collect data on all five fingers. Preliminary investigations with the airpuff stimulator as used in Chapter three showed that the airpuff ‘glove’ became uncomfortable if the subjects had to wear it for a protracted period of time. In addition, as stimuli were being compared between session, I was concerned about the stability of the stimulator and its ability to deliver repeatable stimulation patterns over five sessions of scanning. To address these concerns, a new stimulator nozzle apparatus was designed and constructed, and the entire stimulator setup calibrated.

5.2.1 Design and Construction of Finger-Specific Airpuff Stimulators

The stimulator used for the experiment in this chapter was similar to that employed for the experiments in the second half of Chapter three (as depicted in Figure 3.6). The only difference was in the construction of the nozzles used to deliver the airpuff stimuli. My primary concern was to standardise the construction of the nozzles, and to maximise subject comfort over potentially protracted scanning sessions. For future studies, I also wanted to have the ability to deliver independent stimuli to the volar skin of different phalanges of the same finger. These concerns resulted in a new stimulator design. A schematic diagram of one individual finger stimulator or ‘gutter’ is shown in Figure 5.2 below.

Each gutter was hollow Perspex half-cylinder, closed at its distal end. The length of the gutter could be altered by turning a plastic screw that moved a disk of Perspex (Fig.5.2, red arrow) proximally/distally from the distal end of the cylinder. The gutters were designed to match the size and shape of different fingers. Three different kinds were made: a 'thumb' stimulator that had only two stimulator lines (to match the two phalanges of the thumb), a 'finger' stimulator that fitted the index, middle and ring fingers equally well, and a 'pinkie' stimulator. To ensure that each airpuff only stimulated skin in the appropriate phalange each finger rested on ridges within the gutter (Fig.5.2). The position of the ridges could be moved to accommodate the sizes of individual subject's phalanges. The gutters were connected to the airlines from the stimulator as before.

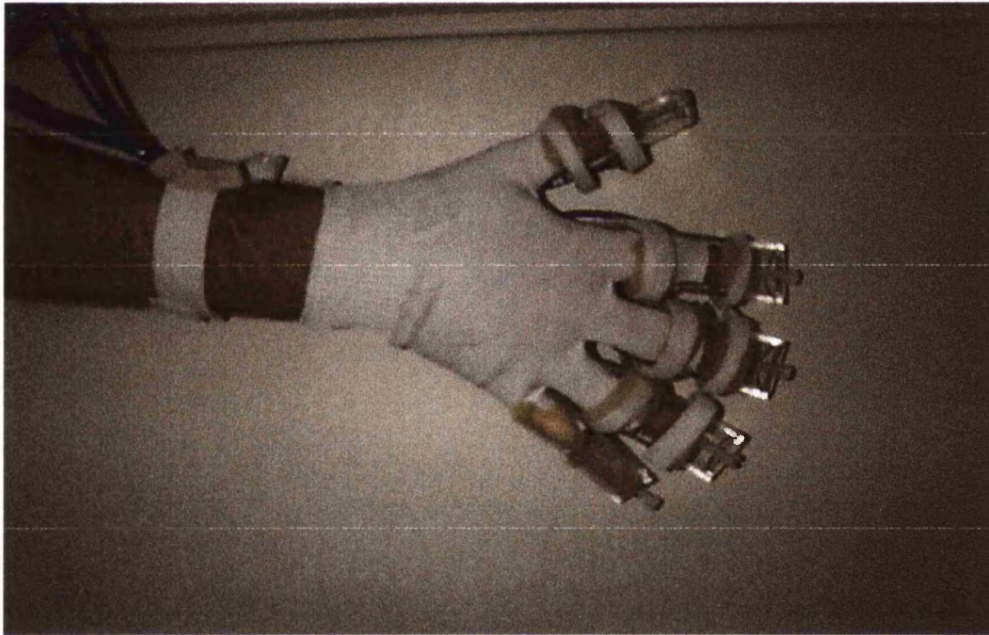


Figure 5.3. Single hand setup of airpuff gutters. Note the glove on subject's hand – this was to keep the hand warm during scanning and to ensure that any expelled air from the gutters would not stimulate adjacent fingers (each gutter contained two holes per nozzle to allow excess air to dissipate).

Figure 5.3 above displays a subject's hand with the gutters set up to stimulate the distal phalanx across all five fingers. The gutters were held in place using velcro strips lined with foam padding for subject comfort. To maximise comfort and restrict the exposed surface of the skin, the subject wore a white cotton glove with the fingertips cut to expose the volar surface of the digits.

5.2.2 Calibration And Physical Properties of Airpuff Stimulators

A force transducer (Honeywell Force Sensor - stock no. 235-6210, R&S, Northants, UK) was used to measure the force produced by the gutters and to examine the evoked waveforms produced by each of the rates used in the current experiment. The transducer was mounted in a thin plastic rod designed to mimic the dimensions of a finger. It produced a changing voltage that correlated with the force applied to its surface.

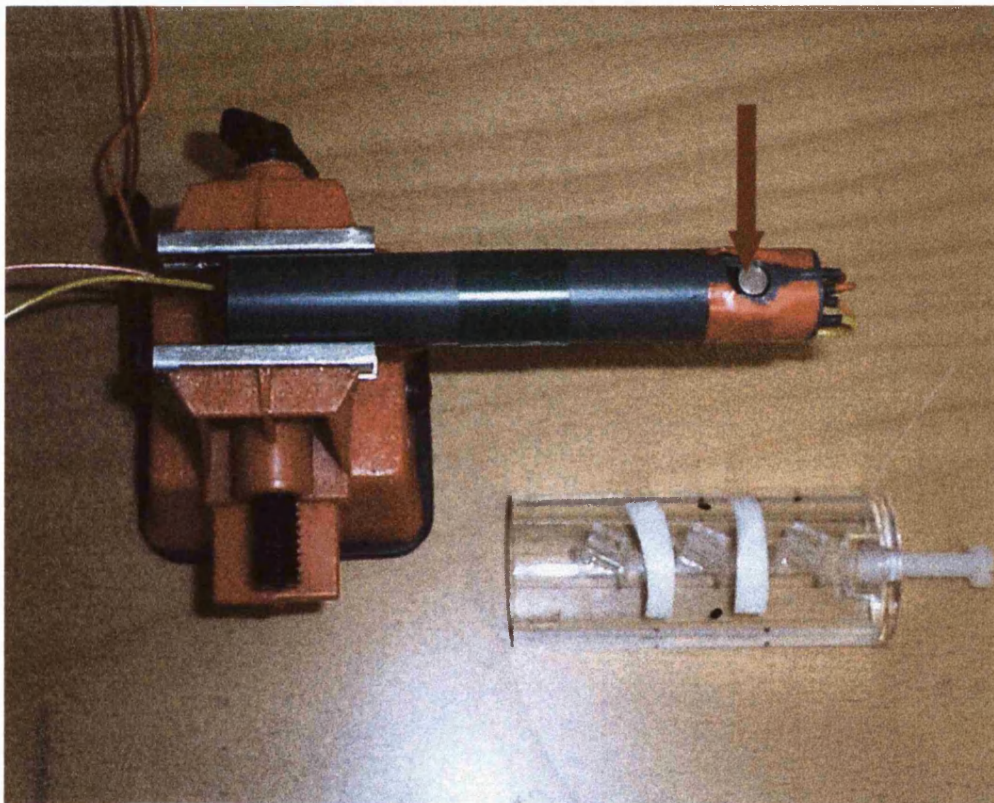


Figure 5.4. Setup of transducer during calibration procedure. The red arrow indicates the position of the force transducer in the 'finger', designed to mimic the typical position of the skin surface being stimulated. A gutter is shown for scale.

The transducer's output was first sent to a 1902 amplifier (CED, Cambridge, UK), connected to a 1401*plus* data acquisition interface (CED, as before) using a PC computer as its host. All data acquired was analysed using Spike 2 v.3 software (CED, as before).

5.2.2.1 Calibration of Transducer Voltage as a Function of Force (N)

As the surface area of the transducer's head was very small, calibrated weights would not sit on it. Instead, I used a variety of small objects (screws, bolts and sundry electrical components) to calibrate the force output of the transducer. The mass of eight objects was determined three times using digital

scales, and a mean mass for each calculated. The weight of each component in Newton's (N) was calculated by multiplying its mass by the acceleration due to gravity (9.81ms^{-2}). Each component was then placed on the force transducer, and the output voltage recorded. This was repeated three times, and the mean voltage was plotted against the mean force to determine the relationship between the two quantities (Fig.5.5). The relationship is linear over the ranges used in the calibration ($R^2=0.992$ for a linear fit), and was used in all subsequent recording to convert the output voltage of the transducer to Newton's (N).

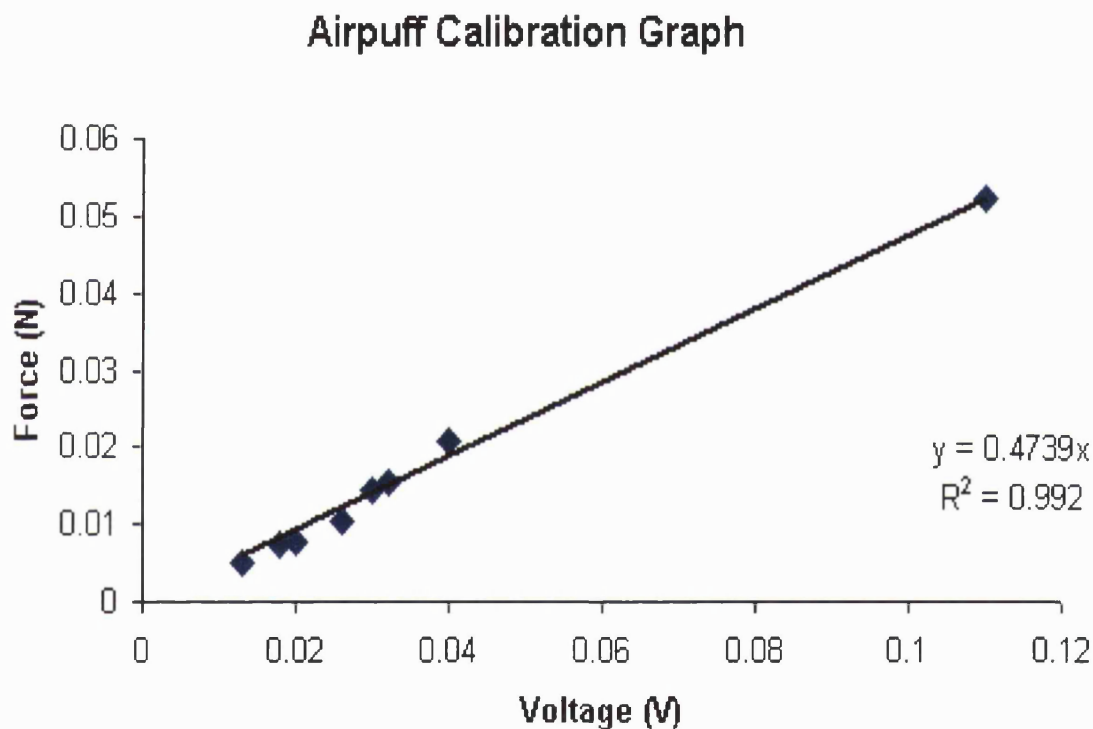


Figure.5.5. Plot of the weight of objects versus the voltage output of the transducer.

5.2.2.2 Relationship Between Airpuff Duration and Force

The duration that the airpuff valve is open will determine the force of the resulting airpuff. To evaluate the relationship between these two variables, a gutter (one of the 'finger' gutters) was positioned over the transducer with a single air line of the same length used during scanning connected to the distal nozzle, mimicking the use of the gutter on a single finger. Twelve recordings of five separate durations of valve opening were tested: 10ms, 25ms, 100ms, 250ms and 500ms. The data were low-pass filtered using Spike 2 software (as

above) with a cut-off frequency of 40Hz and a transition period of a further 12 Hz (Fig.5.6).

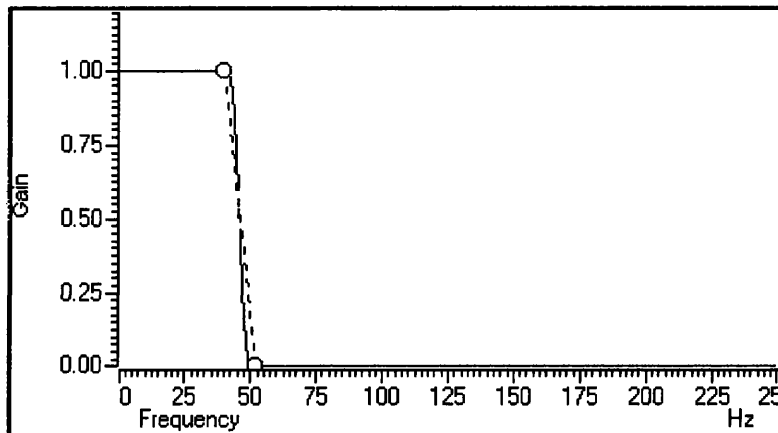


Figure 5.6. Graphical representation of the low-pass filter used by Spike 2. All frequencies above 50Hz have an effective gain of zero, while frequencies below this number are unchanged.

The mean waveforms ($N=12$) for each duration are shown below (Fig.5.7), and resemble the relationship obtained by Hashimoto (1999). The force caused by the airpuff reaches a ceiling between 250ms and 500ms of valve opening duration (compare the yellow and black curves in Figure 5.7). Importantly, it was noted that changing the duration that the valve was open for had little influence on the latency of onset of the evoked airpuff waveform (Fig.5.7). This means that changing the rate of stimulation should not change the time at which airpuffs reach the skin, and so in the current experiment latency is independent of duration and thus frequency.

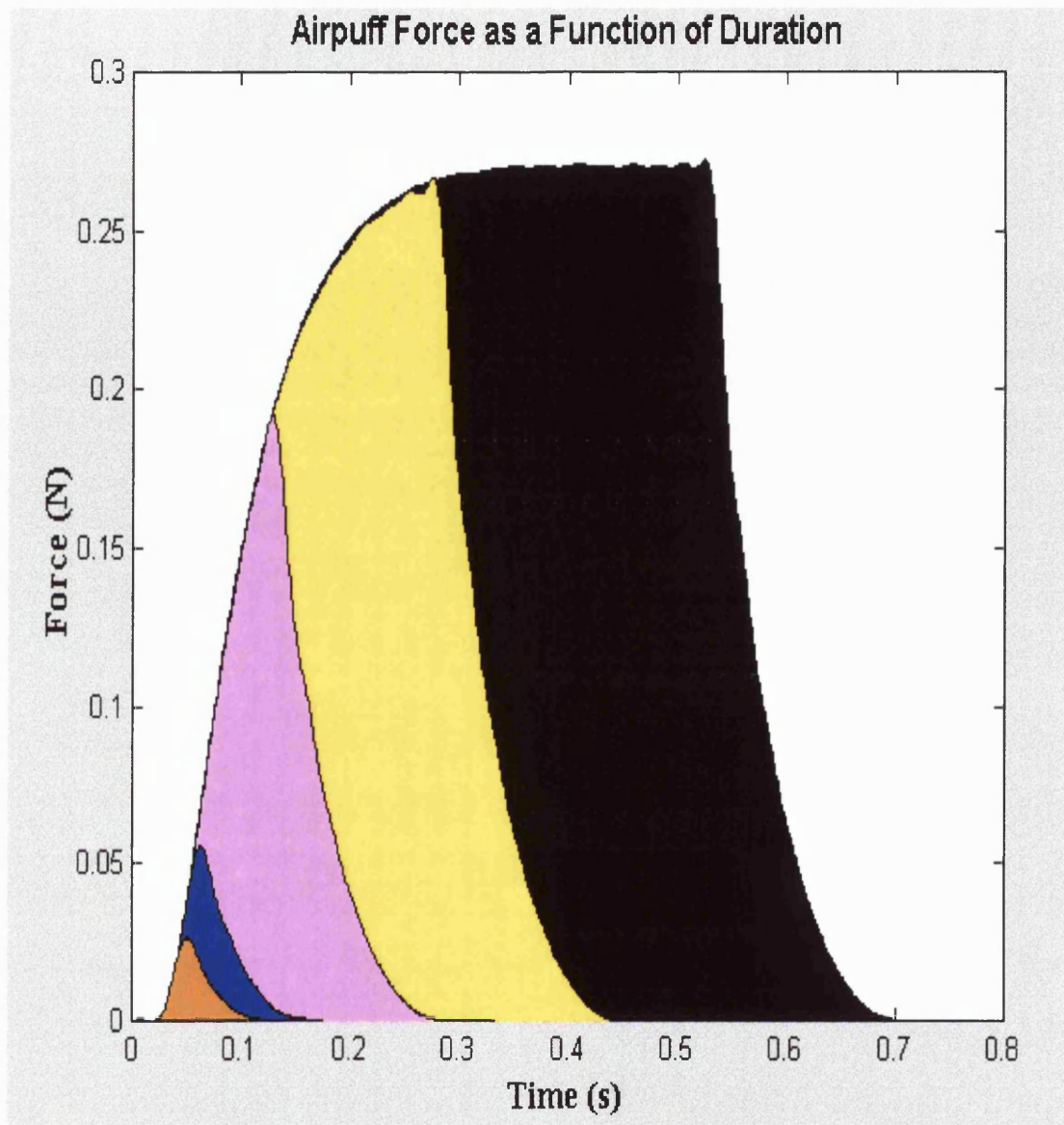


Figure 5.7. Plot of duration of valve opening vs. force of airpuff. Each curve is the mean of twelve individual measurements. The colours of each curve represent a different duration: red, 10ms; blue, 25ms; magenta, 100ms; yellow, 250ms; black, 500ms.

5.2.2.3 Reproducibility of Airpuffs Over Simulated 'Subjects/Sessions'

In this experiment each subject was scanned over five separate sessions. In each separate session a different finger was stimulated. I was therefore interested to examine the stability of the airpuffs over time to ensure that any differences between sessions could be attributed to differences in conditions, and not non-specific differences caused by the gutters themselves.

Each individual gutter (labelled 1-5, 1=thumb...5=pinkie) was positioned over the transducer as above. Ten airpuffs were recorded (duration=105ms) on three separate occasions for each line. In between each run of ten airpuffs the gutters were taken off the transducer and replaced again, to simulate the

differences in positioning that may result between subjects. Two separate variables were used to characterise the airpuffs: peak amplitude and time to peak from valve opening (Figure 5.8).

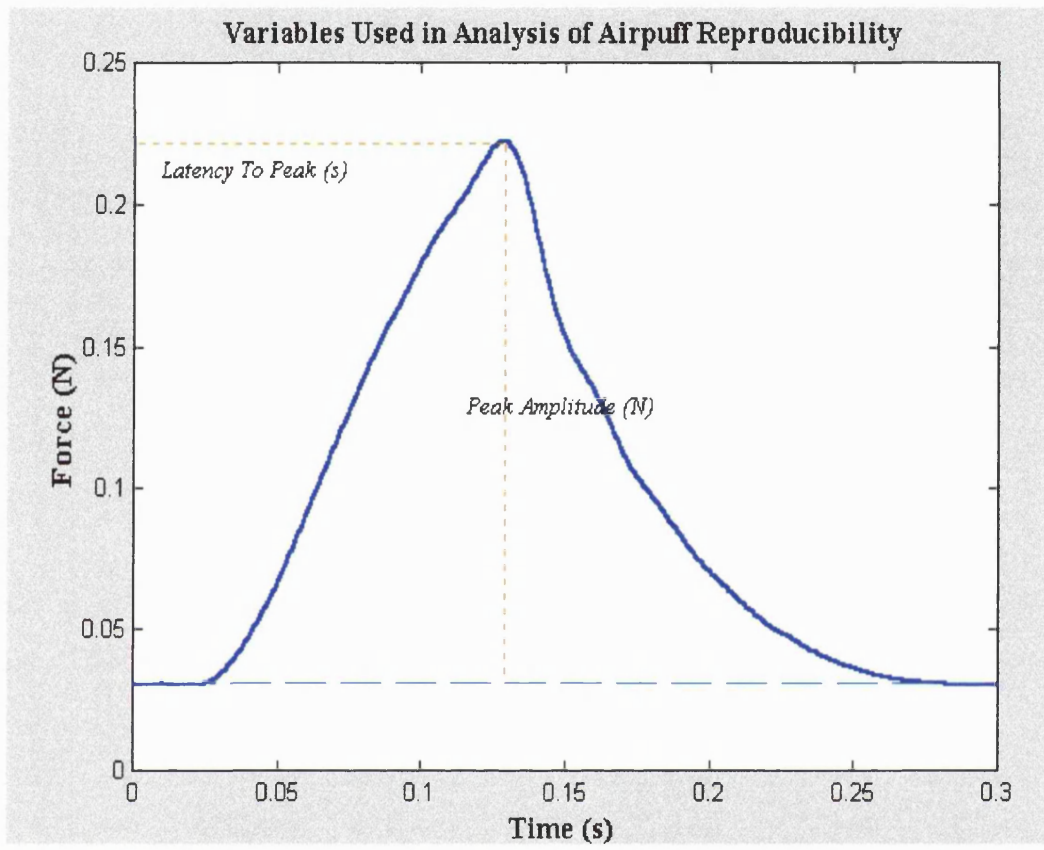


Figure 5.8. Variables used for analysis of airpuff reproducibility. Separate analyses were performed on both the latency to peak of each airpuff and the peak amplitude. The beginning of each airpuff was defined by a trigger that signalled when each valve was opened.

One-way nonparametric (Kruskal-Wallis) ANOVAs were performed individually for each line examining peak amplitude and latency across each of the three repeats of ten runs. No significant effects were found (Line 1: amplitude $\chi^2=1.94$, $p>0.39$; latency $\chi^2=4.5$, $p>0.10$. Line 2: amplitude $\chi^2=3.7$, $p>0.153$; latency $\chi^2=2.43$, $p>0.29$. Line 3: amplitude $\chi^2=2.15$, $p>0.342$; latency $\chi^2=2.97$; $p>0.227$. Line 4: amplitude $\chi^2=2.97$, $p>0.22$; latency $\chi^2=2.15$, $p>0.34$. Line 5: amplitude $\chi^2=.941$, $p>0.62$; latency $\chi^2=3.11$, $p>0.21$). These results suggest that any significant differences between sessions/subjects in this experiment are unlikely to be solely attributable to instabilities in the stimulators themselves, at least as defined by the two variables used. A graphical representation of the average waveforms from line 3 is displayed in Figure 5.9 below.

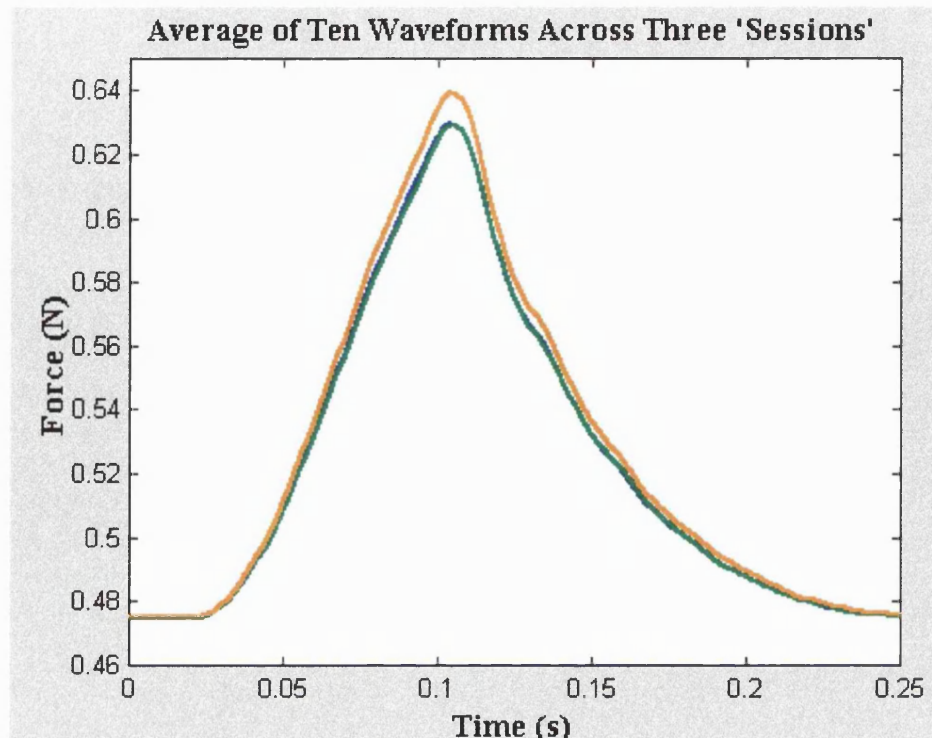


Figure 5.9. Three average waveforms ($N=10$ for each) from line 3. Each waveform has been plotted using a different colour (red, green and blue), but it is difficult to distinguish the green and blue because they are almost identical in appearance.

5.2.2.4 Investigation of Power Spectra of Rate Stimuli

In order to ensure that the output frequency of the rate waveforms matched the frequencies that the stimulator was programmed with, power spectrum analyses were performed on representative examples of each waveform using Spike 2 software on a PC as before (2056 bins used). The spectra are shown below (Fig. 5.10), showing that the fundamental frequency of each waveform is situated at the input frequency of the stimulator. However, there is a reduction in the power (and thus the maximum force produced by the airpuffs) as frequency increases. For example, the height of the maximum component in the 10Hz is roughly x16 less than that in the 1Hz spectrum. This point will be revisited in the discussion.

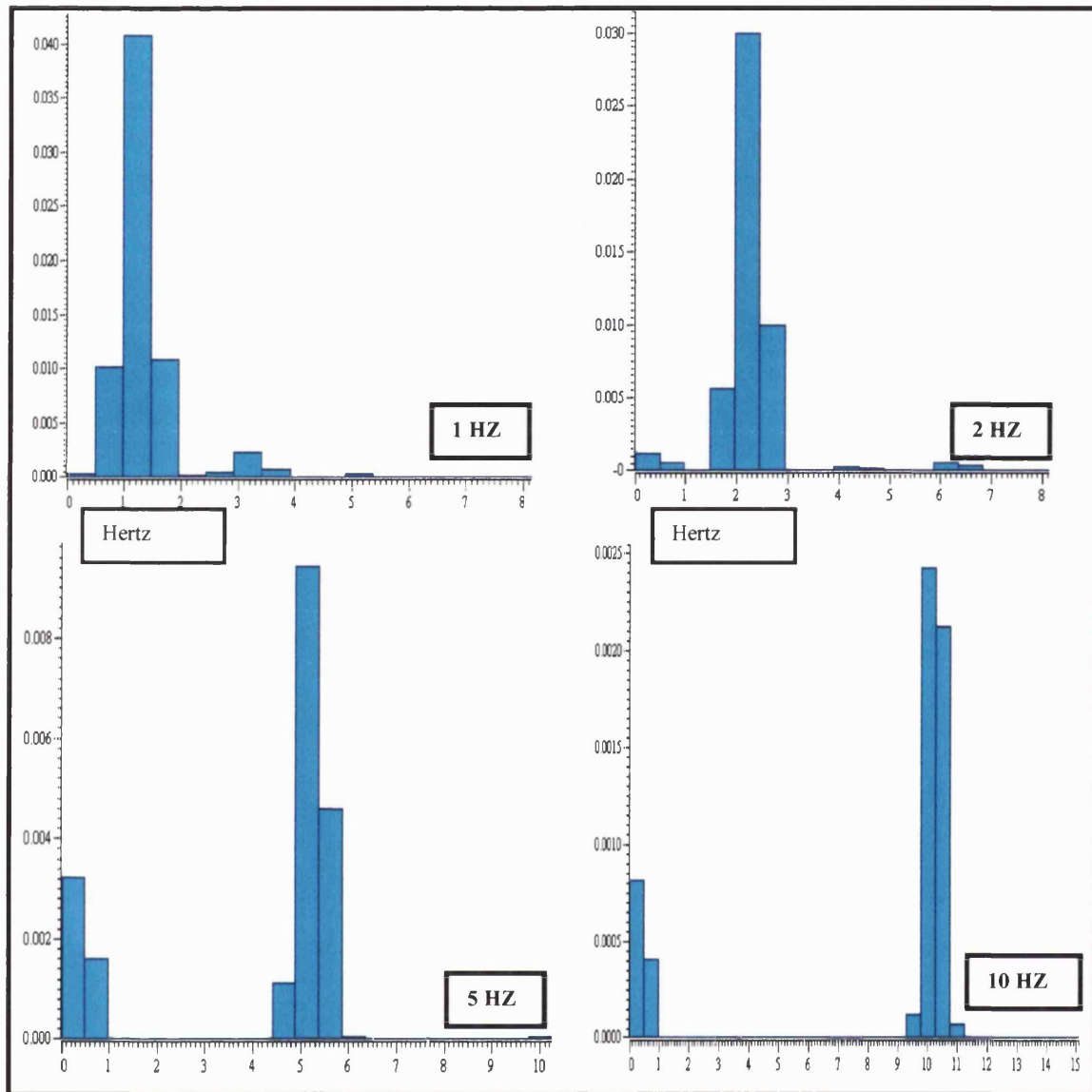


Figure 5.10. Power spectra of rate stimuli used in current experiment. The frequency of each component is depicted on the x-axis, and the respective power (in units of V^2) is shown on the y-axis. While the fundamental of each spectrum is situated at the correct frequency, as the frequency increases the power of the fundamental decreases. Note the Y-axis scale is different between spectra.

5.3 Methods – Experimental Setup And Scanning

The aims of the current experiment were to determine the optimal stimulation rates that would produce either the clearest delineation of somatopy or the most consistently statistically significant change in BOLD signal in SI.

5.3.1 Subject and Scanning Details

Nine right-handed males (mean age 25, age range 21-34) served as subjects. The local ethics committee approved the experimental procedure and all subjects signed a consent form before being scanned. The data were acquired on a Siemens MAGNETOM Vision (Siemens, Erlangen, Germany) at 2T. Each BOLD-EPI volume scan consisted of 48 transverse slices (inplane matrix 64x64; voxel size 3x3x3mm; TE=40ms; TR=4.11s).

1120 volume scans in total were collected from each subject (5 sessions x 224 scans per session). A T1-weighted high-resolution MRI of each subject (1 x 1 x 1.5mm resolution) was acquired to facilitate anatomical localisation of the functional data. Auditory stimuli were delivered by a custom-built sound delivery system, with headphones designed to attenuate scanner noise (Palmer et al., 1998).

5.3.2 Experimental Setup

The five gutters were positioned on the appropriate fingers of the right hand of each subject, and adjusted so that the distal nozzle was positioned over the centre of the digit pad (in a similar fashion to Figure 5.3). The five distal nozzles were connected to individual airlines so that each of the digit pads could be stimulated independently. Examples of stimuli at each frequency were delivered before scanning to ensure that subjects could perceive the stimuli, and that similar intensities were perceived on each finger. Most subjects (7/9) reported that the 10Hz stimulation felt slightly weaker than the 1Hz stimulus.

During scanning, subjects lay supine on the scanner bed with their right hand resting on their torso. They were instructed to close their eyes and concentrate on the pattern of stimulation. Subjects received 24 epochs of airpuff stimulation (6 epochs x 4 different rates – 1,2,5 and 10Hz) per session (224 scans in length), delivered to a single digit. Each subject received five sessions of stimulation, one per digit. Each epoch of stimulation was 5 scans in length (5x4.11 TR = 20.55s) and was alternated with periods of no stimulation lasting

4 scans ($4 \times 4.11 = 16.44$ s). Epoch order was pseudo-randomised (i.e. blocks of epochs of 1, 2, 5 and 10Hz stimulation were randomised) within-sessions and across subjects to account for possible expectation and order effects. Session order (i.e. digit stimulation order) was randomised across subjects.

Amplitude-modulated white noise stimuli were played periodically to prevent subjects hearing the airpuffs during scanning (repetition rate 1Hz; duration 500ms, attack 50ms decay 450ms; programming by I. Johnsrude). All subjects reported being unable to hear the stimuli.

5.3.3 Image Preprocessing and Data Analysis

5.3.3.1 *Spatial Preprocessing*

Data preprocessing was carried out using SPM99 (Wellcome Dept. of Cognitive Neurology, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>) implemented in Matlab5 software. All preprocessing was carried out in a similar fashion to previous experiments (as described in section 3.2.3.3). The initial four scans were removed to allow for T_1 saturation effects (as opposed to two in section 3.2.3.3), and subjects' scans were realigned across all five sessions. Two subjects' data sets contained significant amounts of task-correlated motion (as detected by inspection of movement parameters) and were therefore excluded from subsequent analysis. All functional volumes were smoothed using a 8mm FWHM isotropic Gaussian kernel.

5.3.3.2 *Data Analysis*

Data analysis used SPM99 as before. Functional volumes from all sessions were treated as a timeseries, and experimental effects estimated using a multi-session design matrix that included separate session mean terms. Each subject's data were analysed separately in a single-subject, five-session design matrix. Individual session partitions of the design matrix consisted of the timecourse of the four experimental covariates (1Hz, 2Hz, 5Hz and 10Hz stimulation) modelled as box-car functions convolved with the expected HRF, and six covariates representing the estimated movement parameters for each scan (obtained from the realignment parameters). To remove low-frequency noise the data were high-pass filtered using a set of discrete cosine basis functions with a minimum cut-off period of 370s. Temporal autocorrelation was dealt with using the method of Worsley and Friston (1995), by temporally smoothing the session time series with a Gaussian kernel of 6s FWHM.

Linear contrasts of the covariates were evaluated for the effects of stimulation at each rate/digit ($4 \times 5 = 20$ contrasts) and the average effect of stimulation at all rates/digit ($1 \times 5 = 5$ contrasts). Results were displayed as a voxelwise statistical parametric map of t values. As I was most interested in the contralateral SI and bilateral superior lateral sulcal areas, voxels in these areas were reported as significantly active with a p value of $p < 0.00001$ (corrected for the number of voxels using the areas' estimated volumes; Kennedy et al., 1998). Voxels in other brain areas were reported as significant if they survived a correction for multiple comparisons over the entire volume ($p < 0.05$ corrected). I did not use a cluster threshold for the current analysis to ensure maximal sensitivity to potentially small effects.

5.4 Results

5.4.1 Single Rate/Digit Contrasts

The main effects of each single digit/frequency contrast ($5 \text{ digits} \times 4 \text{ frequencies} = 20$ contrasts) were examined for each subject. The results of each contrast are summarised in Table 5.1 below. I wanted to address two independent issues: which rate of stimulation produced the 'best' pattern of digit somatopy within SI (i.e. that which agreed with the Penfieldian pattern); and which rate of stimulation was best at eliciting SI activation consistently across digits, whether the spatial pattern was somatopical or non-somatopical. The assessment of both of these hypotheses was made difficult due to the lack of activations in almost half the subjects. Three subjects showed little activation in any of the single rate/digit contrasts tested (subject 4, subject 6 and subject 7). The subsequent analyses therefore focused on the remaining four subjects.

Digit Stimulated															
Thumb				Index			Middle			Ring			Pinkie		
SI	CLs	ILs		SI	CLs	ILs	SI	CLs	ILs	SI	CLs	ILs	SI	CLs	ILs
SI 1hz		+	+				+							+	
2hz	+	+													
5hz														+	
10hz	+							+							
S2 1hz										+					
2hz	+						+								
5hz	+			+	+	+				+					
10hz	+			+				+		+					
S3 1hz	+		+	+		+	+			+			+		
2hz	+	+	+				+			+			+	+	+
5hz				+			+	+					+	+	
10hz	+			+				+	+	+	+				
S4 1hz															+
2hz															
5hz															
10hz				+											
S5 1hz					+	+	+	+	+				+	+	+
2hz	+			+	+	+	+	+	+						
5hz	+			+	+								+	+	
10hz	+	+						+					+	+	+
S6 1hz							+	+							
2hz															
5hz															
10hz															
S7 1hz															
2hz	+														
5hz															
10hz															

Table 5.1. Single digit/rate contrasts, listed by subject. A '+' in the table indicates that the contrast in question contained significant voxels ($p < 0.00001$) in either contralateral primary somatosensory cortex (SI), contralateral superior lateral sulcus areas (CLs) or ipsilateral superior lateral sulcus areas (ILs).

5.4.1.1 Rate Dependence of Somatopy

To assess my first question, subjects where at least 2 digits had significant clusters within SI when stimulated with the same rate were assessed to see if the pattern of evoked activity in SI was similar to the classic Penfieldian somatotopical-pattern (table 5.2). According to the hypothesis presented above, I had expected that stimulation at one particular rate may have been optimal for

the delineation of somatopy. However, a serious assessment of this question was prevented by the small number of subjects who displayed statistically significant BOLD signal changes in SI. Only one subject displayed somatopical order when examined in this fashion (S2, across 5Hz and 10Hz rates).

	<i>1Hz</i>		<i>2Hz</i>		<i>5Hz</i>		<i>10Hz</i>	
	<i>No.of Fingers</i>	<i>?</i>	<i>No.of Fingers</i>	<i>?</i>	<i>No.of Fingers</i>	<i>?</i>	<i>No.of Fingers</i>	<i>?</i>
S2	0	-	2	-	3 T,I,R	Y	3 T,I,R	Y
S3	5	N	4 T,M,R,P	N	3 I,M,P	N	3 T,I,R	N
S5	2	-	3 T,I,M	N	3 T,I,P	N	2	-

Table 5.2. Within-rate comparisons of somatopy. Single rate/digit contrasts were assessed across three subjects (subjects S2, S3 and S5) to investigate patterns of somatopy. This question was only assessed in subjects where at least three digits for the same rate had elicited significantly activated voxels. The digits in which significant activation where elicited are represented by the first letter of their name (i.e. Thumb = T, Middle = M etc.). The '?' column shows if the spatial pattern of digit activation agreed with the medio-lateral/inferior-superior Penfieldian pattern.

5.4.1.2 Rate Dependence of BOLD signal change in somatosensory cortex

To assess if any of the rates used in the experiment elicited significantly more clusters of activity in SI than other rates, a one-way non-parametric (Kruskal-Wallis) ANOVA of the occurrence of significant activity in digits per rate was carried out. This analysis revealed nothing significant for contralateral SI ($\chi^2=0.678$, $p>0.89$). Similar tests carried out on activity in contralateral and ipsilateral lateral sulcal areas revealed the same negative result (contralateral LS: $\chi^2=.37$, $p>0.95$; ipsilateral LS: $\chi^2=5.2$, $p>0.16$). Thus, as assessed across the group of subjects, there were no significant differences between the number of significant activation clusters elicited per rate across digits. Therefore there was no evidence for rate tuning in somatosensory cortical areas. All data from these contrasts are shown in Figure 5.11 below.

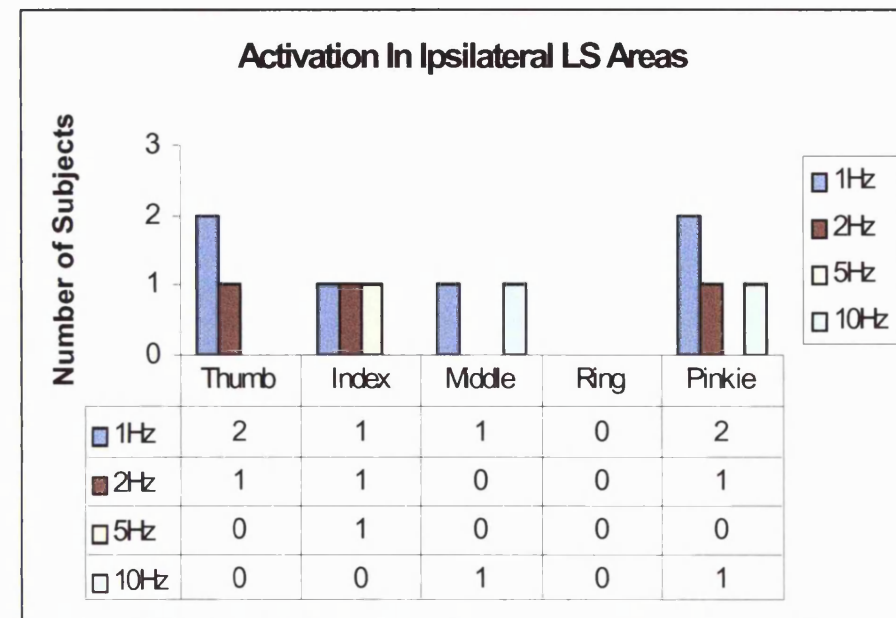
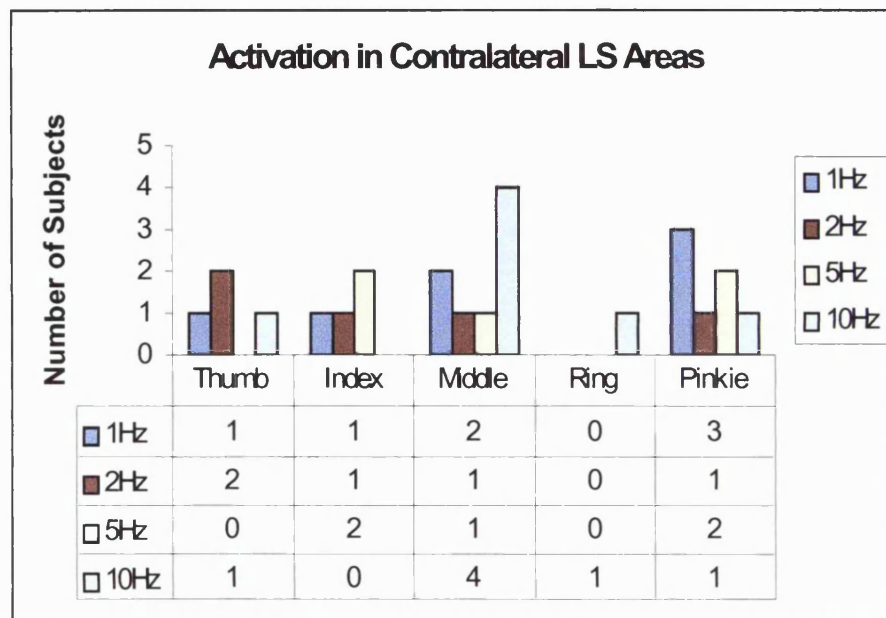
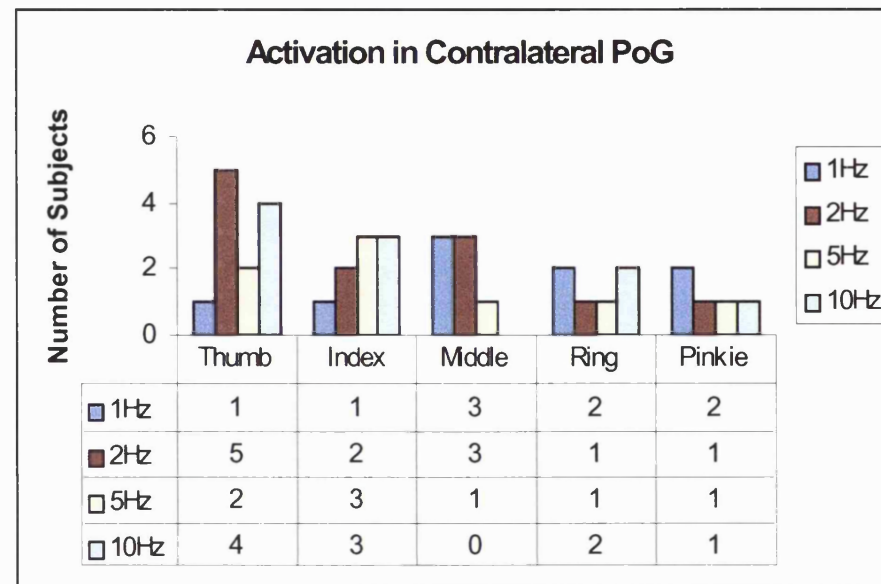


Figure 5.11. Representation of the number of activated clusters across all 7 subjects, grouped by cortical area, digit and stimulation rate.

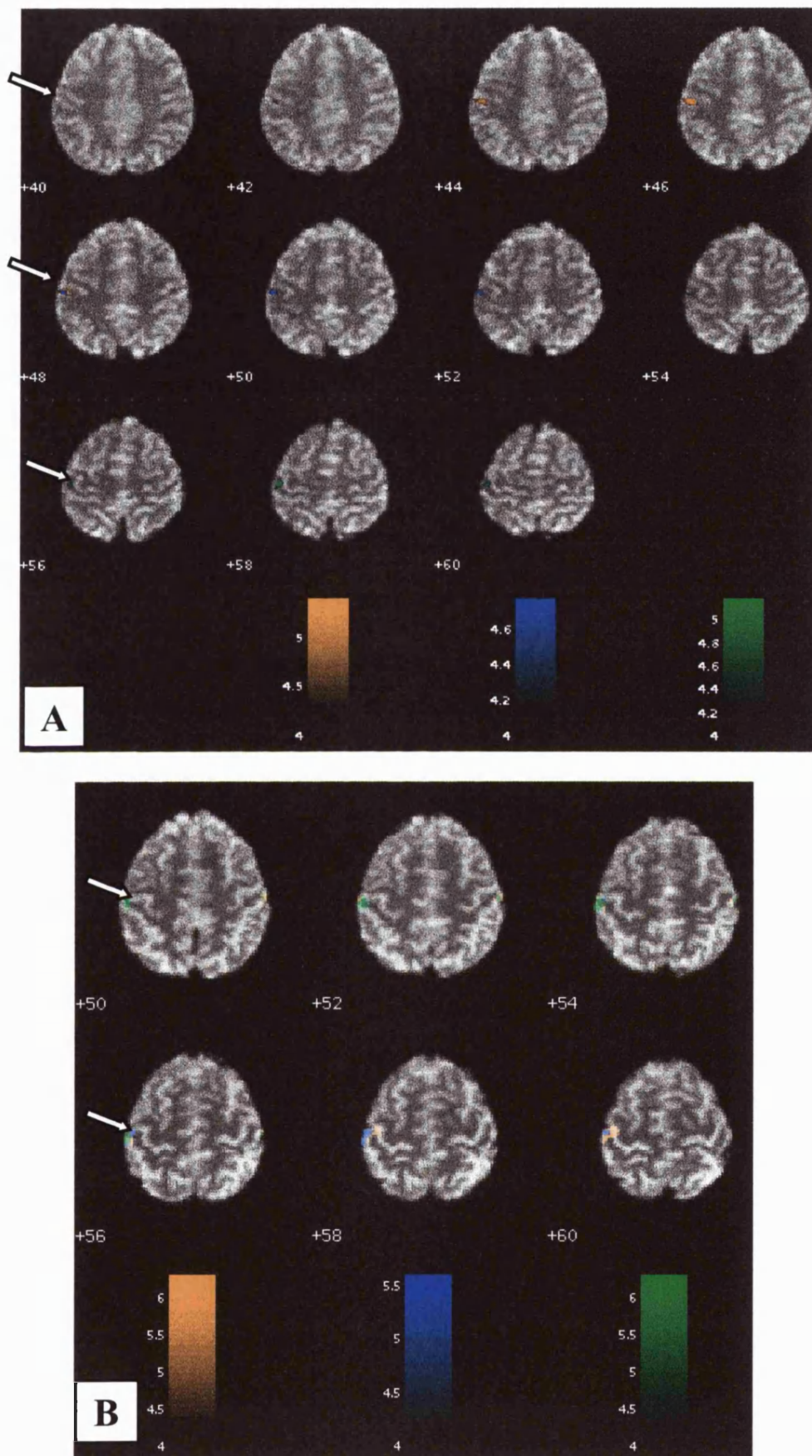


Figure 5.12. Comparisons between spatial patterns of somatopy between two subjects. A) S2. Somatopy pattern, 10Hz contrast. B) S3, Nonsomatopy pattern. Activated voxels are displayed on 2mm thick axial slices from the subject's mean functional volume. Different colours represent different digits – red, thumb; blue, index; green, pinkie. The graduations in brightness reflect voxel t -values, and the white arrow designates the position of central sulcus.

5.4.2 Main Effect Contrasts

The main effect of stimulation (averaged across all rates) was examined across all digits/subject. Although I wanted to concentrate on examining specific differences that related physiologically to the variables used in the study, I was also interested to see if, on average, the somatosensory cortex responded to stimulation in a more robust way than previously (e.g. in Chapter three). Average contrasts are also likely to produce a gain in the signal to noise ratio, as they focus on more periods of stimulation.

The results of each contrast are presented below in Table 5.3. Although the three subjects without activation in the previous contrasts (subjects 4, 6 and 7) still displayed showed little activation, the other four subjects displayed significant amounts of activation across each contrast in each of the three areas of interest. Note that this table is not merely a summary figure of the results of table 5.1 but represents results that address a different experimental question. Again there was little somatopical order found in SI.

	Digit Stimulated														
	<i>Thumb</i>			<i>Index</i>			<i>Middle</i>			<i>Ring</i>			<i>Pinkie</i>		
	SI	CLs	ILs	SI	CLs	ILs	SI	CLs	ILs	SI	CLs	ILs	SI	CLs	ILs
S1	+	+			+	+	+	+						+	
S2	+			+	+		+	+		+	+		+	+	
S3	+	+	+	+			+	+	+	+	+	+	+	+	
S4															
S5	+	+		+		+	+	+	+				+	+	+
S6															
S7											+				

Table 5.3. Main effects of digit stimulation per subject averaged across all stimulation rates. A '+' indicates that the subject contained significant voxels ($p < 0.00001$) in the cortical area indicated. SI= contralateral primary somatosensory cortex, CLs = contralateral lateral sulcus areas, ILs = ipsilateral lateral sulcus areas.

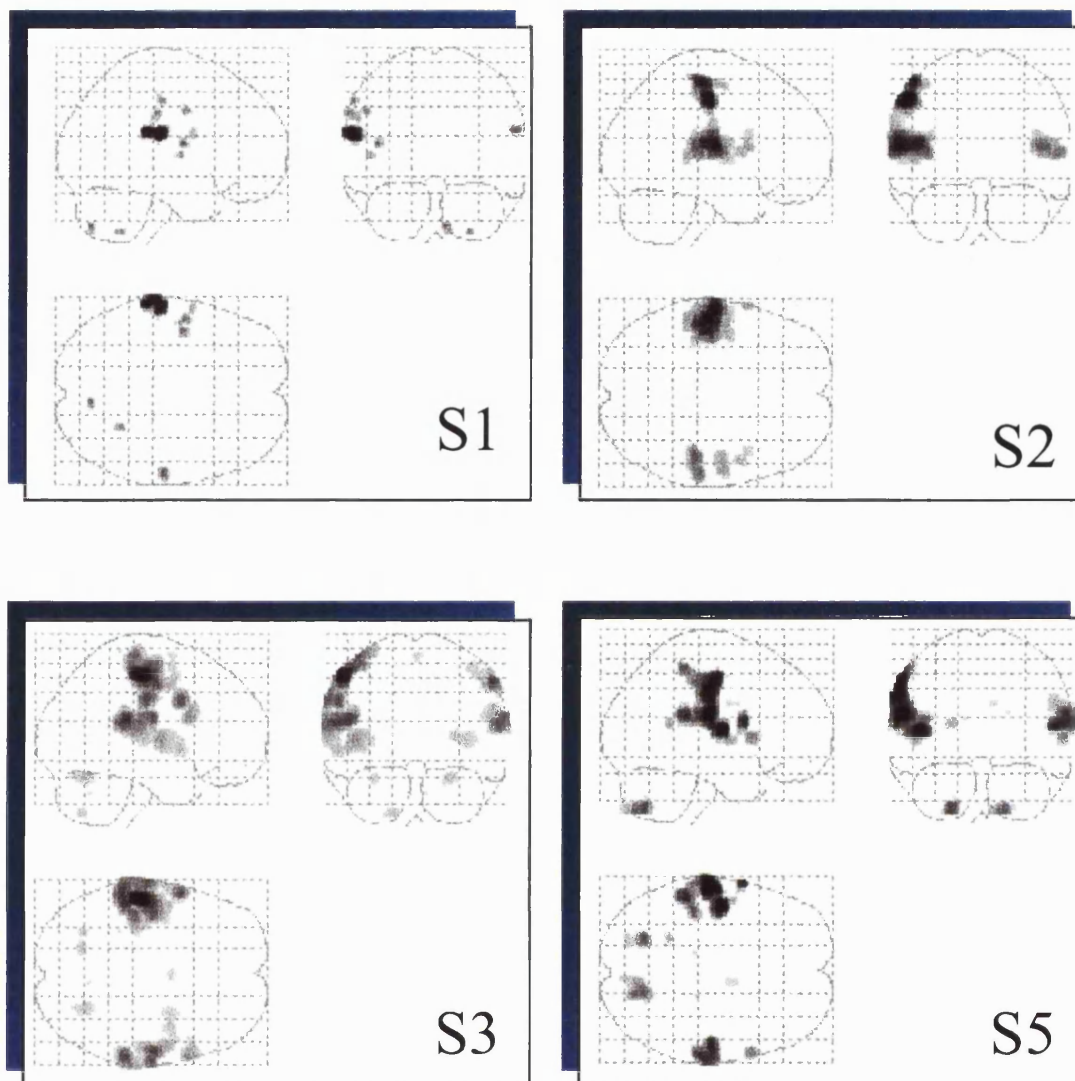


Figure 5.13. Main effects of middle digit stimulation across all rates of stimulation in four subjects (S1, S2, S3 and S5). The results are displayed as maximum intensity projections (MIPs) across three orthogonal planes. Voxels surviving the statistical threshold are displayed in greyscale, with lower shades of grey depicting greater significance. Across these four subjects a broadly similar pattern of activations can be observed in contralateral SI and bilateral lateral sulcal areas.

5.4.3 Rate-Dependent Responses in SI

While evaluating the above contrasts I observed that the digital BOLD signal responses were rate-modulated— in other words, the magnitude of the response across epochs varied positively with the rate of stimulation. In order to assess this finding systematically across digits and subjects, all digits for which significant responses in SI were observed at two or more rates were examined. Out of 13 such comparisons across four subjects (S1, S2, S3 and S5), 11 plots displayed parametrically varying responses in SI (85%). Examples of this effect in two clusters from two different subjects are displayed below (Fig. 5.14).

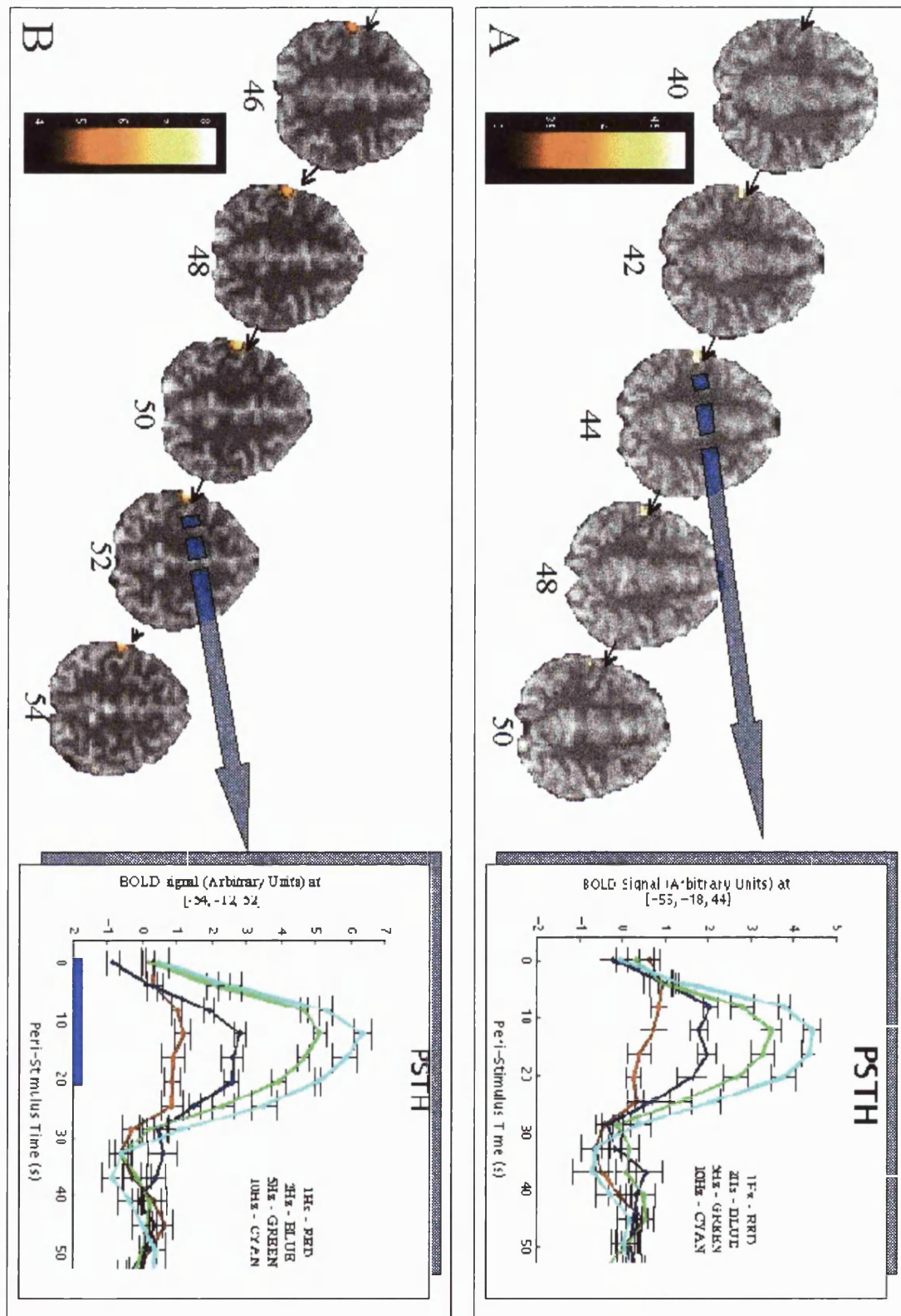


Figure 5.14. Effects of stimulation rate on BOLD signal in contralateral SI. **A)** 10Hz Thumb contrast, Sub. 2. **B)** 10Hz Thumb contrast, Sub. 5. Activated voxels surviving the statistical threshold (as before) are shown rendered on to 2mm axial slices of the subject's mean functional image. The black arrow points to the central sulcus. The plots to the right of each series of slices are peri-stimulus time histograms (PSTHs) of activity in the peak voxel, plotted as a function of peri-stimulus time across each rate contrast. The error bars represent the standard error of the mean at each point. Each rate is plotted in a different colour – 1Hz, red; 2Hz Blue; 5Hz, green; 10Hz, cyan. The blue bar in **B** represents stimulus duration.

5.5 Discussion

5.5.1 Aims and Results

The experiment was motivated by the somewhat disappointing results of Chapter three. In those experiments the presentation of supra-threshold somatosensory stimuli failed to produce robust patterns of activation in cortical somatosensory areas (contralateral SI, bilateral lateral sulcus areas). The stimuli used were typical of those employed in previous PET studies (e.g. Fox et al, 1987) and MEG studies (for review see Kakigi et al., 2000) to stimulate somatosensory cortex. Yet, using fMRI, I was unable to elicit robust and reproducible responses in SI - or, when I was able to produce separate foci in SI for different digits, the spatial configuration of these clusters did not agree with the widely accepted Penfieldian somatopical map.

The results of chapter 3 led me to focus in more detail on the *characteristics* of stimuli used to map SI, and to explore this area in an attempt to explain the discrepancies between my results and neurophysiological studies in both animals and man. It is not unknown for functional imaging to produce results that are seemingly at odds with results from other modalities and species. For example, the lack of hippocampal activation in neuroimaging studies of episodic memory (e.g. Shallice et al., 1994) was at odds with the known memory deficits arising from bilateral resection of this structure (Scoville and Milner, 1957). Only when the activation paradigm used in these studies was refined did studies begin to detect hippocampal activation (Dolan and Fletcher, 1997). Thus *tuning* of stimulus presentation and context is an essential component of paradigm design. For example, the human auditory system is widely thought to act as a frequency analyzer. High frequencies are represented by hair cells at the base of the cochlea, and low frequencies at the apex. This results in a spatial mapping of the frequency of the sound onto a specific location. However, even though hair cells will respond maximally to a particular frequency (they are ‘tuned’ to that frequency), they will also respond to neighbouring frequencies, as the peaks of sound waves are often broad.

This example from a different sensory modality demonstrates that, even in the periphery, receptors and primary afferents are tuned to be maximally responsive to different dimensions of stimuli. My lack of significant results in previous experiments may have therefore been due to the fact that my stimuli,

while highly perceivable, were not optimal for metabolically based mapping methods such as fMRI. Work in rat barrel cortex using differential stimulation rates has previously shown that the region of cortex activated by stimulation of a single vibrissa at 1Hz is *more* diffuse than that activated by greater stimulation rates (up to 10Hz; Sheth et al., 1998). The authors concluded that ‘...the spread of activation in rat barrel cortex is modulated in a dynamic fashion by the frequency of vibrissa stimulation’. I therefore scanned nine subjects using different rates of airpuff stimulation (1,2,5 and 10Hz) to investigate if an analogous relationship existed in human SI. If the lack of somatopy demonstrated previously had been caused by similar mechanisms to those demonstrated by Sheth and colleagues (1998), I would have a ‘correct’ pattern of digit somatopy at higher rates (10hz) due to the attenuation of neighbouring inputs at higher input frequencies. However, with techniques with lower spatial resolution than optical imaging (like fMRI), the attenuation occurring at higher frequencies may cause a mean decrease of signal change when measured over the entire digit. Thus, while a more discrete map may be obtainable, the signal: noise ratio of fMRI may result in false negatives at higher frequencies. My ability to evaluate these questions was limited because only a small number of subjects displayed significant activation foci. Three out of my seven subjects (from the nine scanned) displayed little significant signal change to *any* combination of rates/digit. The results in the remaining four subjects were more encouraging, yet due to the relative reduction in sample size from seven subjects to four, I was unable to address my experimental aims in an entirely systematic fashion. Nevertheless, some conclusions can be drawn from my results.

5.5.2 Rate-Dependent Responses - Methodological Issues

It is often difficult to know how compatible results *should* be between techniques that record electrical or magnetic fields generated by cortical neurons (EEG/MEG) and techniques that rely on neurovascular coupling mechanisms (PET/fMRI). In fMRI, rate-dependent effects may be present in the underlying generators of the signal, but also in the mechanisms that couple blood flow to neuronal firing. Friston and colleagues (1998) found that responses at high stimulus presentation rates caused an initial saturation of BOLD responses followed by a subsequent attenuation. The authors suggested that this behaviour may be specific to the BOLD effect and may represent a ‘hemodynamic refractoriness’. Similarly, Canestra and

colleagues (1998) found that fast stimulation rates in human auditory and somatosensory cortex caused refractoriness of the signal recorded with optical imaging, yet did not affect the amplitude of surface cortical potentials. These findings have been reinforced by work in rat somatosensory cortex by Ances et al. (2000), who found similar evidence of hemodynamic but not neuronal refractoriness.

Although the hypotheses of this work focused on the effects of different rates of somatosensory stimulation on the evoked BOLD signal in SI, the rate-responsiveness of primate sensory systems is not limited to the cortex. *In vivo*, intra-areal, inter-areal and projection (from the thalamus) mechanisms combine to produce a dynamic context for somatosensory representations (e.g. Pearson et al., 1987; Moore et al., 1999). However, rate-dependent effects are only seen in primary afferents when inter-stimulus intervals (ISIs) are extremely short (less than 5ms), and then only when subjects are exposed to trains of stimuli delivered over a protracted period of time (on the order of minutes; McLaughlin and Kelly, 1993). Recent work by Whitsel and colleagues (2000) on the stability of discharge rate from rapidly adapting (RA) mechanoreceptor afferents in cats and monkeys to 15-30Hz stimuli support this argument. Of the stimulation rates used in my study, only 10Hz stimulation would have been expected to cause 'habituation' or 'adaptation' (the amplitudes of ERPs are unaffected at stimulation rates of longer than 200ms i.e. 5Hz; Huttunen and Homberg, 1991). It is accepted that rates of above 4-5Hz produce quite pronounced amplitude reductions in ERPs (reviewed in McLaughlin & Kelly, 1993). McLaughlin and Kelly argue that these effects are specific to cortex and involve "...more than simply a projection to that level of changes occurring at earlier stages of afferent processing" (1993). A similar effect was found by Ibanez and colleagues (1995), who found that the rCBF response in SI to increasing median nerve stimulation in PET was linear until 4Hz, but non-linear with faster rates (over and above 8Hz). Other authors, however, failed to replicate this result in fMRI (Kampe et al., 2000), and others have found that, while the amplitude of SEFs are attenuated at certain rates of repetition, other stimulus rates cause enhancement of some components of the frequency spectra of the SEFs (Rush et al., 1976).

McLaughlin and Kelly (1993) suggest that the model of Whitsel and colleagues (1991) may explain the pattern of SEF results. This model

(Whitsel et al., 1991) combines structural (lateral inhibitory connections) and functional (temporal dynamics of incoming afferent stimuli to SI) factors to produce a model of columnar dynamics in SI in response to trains of afferent stimuli. Briefly, this model suggests that both habituation and enhancement of neuronal responses within SI interact, such that over the course of delivering a train of stimuli an initially diffuse pattern is ‘tuned’ such that differences between columnar responses to extrinsic excitatory drive are enhanced. Furthermore, as Whitsel and colleagues used the 2DG method to obtain a metabolic map of the evoked patterns within SI, these results are broadly comparable to those expected using indirect measures of cortical metabolism such as PET and fMRI. However, the results of Whitsel and colleagues focus on *columnar* dynamics within SI, a spatial scale that is currently not accessible using fMRI in somatosensory cortex. It is therefore difficult to extrapolate results produced at this scale to the patterns detectable using fMRI.

However, while evidence for these effects exist, no evidence for ‘refractoriness’ was observed in my data set. Instead a positive trend was observed over increasing rates, up to and including 10Hz stimulation. These results are similar to those found by Kampe and colleagues (2000), who failed to detect any refractoriness of BOLD signal to different rates of median nerve stimulation, even at 100Hz. However, it is important to distinguish between their conclusions (‘larger fMRI responses can be obtained...at higher frequencies’), and those of my study. While I found that voxels within SI displayed rate-dependent effects, I did not find that I was more likely to detect SI activation using higher rate stimulation.

5.5.3 Somatosensory Rate-Dependent Responses – Neurobiological Issues

The field of computational neuroanatomy (Schwartz, 1980) treats the anatomical structure of the cerebral cortex as a ‘footprint’ of the functional computations performed in specific spatial locations. The topographical maps of the somatosensory cortex have been studied in a number of different species because they represent an ‘assay’ to test various neurobiological theories. In particular, the barrel cortex of the rat (in which segregated groups of neurons [barrels] receive afferent projections primarily from single vibrissae) has been studied in some detail. However, even in rat barrel cortex, point-to-point connectivity between whisker and cortex does not preclude the possibility of lateral cortical interactions increasing the area responsive to

stimulation. Using optical imaging, an area of approximately 2mm^2 is activated upon stimulation of a single whisker (Sheth et al., 1998). This is thought to cover the principal barrel-column for the whisker *and* all surrounding barrels. Thus even in the barrel cortex of rat, some spread of excitation to surrounding barrels may result from stimulation of a single vibrissae. However, as discussed above, there is some evidence that the influence of these intra-cortical influences can be lessened by presenting stimuli at certain rates.

As suggested by the references discussed in section 5.1., similar patterns of intracortical connectivity (albeit on a larger, more widespread scale) exist in human SI. If the lack of somatopical order over the configuration of the five digits that I observed in SI was due to smearing of the BOLD effect between neighbouring representations, then I would have expected to observe clusters within SI occupying extremely similar locations. Thus, although somatopical order could not be detected, the spread of lateral activation should have meant that a broadly similar lateral stretch of SI was be activated. This was not often the case. While it was possible to discern separate activation foci in the majority of cases, the order of these foci in SI did not conform to the Penfieldian pattern.

Similarly, there was no significant effect of stimulation rate on the production of significant activation foci. As with my first question, my motivation for this hypothesis was driven by the extensive literature on both rate- and intensity-dependent responses in SI. I hypothesised that some stimulus rates might recruit a greater number of surrounding neurons and thus, when averaged across a $3\times3\times3\text{mm}$ voxel, produce a higher mean intensity change (as, even if these neurons were involved in lateral inhibition, they should still produce a net *metabolic* gain across a voxel). However, I could not find evidence in favour of this postulation. Although I was able to activate SI in a greater number of single digit stimulation trials than in the second experiment presented in Chapter three, these responses did not behave as one might have expected given a purported somatopical organisation.

Detection of a somatopic pattern has been argued by some to be a ‘gold standard’ with which to benchmark the use of any new technique of imaging SI (Francis et al., 2000). My failure to detect any such pattern may argue that a non-physiological mechanism underlies my results, or that they may be prone to artefacts that act to obscure the ‘true’ organisation. However, there

are aspects of my results that argue against such pessimistic conclusions. A significant number of digit foci within SI displayed a parametric response that varied with the frequency of stimulation. While this finding is descriptive and not inferential, it is extremely unlikely to have arisen by chance (in 11/13 contrasts examined, rate-dependent responses in the amplitude of the sustained BOLD response across epochs were observed). Furthermore, activated voxels are on average limited to areas that, neurophysiologically, one would expect to be activated by the stimulus (contralateral SI, bilateral lateral sulcal areas, and in some cases cerebellum, insula and posterior parietal areas). The pattern of activation in Fig. 5.13 across four subjects argues in favour of this point. Thus, the current analysis seems more prone to type I, rather than type II, errors. This conclusion is reinforced by the PSTH plots of Figure 5.14. While clear evoked responses are seen in both subjects at all frequencies, the 5Hz thumb contrast in subject 2 produced no significant activity in SI. The difference between the evoked waveform and the modelled BOLD response was therefore not great enough to produce a significant result. However, the shape of the evoked waveform (green trace in Fig 5.14A) is not remarkably different from the other responses. This observation argues for the use of a more lenient experimental model to fit such ‘non-canonical’ responses, in which a single convolved function may not be sufficient to significantly model the shape of the evoked response. This argument may also explain the lack of significant responses in some of the subjects in the study.

5.5.4 Who To Tune?

The aim of this study was to investigate physiologically motivated questions, in which the responsiveness of somatosensory cortex was hypothesised to depend on endogenous cortical mechanisms that could be entrained by particular spatiotemporal patterns of somatosensory stimuli. No evidence was found to support either of the two positions initially proposed. However, while half of the subjects tested did not, on average, show responses within contralateral primary somatosensory cortex (SI), the remaining subjects demonstrated results that were neurophysiologically valid and spatially restricted. The results were therefore not consistently robust enough to support the initial hypotheses, yet not consistently negative to allow their outright rejection. Therefore, whereas my intention had been to focus on the use of stimulus characterisation as a means to optimally activate somatosensory cortex, the results of in this chapter suggest that the variability

may be due to between-subject factors. One can never be sure in passive attention experiments whether the subjects are doing what they are supposed to do, because there is no measure that can be used to rate subjects' performance. Therefore, in the next chapter I used a neuroimaging task that required processing of somatosensory stimuli to explore if *this* kind of tuning, focussing on subject factors rather than stimulus attributes was efficient in eliciting reliable activation of somatosensory cortex.

6 The Functional Neuroanatomy of Passive Tactile Discrimination

6.1 Goal-Directed Tactile Processing

The previous experiments presented in this thesis examined the change in BOLD activity in somatosensory cortical areas evoked by simple, passively applied stimuli. Although this approach was motivated by a justifiable need to simplify stimulus presentation, this situation is artificial. As discussed in Chpt.1, the generation of muscular action – movement – is the central nervous system's only external response to sensory information (Cotterill, 1996). Yet, while it is rare for stimuli *not* to be used to drive goal-directed behaviour, perception does not *have* to lead to a subsequent motor action.

The studies presented in Chapters 3 and 5 did not require subjects to acquire, store, or utilise any feature of the patterns of stimulation to guide behaviour. Subjects were told to attend to the pattern of stimulation, but were not required to process the stimuli in any way. This was deliberate: the tasks were initially intended to be 'probes' of the topographical organisation of somatosensory areas in patients who may have been unable to carry out even simple tasks in the scanner. Passive stimulation paradigms are also desirable when subjects have to be scanned over protracted periods of time, as they reduce possible confounds resulting from the effects of changing performance. However, this experimental design proved to be suboptimal. No clear definition of somatopical order could be shown within primary somatosensory cortex (SI). This obviously makes it difficult to evaluate any experimental questions that predict the spatial shift of representations within SI due to reorganisation after injury or experimental challenge.

However, the integrity of SI is not critical for all aspects of somesthetic perception. For example, after lesions to SI (particularly BA3b), macaque monkeys trained on a speed discrimination task could still signal the presence of a punctate tactile stimulus, although they could no longer classify its speed (Zainos, 1997). Thus not all computations performed by the somatosensory system necessarily require topographic maps as their substrate. The frequency-dependent

(and thus physiologically rational) responses found in SI in Chapter five suggest that the BOLD signal in response to somatosensory stimulation detected in previous experiments is indeed a measure of the underlying neuronal activity. However, the technique (as applied in this thesis) may produce occasional spatial mismatches between flow and firing, caused by as-yet-unknown variables. A logical progression when faced with such a problem is to look at somatosensory cortical areas in which information processing may not require a spatial metric – in other words, cortical areas that are ‘higher’ in the sensory processing hierarchy. I therefore shifted the focus of my work in order to develop tasks that would probe other cortical areas associated with tactile processing.

6.1.1 The Somatosensory System: Beyond SI

My previous experimental questions were focused on the internal organisation of the primary somatosensory cortex (SI). However, SI does not operate in a vacuum. Combinations of different methods of areal classification (cytoarchitectonic, neurophysiological, tract-tracing) have identified ten separate areas within the parietal cortex as ‘somatosensory areas’ (Burton and Sinclair, 1996). In the macaque, Burton and Sinclair (1996) list these areas as BA1, 2, 3a and 3b (the four anterior parietal regions), BA5 and 7 (lying in posterior parietal cortex), and a further four lateral sulcal regions (SI_l, SI_p [SII and PV of Krubitzer et al., 1995], retroinsular cortex, and granular insula). Like other primate sensory systems, these areas are considered to be hierarchically organised, as determined by analysis of the density and direction of inter-cortical connections (Felleman and Van Essen, 1991). The implication of this is that information should flow from early sensory cortex (SI), which receives direct thalamocortical projections, to later cortical areas that are specialised for distinct aspects of somesthetic processing. This has been confirmed by a number of studies in non-human primates: receptive field complexity and size increase as one proceeds from anterior parietal cortex (SI) to parietal (BA5/7) and temporal (insula) association areas (reviewed in Iwamura, 1998). Thus, at a gross anatomical level at least, the somatosensory system can be considered to have a similar cortical organisation to the visual system. However, the relationship between structure and function is less certain in the somatosensory system.

In the visual system there are a number of dominant theories that link patterns of connectivity to behavioural theories of how areas interact to produce complex behavioural and perceptual phenomena (e.g. Ungerleider and Mishkin, 1982; Milner and Goodale, 1996; Zeki and Shipp, 1988). The dissociation between the ‘dorsal’ and ‘ventral’ processing of visual information has proven to be an influential impetus for ongoing programs of research. Similar schemes have been proposed in other modalities. In the auditory system recent studies have proposed analogous organisational principles to the visual dorsal and ventral regions (Rauschecker 1998; Romanski et al., 1999). In the somatosensory system a similar organisation may also exist. This was first proposed by Mishkin (1979), who argued from lesion data in non-human primates that a pathway between anterior parietal and medial temporal lobe areas may mediate tactile learning and memory (Fig. 6.1. below). However, although subsequent neuroanatomical work (Friedmann et al., 1986) illustrated that such a ‘ventral’ complex of somatosensory regions does indeed exist in the macaque, it is still unclear if this projection system mediates similar *functions* to the ventral visual pathway. Nor has there been much success in demonstrating this role physiologically – to date, there has been only a single PET study reporting activation of ‘ventral’ somatosensory and temporal areas in response to tactile memory paradigms (Bonda et al., 1996).

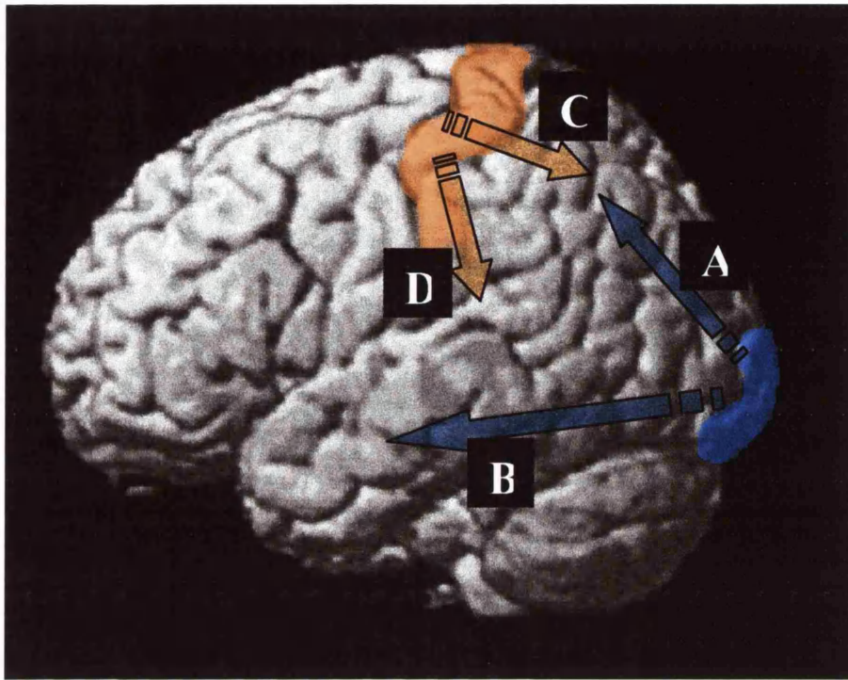


Figure 6.1. Illustration of the 'dorsal' and 'ventral' pathway hypotheses in vision and somesthesia. In vision (blue pathways) information flow from V1 (solid blue area) is hypothesised to be segregated into 'dorsal' (arrow A) and 'ventral' (B) processing pathways (Ungerleider and Mishkin, 1982). It is currently unclear if a similar distinction exists in somesthesia (SI is shown in red), although a ventrally directed pathway from SI has been proposed by Mishkin (1979, arrow D) and confirmed by tract-tracing studies (Friedman et al., 1986). In addition, SI sends dense afferent projections to the posterior parietal cortex (C) (Vogt and Pandya, 1978; Jones et al, 1978; Jones and Powell, 1970).

If the somatosensory system in humans is organised in a similar fashion to the visual system, the conceptual framework suggested above may prove to be a catalyst for the generation of further hypotheses. Yet, while the patterns of anatomical connectivity between somatosensory cortical areas are reasonably well documented, the functional relationships between them remain somewhat opaque. For example, the somatosensory areas of the lateral sulcus (SII/PV) occupy a relatively early position in the hierarchy of somatosensory cortical processing?. Nevertheless, little is really known about their functional role. They were first discovered in cats and named the 'second' somatic receiving zone by Adrian (1941). Although this classification scheme was primarily chronological, SII and PV have been traditionally considered as 'higher' somatosensory areas. However, the direction of information flow between SI and SII is still contentious. While ablation experiments in higher primates (Burton et al., 1990; Garraghty et al.,

1990; Pons et al., 1987, 1992) and analysis of SEF latencies between SI and SII (Hari et al., 1993) suggest that tactile information is processed serially from the thalamus to SI and then SII, the existence of direct thalamic projections from the ventrobasal nucleus of the thalamus to SII coupled with deactivation studies (Rowe et al., 1996; Zhang et al., 1996) calls into question the veracity of this idea. Thus, knowledge of the functional specialisation of different somatosensory areas for different aspects of somesthesia has not advanced far beyond the level of speculation.

6.1.2 Previous Studies of Functional Segregation in the Somatosensory Cortices

While little consensus has yet to emerge regarding the assignment of different functions to different somatosensory cortical areas, there have been a number of interesting experiments that suggest that these distinctions at least exist in some form in humans and higher primates. The behavioural characterisations of patients with focal cortical lesions carried out by Caselli, Reed and colleagues (Caselli, 1993; Reed and Caselli, 1994; Reed et al., 1994) and Saetii et al. (1999) suggest that lesions to different 'somatosensory' cortices can produce different patterns of behavioural deficits. According to Reed and colleagues, lesions to dorsomedial cortex (including the supplementary motor area [SMA] and the medial aspects of BA5 and BA7) result in the disruption of somesthetic processing *per se*, whereas ventrolateral lesions (including SII and PV) disrupt tactile object recognition (Caselli, 1993). These researchers suggest that there may be dorsal and ventral somatosensory pathways that process distinct aspects of somesthesia. However, focal lesions that disrupt only somatosensory cortical areas are rare. Thus, however compelling these results may be, lesion studies considered in isolation are not sufficient evidence for the segregation of cortical areas physiologically.

Physiological evidence for segregation of function in the somatosensory system has been similarly sparse, although haptic processing and discrimination has been examined in some detail using PET. Roland (1987) was amongst the first to introduce the concept that, in a similar fashion to the parvocellular and magnocellular pathways of the primate visual system, ascending somatosensory information may stay segregated at the level of the cortex, where it may in turn be

processed by separate areas. If this assertion is correct, ‘probing’ the somatosensory system by presenting or requiring subjects to attend to different stimulus dimensions could reveal the functions of different cortical areas. However, one must first decide what features are the most appropriate to use.

Some researchers (e.g. Roland, 1987) have focused on classifying stimuli according to either surface (*microgeometry* e.g. roughness) or object features (*macrogeometry* e.g. length). These features are thought to be combined during active touch (haptic exploration) to build up a three-dimensional percept of an object. However, haptic discrimination tasks involve both sensory *and* motoric processes. The analysis of individual haptic features through active touch contributes not just to the identification of a given three-dimensional object, but also to the selection of future movements that facilitate a subject’s sampling of an object. This interaction between sensory and motoric processing during haptic discrimination makes it difficult to claim conclusively that one can control for the motoric component of haptic touch by comparing/subtracting movement conditions from active touch conditions, even when using sophisticated measures to characterise movement such as kinesthetic analysis.

Even comparing differential activations between haptic tasks may not be sufficient. For example, O’Sullivan and colleagues (1994) found that, while they could control for finger contact time, number of downward movements and peak finger velocity when using PET to compare roughness discrimination and length discrimination, subjects used different ‘sampling strategies’ between the two tasks. During length discrimination, subjects spent far longer exploring the upper edge of the stimulus than during roughness discrimination. While it can be argued that it is simply impossible to control for every contingency between different perceptual tasks without reducing the very attributes that make them different in the first place, it may be expedient at present to avoid tasks of this sort until more basic research on the neurovascular correlates of exploratory hand movements has been done, so that these can be controlled for. Another approach to this problem is to simply compare activity during tactile exploration with that during a ‘rest’ state, thus tacitly accepting that both motoric and sensory activity related to haptic

processing will be present in subtraction images (e.g. Boecker et al., 1995; Deibert et al., 1999).

These concerns motivated the design of the current experiment. As haptic tasks may produce potentially ambiguous activation patterns because of their active component, a purely passive stimulation task was chosen. This task allows potential motoric confounds to be reduced, as subjects are passively presented with tactile stimuli that can be discriminated according to different criteria. This approach has proven useful in neuroimaging studies of the human visual system. In these paradigms, subjects are typically asked to attend to different dimensions of the same stimuli, thus increasing neurovascular activity in the cortical areas specialised for processing such attributes (Corbetta et al., 1991; Sergent et al., 1992; Haxby et al., 1994; DeYoe et al., 1995). A similar strategy is to require subjects to perform different perceptual tasks using the same visual stimuli (e.g. Dupont et al., 1993). These studies suggest that experiments that require subjects to selectively analyse the different features of stimuli can be a powerful tool to elucidate the cortical organisation of sensory systems.

Early neuroimaging studies of visual attention examined the cortical responses to simple, impoverished visual stimuli, even though much of visual perception is undoubtedly concerned with the processing of objects (e.g. Olson and Gettner, 1996). The use of simple stimuli passively applied to the skin surface allows a number of potentially confounding influences on tactile processing to be controlled. In this study I used a passive touch paradigm and punctate stimuli, attempting to demonstrate functional specialization within higher-order somatosensory areas by manipulating the task demands and thus the stimulus dimensions that subjects attended to.

6.2 Materials and Methods

In the current experiment I was interested to see if it was possible to differentiate between the putative roles of different somesthetic cortical regions by using a design that required subjects to discriminate stimuli according to different task demands. This question has been previously addressed by Roland and colleagues (1998) and Burton and colleagues (1997a, 1999) using PET. However, there had been, to the best of my knowledge, no studies performed using fMRI.

6.2.1 Stimulus Delivery

The dorsal/ventral distinction made in the visual system subdivides cortical processing areas by their involvement in ‘what’ an object is versus ‘where’ that object is located in space. The possibility that this distinction exists in the somatosensory system motivated the design of the current experiment (there is anatomical support for this view – see arrows C & D in Fig 6.1.). It is important in studies of this nature to balance task difficulty, motor responses, and stimulus presentation between the behavioural tasks to be compared, so as not to confound the results. This task is made easier if compound stimuli are used that can be classified in a number of ways. Figure 6.2. below shows the stimulator setup used in the current experiment. The stimulus array was placed on the volar skin of the subject’s left thumb, leaving a gap between the skin and the end of the airpuff nozzle. As in Chapter five, the only changes to the airpuff stimulator setup was the different stimulus array, so that airpuffs separated by a short distance on the skin could be delivered.

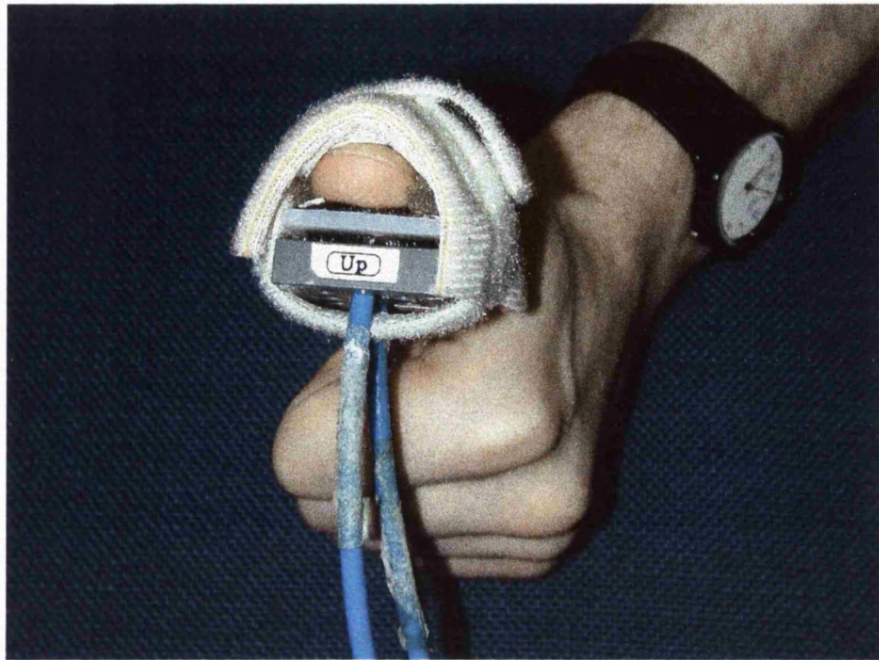


Figure 6.2. Airpuff stimulator used in the current experiment. Two separate channels were used, separated by 15mm. At each channel, two intensities could be delivered – 0.19N (low intensity) and 0.4N (high intensity). Thus a total of four stimuli could be delivered to the subject, each composed of a single level of both factors – intensity and location.

Using the current airpuff stimulator, the simplest compound stimuli that can be delivered are airpuffs that can be identified using different stimulus dimensions. The stimuli used in the experiment could be classified according to either intensity or location, each of which had two levels – high and low. Using stimuli of this kind ensures that, while the stimuli remain constant, task demands can be changed to require subjects to process and discriminate according to different criteria. ‘Location’ was chosen as this is a common attribute examined in analogous studies in the visual system, and ‘intensity’ because, although the stimuli could not be said to be ‘objects’, intensity discrimination tasks require subjects to focus on a feature of the airpuffs that is not related to their location.

6.2.2 Behavioural Task – Location and Intensity Discrimination

The task was designed to allow subsequent analyses to evaluate task-related differences in activation (i.e. were subjects performing location or intensity discrimination tasks?). A single experimental ‘trial’ is depicted in Figure 6.3. below.

Each trial consisted of the sequential delivery of three airpuff stimuli. Trials were delivered in blocks, such that each block contained four trials (so a block contained twelve separate airpuff stimuli). At the beginning of each block, subjects received an auditory signal that informed them of the task to be performed on trials in that block. This could be either 'location' (location discrimination), 'intensity' (intensity discrimination) or 'control' (subjects were not required to discriminate stimuli in this block). Successive stimuli within a trial were separated by a variable delay lasting from 0.5s-8s (mean delay 5.5s). This served two purposes: it ensured that subjects were not able to predict in advance when the stimuli would occur, thus making certain that they had to pay close attention throughout each trial, and it also increased the relative frequency at which the haemodynamic response (hrf) was sampled. By using a 'jittered' stimulus onset (Josephs et al., 1997) it is possible to sample the evoked hrf at a particular voxel with a higher frequency than that expected from the TR of the experiment.

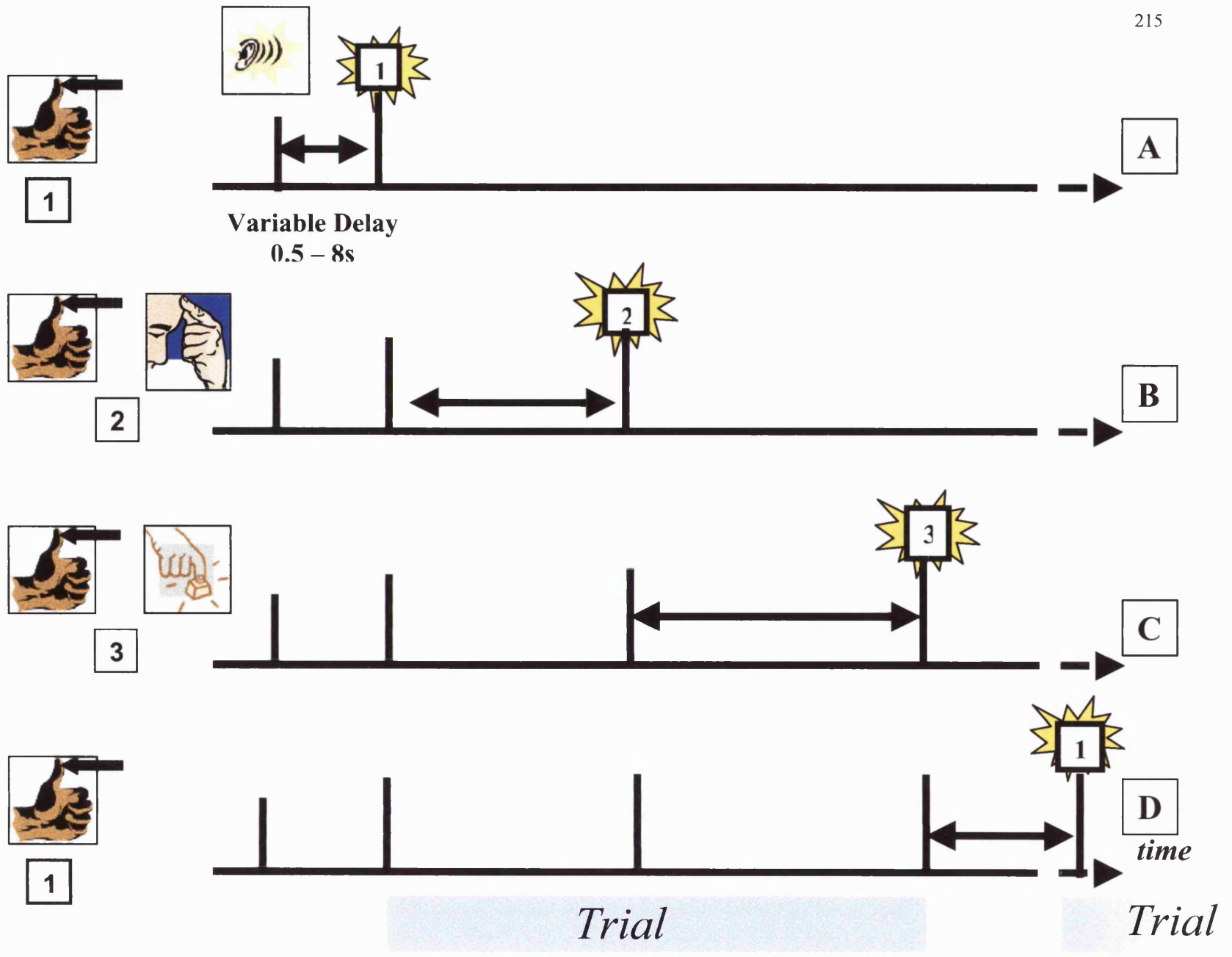
The three stimuli that comprised a trial were composed of 'target', 'probe', and 'response' stimuli. Stimuli always occurred in this order. Subjects were required to perform a same/different judgement on the target and probe stimuli, and respond (if required) when cued by the response stimulus. To dissociate categorical sensory decisions (i.e. 'were the pair of stimuli the same or different?') from the subsequent motor response, subjects underwent two separate scanning sessions. In one session, subjects pressed a button when the stimuli were the same, and vice versa in the second. Subjects did nothing when cued to respond to a perceptual judgement that did not require a motor response. Using this design, categorical sensory judgements can be dissociated from motor responses, as on average, across both sessions, each subject responded with a button press 50% of the time to a 'same' stimulus pair, and 50% to a 'different' stimulus pair. . In a similar manner, motor responses can be disambiguated from sensory decisions (although this was not the specific aim of the current analysis).

A typical trial at the beginning of a 'location' block is shown graphically in Figure 6.3. below (p.215). The four different timelines represent subsequent periods of time, beginning with the first timeline 'A'. Here an auditory signal

(‘location’) identifies the task to be performed during the block. After a variable delay the subject receives a single airpuff to the thumb. Depending on the location that the airpuff is delivered to, the subject must classify it as high or low, and hold this information online until the delivery of the second airpuff (timeline ‘B’). Subjects must categorise the second (probe) airpuff and then decide if it is the same or different to the first (target) puff. In addition, depending on the scanning session, this categorisation may or may not result in subjects having to make a subsequent motor response. If a motor response is required, it is signaled by the third (response) puff, shown in timeline ‘C’. If subjects are not required to respond, they do nothing when the response puff is given other than note its occurrence. During control blocks, subjects were told not to attend to the stimuli.

The period between the delivery of the first ‘target’ and the third ‘response’ stimulus is classified as a trial. When the next airpuff is delivered, a new trial begins and so on, until the block ends and a new block is signaled by an auditory cue as before. Each trial thus contains a number of separate components: the detection and categorisation of somatosensory stimuli according to different criteria (location or intensity), and the transformation of a purely sensory decision into a motor response (or not). However, by keeping the stimuli and difficulty of each task constant, and systematically changing stimulus/response criteria across sessions, it is possible to examine differences in the pattern of neurovascular signal change between each of these separate processes. In addition, the comparisons between each of these conditions and the control blocks allow differences between actively processing tactile stimuli and passively receiving them without task demands to be compared.

Figure 6.3. (next page). Schematic illustration of the different components (‘target’, ‘probe’ and ‘response’) comprising each discrimination trial. The four timelines (A-D) show successive events comprising a single trial. The symbols to the left of each timeline graphically depict the different processes involved in each component i.e. 1 – airpuff, 2 – airpuff and discrimination, 3 – airpuff and conditional motor response.



6.2.3 Subject and Scanning Details

Eight right-handed males (mean age 26, age range 21-34) served as subjects. The local ethics committee approved the experimental procedure and all subjects signed a consent form before being scanned. The data were acquired on a Siemens MAGNETOM Vision scanner (Siemens, Erlangen, Germany) at 2T. The EPI volumes in the current experiment were acquired using slightly thicker slices than previously (4mm vs. 3mm) to enable whole-brain data to be acquired with a shorter TR, as the high spatial resolution of previous experiments was not required. Each BOLD-EPI volume scan consisted of 32 transverse slices (inplane matrix 64x64; voxel size 3x3x4mm; TE=40ms; TR=3.16s). 1030 volume scans in total were collected from each subject (2 sessions x 515 scans per session). A T1-weighted high-resolution MRI of the subject (1 x 1 x 1.5mm resolution) was acquired to facilitate anatomical localisation of the functional data. Auditory stimuli were delivered via a custom-built sound delivery system, with headphones designed to attenuate scanner noise (Palmer et al., 1998).

6.2.4 Experimental Setup

Each subject was familiarised with the stimuli outside the scanner, and performed a short run (roughly 5 minutes) of the experimental paradigm to ensure that they understood the tasks. Due to difficulties observed in subject performance on the tasks during pilot studies, subjects were explicitly told that they would only be receiving four possible stimuli during scanning. This allowed subjects to instantly categorise stimuli when they received them (thus making the task easier).

Stimuli were always delivered to the volar surface of the subject's left thumb. The array was positioned so that the locations of the two nozzles in the stimulus array (constructed from Perspex, nozzles similar to chapter 5) were roughly similar between subjects. Behavioural responses were made with the index finger of the right hand using an MRI-compatible button box. Subjects were only required to respond to trials when a particular response was the outcome of a perceptual discrimination. The order of this response was counterbalanced over subjects i.e. four subjects had to respond to 'same' trials in their first session, and four to 'different' trials. While in the scanner, subjects kept their eyes open but were not required to fixate. Amplitude-modulated periodic white noise stimuli were played to

prevent subjects hearing the airpuffs during scanning (noise parameters as chapter 5).

The experiment was designed so that subjects performed the same number of same/different trials in both location and intensity tasks in each session, thus balancing both the motoric and categorical sensory decision elements between tasks. During each session, subjects received a total of 24 blocks, 8 of each type (either location, intensity or control). The order of blocks was pseudo-randomised across each session controlling for first-order transitions between block types. As mentioned above, each block contained 4 trials, and so subjects were presented with a total of 32 different trials per session. These trials were balanced so that the correct response to 16 trials was 'same' and to the remaining 16 trials was 'different'. This was similar across all block types. Therefore in both sessions subjects received a total of 32 separate location or intensity discrimination trials. In half of these trials, they were required to make a motor response if they discriminated the stimuli correctly. The order of same/different trials across blocks was individually randomised for each subject using software written on the MATLAB 5 platform.

6.2.5 Image Preprocessing and Data Analysis

6.2.5.1 *Spatial Preprocessing*

Data preprocessing was carried out using SPM99 (Wellcome Dept. of Cognitive Neurology, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>) implemented in Matlab5 software. All preprocessing was carried out in a similar fashion to that in previous experiments (as described in section 3.2.3.3). Four scans were removed to allow for T_1 saturation effects, and subjects' scans were realigned across both sessions before spatial normalisation. All functional volumes were smoothed using an 8mm FWHM isotropic Gaussian kernel.

6.2.5.2 *Image Data Analysis*

Data analysis used SPM99 as before. Functional volumes from all sessions were treated as a timeseries, and experimental effects estimated using a multi-session design matrix that included separate session mean terms. Data from each subject were modeled as a multi-session, multi-subject design matrix, with a total of 2 sessions/8 subjects modeled (16 sessions total). Each single session partition of the

design matrix consisted of 5 covariates of interest, partitioned according to the scheme in Fig 6.4. below. Intensity and position trials where subjects responded wrongly were modeled separately per session and condition.

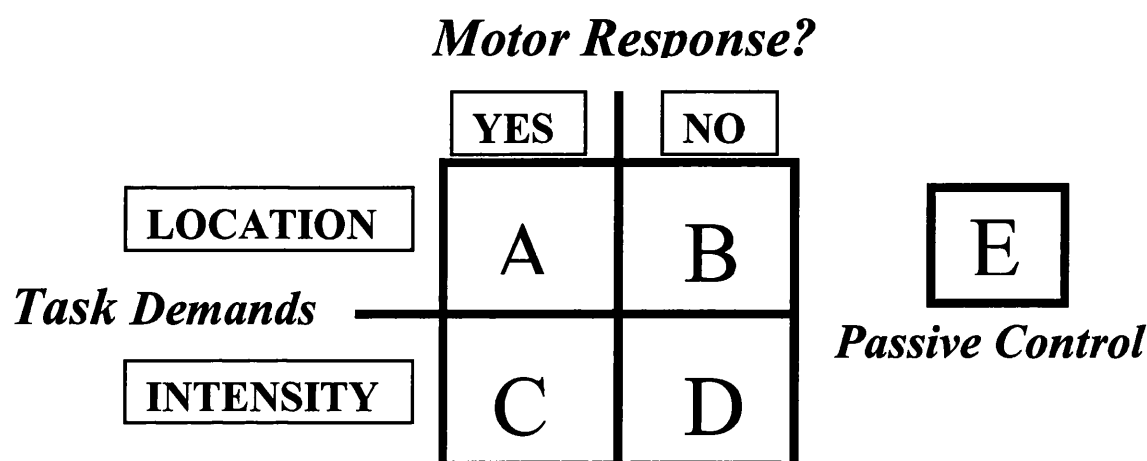


Figure 6.4. Different classification of covariates in each subject's experimental model. Each trial within a block is classified according to block type (location [A and B], intensity [C and D], and passive control [E]). It is then possible to further divide these trials into those in which subjects made a motor response (A/C) versus those when they did not (B/D). Thus each subject's single session model consisted of a minimum of five covariates (trials on which subjects responded incorrectly were also modeled to ensure that as much experimental variance as possible was modelled).

The experimental covariates were modeled as in previous experiments as box-car functions convolved with the expected HRF. In addition, six covariates representing the estimated movement parameters for each scan (obtained from the realignment parameters) were included per session. To remove low-frequency noise the data were high-pass filtered using a set of discrete cosine basis functions with a minimum cutoff period of 32s. Temporal autocorrelation was dealt with using the method of Worsley and Friston (1995), by temporally smoothing the session time series with a Gaussian kernel of 4s FWHM.

Linear contrasts of the covariates were evaluated per session for the comparisons (location with no motor response, **B**) – (passive control, **E**) and (intensity with no motor response, **D**) – (passive control, **E**) and the average effect of task (i.e. covariates **A,B,C** and **D**) - passive stimulation (**E**). As the current analysis explored only fixed-effects levels of significance (see chapter 4 for a more detailed discussion of the benefits and costs of random-effects models) conjunction analyses

(Friston et al., 1999) were used in the B–E and D–E comparisons. The conjunction analysis assesses significance by calculating the probability that a given voxel would have a T value T_{min} by chance across all n (here $n=16$) independent contrasts. Thus a conjunction analysis identifies voxels that are significantly activated across all subjects/sessions, at a significance value adjusted for the number (n) of independent T -fields used in the analysis. All results were displayed as a voxelwise statistical parametric map of t values. All maps were thresholded at a significance level of $p<0.05$ corrected for multiple comparisons across the entire image volume. This conservative threshold reflects the fact that I did not have any strong *a priori* hypotheses about the locations of activated voxels.

6.2.5.3 Behavioural Data Analysis

Subjects' responses to location and intensity trials were evaluated to compare the percentage responses correct between different tasks. Wrong responses were classified as trials in which subjects made motor responses when they should not have or failed to make responses when a trial demanded it.

6.3 Results

6.3.1 Behavioural Results

To compare the difficulty of the location and intensity trials, the mean numbers of correct responses to trials was compared across tasks. Performance on the two tasks was very similar – mean performance across sessions and subjects on intensity trials was 29.7 ± 1.8 correct responses out of 32 (92% correct, $N=16$), while mean performance on location trials was 30.06 ± 2.1 (94% correct). No significant difference was detected between performance on either task (2-tailed Wilcoxon signed ranks test, $N=16$, $p>0.204$). Therefore, as assessed by this measure, the two active tasks were matched for difficulty.

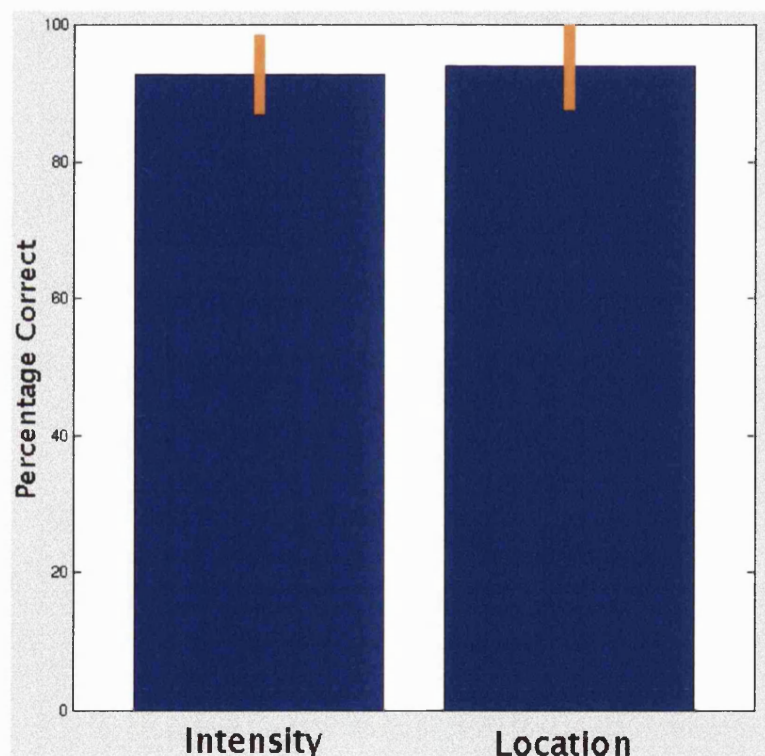


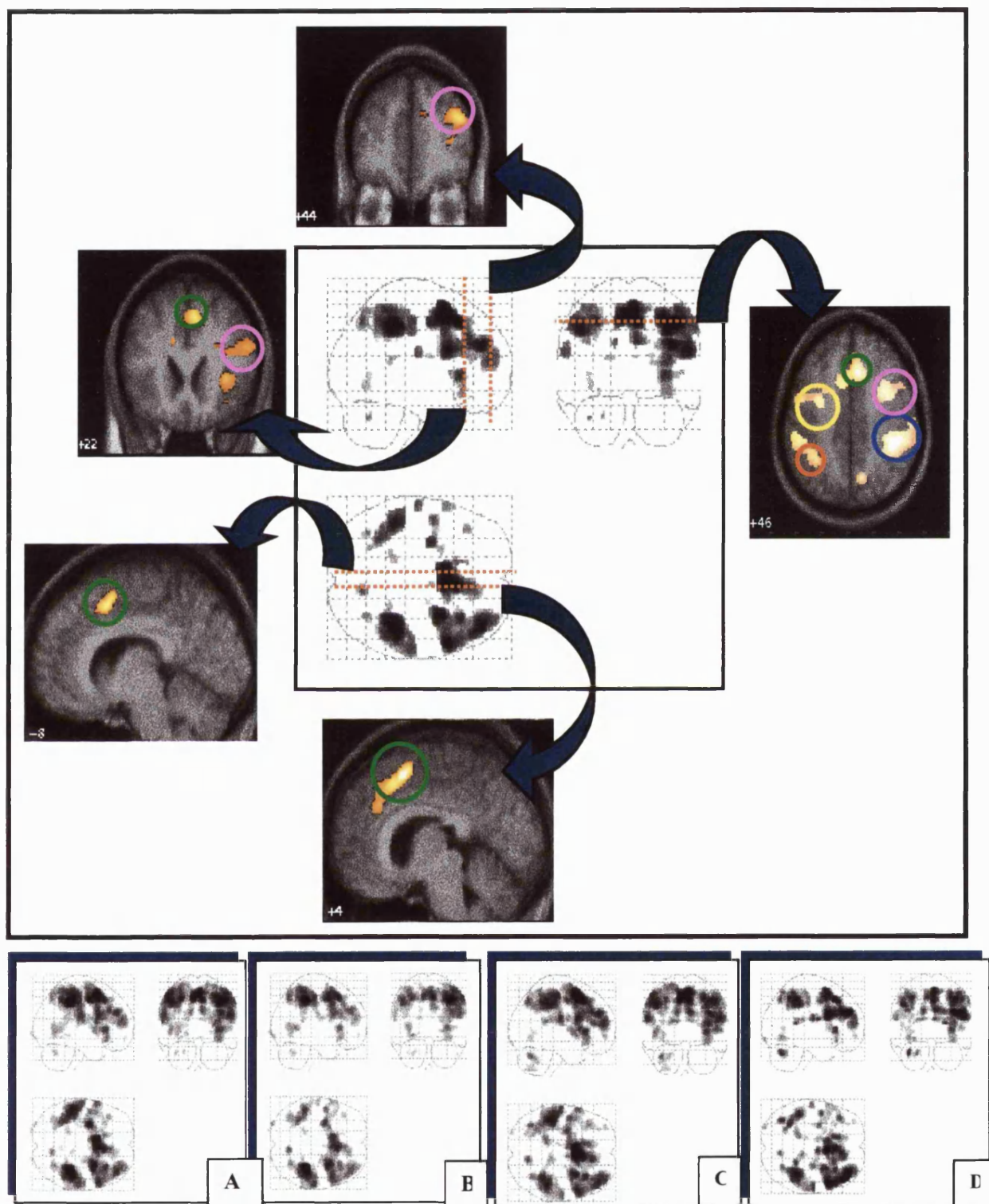
Figure 6.5. Mean percentage correct trials across all sessions and subjects (8 subjects, each of whom were scanned twice; $N=16$). The red bars in the centre of each column represent the standard error on the mean of each mean score.

6.3.2 Imaging Results

6.3.2.1 *Categorical Comparisons – Areas activated across all conditions > control*

Fig. 6.6 shows the maximum intensity projections (MIP) of the average comparison across all sessions $[(A+B+C+D) - (E)]$ – in other words, the main effect of somatosensory discrimination across all conditions minus activation due to passive presentation of the stimuli. As the results of this contrast can be disproportionately weighted by a large enough effect in conditions **A**, **B**, **C** or **D**, the contrast was inclusively masked at $p < 0.05$ corrected for multiple comparisons by the simple effects **A-E**, **B-E**, **C-E** and **D-E**. This ensures that the MIP contains *only* voxels that show a significant effect in *each* of the simple contrasts. This contrast can thus be interpreted as showing areas belonging to a network of areas involved in the discrimination task, irrespective of the criteria used to discriminate or whether the decision was transformed into a motor response. The areas significantly activated in the MIP are listed in Table 6.1 below. These included bilateral posterior parietal cortex, bilateral frontal eye fields (FEF), right middle and inferior frontal gyri, and bilateral anterior cingulate gyrus.

Figure 6.6. (Next page). Maximum intensity projection (MIP) of voxels showing a significant ($p < 0.05$ corrected for multiple comparisons) effect in the masked $(A+B+C+D) - E$ contrast. The red lines denote plains of section that are displayed in the rendered brain slices. Activated voxels are displayed on 2mm slices of a normalised T1-weighted structural scan constructed by averaging together all eight subjects' normalised structural scans. The intensity of voxels in the colour slices is indicative of their statistical significance. The simple effect contrasts used to mask the main MIP are shown at the bottom of the figure (e.g. 'A' is the contrast A-E, and so on. The coloured circles around activations denote different areas listed in Table 6.1.



Area	Cluster Size (<i>k</i>)	<i>T</i> Value	Talairach Co-ords		
			X	Y	Z
Right Posterior Parietal*	1701	14.07	40	-36	44
Right Pre-SMA/Anterior Cingulate, Left Anterior Cingulate*	1247	13.94	4	10	56
Right FEF, Right Middle Frontal Gyrus*	2797	12.42	32	6	50
Left Posterior Parietal*	1024	11.99	-46	-36	40
Left FEF	233	11.11	-30	-4	46
Right Inferior Frontal Gyrus	325	10.77	34	24	4
Left Parietal Operculum	47	9.71	-60	-16	22
Right Parieto-Occipital Junction	95	9.63	10	-68	48
Rostral Left Anterior Cingulate	20	9.31	-12	22	30
Left Anterior Parietal Operculum	64	8.94	-60	12	26
Left Lateral Anterior Lobe of Cerebellum	4	8.93	-38	-64	-32
Right IPS	45	8.77	32	-64	56
Left Middle Frontal Gyrus	29	8.77	-40	30	30
Rostral Left Anterior Cingulate	6	8.76	-14	28	30
Left Medial Anterior Lobe of Cerebellum	10	7.92	-24	-60	-30
Right IPS	7	7.70	34	-62	42
Left Lingual Gyrus	40	7.63	-36	-64	-6
Left Lateral Premotor	6	6.77	-42	4	32

Table 6.1. Areas significantly activated in the masked (A+B+C+D) – E contrast. The coloured asterixes refer to similar areas activated in Figure 6.6. above.

6.3.2.2 Individual Task-Control Contrasts - Conjunctions

To identify areas preferentially activated during the different somatosensory discrimination tasks, task-specific conjunction analyses were performed. Areas significantly activated ($p < 0.05$ corrected for multiple comparisons) across all sessions ($n=16$) in the contrast ‘intensity no motor response (B) – passive control (E)’ are shown in Figure 6.7A. Areas significantly activated ($p < 0.05$ corrected for multiple comparisons) across all sessions in the contrast ‘location no motor response (D) – passive control (E)’ are shown in Fig. 6.7B. These two contrasts identify voxels in which there was a significant experimental effect that could not have been caused by motoric responses, removing this potential ambiguity.

The two contrasts contain both similar and task-specific areas of activation: right posterior parietal cortex (blue circle in Fig. 6.7 A&B) and right middle frontal gyrus (green circle in Fig. 6.7 A&B) were activated in both contrasts. Other cortical areas were differentially activated across both contrasts (e.g. medial frontal gyrus in intensity > control conjunction, left posterior parietal cortex in location>control conjunction). Somewhat surprisingly, no early somatosensory cortical areas (postcentral gyrus, SII or PV) were activated in either of these contrasts.

6.3.2.3 Differential Activations – Task-Related Comparisons

No significantly activated voxels ($p < 0.05$) were found when evaluating the contrasts (Intensity No Motor Response) > (Location No Motor Response) or (Location No Motor Response) > (Intensity No Motor Response).

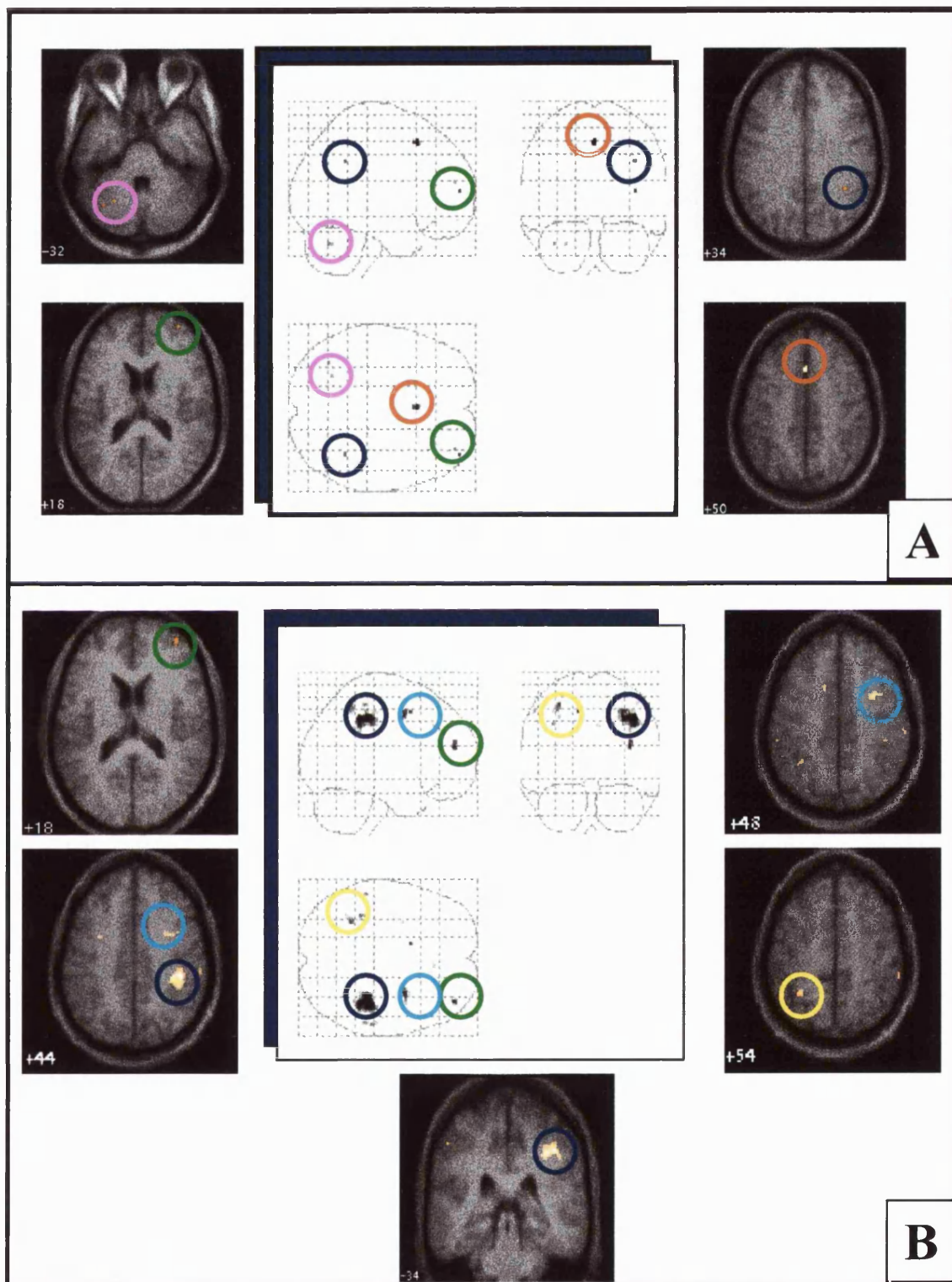


Figure 6.7.A. MIPs displaying significantly activated voxels in (Intensity no Motor Response) > (Passive Control) conjunction. B. MIPs and axial slices (2mm thick) displaying significantly activated voxels in (Location no Motor Response) > (Passive Control) conjunction.

Area	Cluster Size (<i>k</i>)	Z Value [#]	Talairach Co-ords		
			X	Y	Z
Medial Frontal Gyrus*	10	6	-2	18	50
Right Middle Frontal Gyrus*	2	5.57	38	58	10
Right Posterior Parietal*	2	5.50	38	-48	34
Left Anterior Lobe of Cerebellum*	1	5.44	-36	-64	-32
Right Middle Frontal Gyrus*	1	5.43	34	54	18
Left Anterior Lobe of Cerebellum*	1	5.38	-26	-60	-32

Table 6.2. Areas significantly activated in the conjunction analysis (Intensity no motor response) – (passive control). The coloured asterixes refer to circled cortical areas in Fig. 6.7A above. [#]T-values are not available for conjunction analyses – the Z values are normalised *T* scores.

Area	Cluster Size (<i>k</i>)	Z Value [#]	Talairach Co-ords		
			X	Y	Z
Right Posterior Parietal*	237	12.00	40	-32	44
Right Middle Frontal Gyrus*	18	7.24	38	50	18
Right FEF/Premotor*	36	7.12	30	2	46
Left Anterior Cingulate	3	6.76	-12	8	48
Left Posterior Parietal	22	6.51	-30	-50	54
Left Posterior Parietal	3	6.1	-36	-40	38
Right Posterior Parietal*	7	6.08	58	-26	48
Right Posterior Parietal*	3	6.01	56	-36	54
Left Posterior Parietal	2	5.92	-54	-34	48
Left FEF	2	5.52	-30	0	44

Table 6.3. Areas significantly activated in the conjunction analysis (Location no motor response) – (passive control). The coloured asterixes refer to the areas circled in Fig 6.7B above.

6.4. Discussion

6.4.1 Aims and Results of the Experiment

The current experiment was designed to dissociate the functions of different somatosensory cortical areas by requiring subjects to use different discrimination criteria to perform a simple tactile task. The two different paradigms used (location discrimination and intensity discrimination) were selected to have matched difficulty, and used the same stimuli to ensure that any differences seen would specifically reflect the computations involved in performing each task. In addition, because of the spatial proximity of somatosensory and motor cortical areas, 50% of the trials did not require subjects to make a motoric response to signal their perceptual decision. Thus it was possible to specifically identify cortical areas involved in attending to, comparing and discriminating punctate tactile stimuli.

Two kinds of analyses were performed: first, the main effect of all discrimination task epochs was contrasted with epochs in which subjects passively received the stimuli. This analysis was masked with the simple contrasts between each individual condition (i.e. A (location/motor), B (location/no motor), C (intensity/motor) or D (intensity/ no motor)) and the passive stimulation condition (E). Areas activated in this contrast included bilateral posterior parietal cortex, bilateral frontal eye fields (FEF) and anterior cingulate cortex. These areas are frequently seen in neuroimaging studies of selective attention to peripheral visual (Corbetta et al., 1993; Nobre et al., 1997; Kim et al., 1999), auditory (Griffiths et al., 1998; Bushara et al., 1999) and tactile targets (Johannsen et al., 1997; Burton et al., 1999). The second analyses were designed to identify areas that displayed statistically significant ($p < 0.05$) differences in BOLD signal in either the intensity discrimination or location discrimination tasks, when compared to activation during the passive stimulation condition. A third analysis was also carried out, in which signal change between the intensity and location discrimination tasks was compared; however, this analysis did not contain any significant voxels.

6.4.2 Areas Involved in Attention to and Discrimination of Tactile Stimuli

The first analysis (Figure 6.6, Table 6.1.) was designed to show areas involved in the processing and discrimination of tactile stimuli, irrespective of the criteria used. The masking procedure employed ensured that any voxels that did not display

significant activation in all the simple comparisons (i.e. between each discrimination condition and the passive presentation of stimuli) would be excluded. Thus the voxels in Figure 6.6 are those that are active on average throughout all the tactile task trials.

The MIP presented in figure 6.6. is strikingly similar to previous neuroimaging studies in which subjects were required to attend to and detect visuospatial stimuli, frequently involving a variant of the Posner selective cueing paradigm. Typically, these studies refer to a visuospatial attention ‘network’ (Mesulam, 1981; Coull 1998) that includes bilateral posterior parietal cortex, bilateral FEF and anterior cingulate cortex. These areas were all activated in the current study, even though subjects could not see their hands or the stimuli during scanning. Thus the current results suggest that attention to tactile events in the periphery activates a similar network to studies of visuospatial attention, even though subjects were only required to perform spatial computations in one of the tasks. However, subjects were required to direct their attention covertly to the position of the left thumb throughout all active task epochs to detect the tactile stimuli. The bilateral parietal activation (encompassing both the inferior [probably BA40] and superior [BA7/40] parietal lobules) may therefore reflect a biasing of attention towards a representation of the thumb area in a multimodal spatial representation, such as that contained within the posterior parietal areas (e.g. Andersen et al., 1997). Neuroimaging studies of tactile attention (Johansen et al., 1997; Burton et al., 1999) found similar results to those of the present experiment, although these authors did not detect activation of the frontal eye fields. This discrepancy may have been caused by the fact that in the current study subjects were allowed to keep their eyes open during discrimination tasks, primarily to ensure that they did not fall asleep during scanning. As eye movements were not monitored, and saccadic eye movements activate the FEF bilaterally (e.g. Petit et al., 1997), this may be the cause of the FEF activation.

In addition to the activation of the ‘cortical epicentres of the attentional network’ (Kim et al., 1999), a number of foci specific to the current delayed-matching tactile task were identified. The most extensive of these were found bilaterally in the frontal lobe (including the left middle frontal gyrus and the right middle and inferior

frontal gyri). The greater activation of the right-sided frontal foci is in agreement with the proposed right-hemisphere dominance for attention to peripheral stimuli (Mesulam, 1981). In addition, a similar right frontal area was activated by Pardo and colleagues when examining the effects of sustained attention to tactile stimuli in PET (Pardo et al., 1991). These areas have also been posited as involved in working memory and for the selection of appropriate actions cued by specific stimulus contingencies (for review see Miller, 2000). Again, the current study suggests that information from the tactile modality activates these areas in a similar fashion to visual and auditory information when these stimuli are required for delayed response tasks. Activation in these areas may therefore reflect the maintenance of tactile information during the delay period of the paradigm (i.e. Romo et al., 1999). However, this conclusion is a tentative one, as although subjects were only presented with tactile stimuli during the task, they were aware that only four stimuli could be delivered, and that in a given task only two levels of a factor needed to be discriminated. Thus, unlike the delayed-match tasks used in the neurophysiological studies of Romo and colleagues (Hernandez et al., 1997; Romo et al., 1999) in which monkeys had to discriminate different frequencies of vibrotactile stimuli, subjects did not have to retain an isomorph of the tactile stimulus to perform the task. The activation of left middle frontal gyrus (spreading into left inferior frontal gyrus) supports the hypothesis that subjects may have been using a verbal strategy to keep verbal transformations of the stimuli on-line, rather than representations of the stimuli themselves. Further studies are required in humans to confirm this.

The only uniquely 'somatosensory' cortical area to be activated by the current analysis was the left parietal operculum. No activity was observed in the primary somatosensory cortex when comparing the active tasks with passive stimulation. There are three possible explanations for this result. First of all, the model used in the current experiment is most sensitive to areas that display a mean increase in BOLD signal over the entire course of an experimental trial. During each trial, the subject only received three, discrete airpuffs, and so there may not have been enough stimuli during this period to elicit specific stimulus-related attentional modulation in SI. In addition, as discussed in previous chapters, the most robust

modulations of primary somatosensory cortex in MEG, PET and fMRI have occurred not when comparing passive and active attention to stimuli, but when comparing active stimulation to a distractor condition (e.g. Meyer et al., 1991). There was no such condition in the current experiment. In addition, the current analysis was a group study. The anatomical variability of putative thumb foci in SI (as revealed by previous experiments in this thesis) suggests that, even if thumb SI foci were present in single subjects, they may have been averaged out in the group comparison.

The lack of bilateral parietal opercular activation to unilateral tactile stimuli in the current study is more surprising. Previous neuroimaging studies have reported bilateral activation of parietal opercular areas (including putative SII and PV) to unilateral tactile stimuli (e.g. Burton et al., 1993; Ledberg et al., 1995; Korvenoja et al., 1999; Maldjian et al., 1999; Disbrow et al., 2000; Johansen-Berg et al., 2000), although some studies found only contralateral foci active (Burton et al., 1997a). As the majority of these studies presented stimuli to the right side of the body, the differences between activations of the left and right parietal operculum have been explained by suggesting that the contralateral SII/PV (in the cases above, the left) shows a greater response. However, in the current experiment stimuli were only presented to the left thumb, yet the left parietal operculum (*ipsilateral* to the side of stimulation) was activated. This suggests that there may be hemispheric differences between the somatosensory areas of the lateral sulcus that are expressed independently of the location of tactile stimuli. Although this assertion cannot be formally addressed using stimuli from the current study, a similar observation was made by Simoes and colleagues (2000). Using bilateral stimulation in MEG, they found that differences between right and left parietal opercular areas were best explained by right vs. left differences in these areas rather than contra. vs. ipsilateral site of stimulation differences. In agreement with the present findings, they found that activation of left SII to unilateral stimuli tended to be greater than that of the right SII irrespective of the site of stimulation (on average x2 differences in amplitude). Thus my findings may reflect differential specialisation of the two hemispheres in the processing of unilaterally presented tactile stimuli. The lack of right SII activation may, for example, indicate the lack of motor responses to

perceptual stimuli, as SII has previously been implicated as important for sensorimotor integration (Huttunen et al., 1996; Lin et al., 2000).

The remaining foci active in this contrast (i.e. right parieto-occipital junction and the left lingual gyrus) may reflect the use of visual imagery in both tasks, or the use of verbal strategies to encode the tactile stimuli. A similar focus to the right parieto-occipital region (although located in the left hemisphere, perhaps reflecting that stimuli were presented to the right hand) was previously shown to be active in a PET study of tactile orientation discrimination in which subjects reported using visual imagery (Sathian et al., 1997).

6.4.3 Areas Activated by Location or Intensity Discrimination Task

6.4.3.1 Areas active in both conjunction analyses

Only the right posterior parietal cortex (in the area of the inferior parietal lobule, BA40) and the right middle frontal gyrus were active in both intensity and location discrimination task conjunctions (Figures 6.7A and B; Tables 6.2 and 6.3) in which a motor response was not required. These two areas have previously been identified as mediating ‘supramodal’ sustained attentional processes in the visual and tactile systems (Pardo et al., 1991) and the auditory system (Paus et al., 1997; Zatorre et al., 1999). The current finding is directly comparable to a similar study in the auditory system that also used two separate attentional strategies/cognitive tasks (Zatorre et al., 1999) and found the same right frontoparietal network activated across both tasks. In my study the stimuli were separated by a variable delay of 0.5s-8s, subjects could not predict when stimuli would occur, and thus had to maintain a sustained state of attention. However, as stimuli were only ever presented to the left thumb the current results cannot be said to confirm the findings of Whitehead (1991) that sustained attention has a right hemisphere bias.

6.4.3.2 Areas activated by tactile intensity discrimination task

Two separate foci were also active in the intensity discrimination task conjunction analysis – the left cerebellum, and the right medial frontal gyrus. I would not have hypothesised *a priori* that these areas would be activated by the task. While the cerebellum has been thought to play a role in somesthetic discrimination (e.g. Gao et al., 1996), the tasks used by Gao and colleagues were active, haptic discrimination tasks. The activations in my experiment lie in anterior cerebellar

cortex, in an area consistent with the likely area of termination of spinocerebellar afferents from the left hand. While there has been a recent trend to assign more ‘cognitive’ functions to the cerebellum, these have been hypothesised to lie within a lateral ‘stream’ rather than the ‘sensorimotor stream’ that my locus of activation suggests (Schmahmann, 1996). And, although a number of studies have suggested a putative role for the cerebellum in attentional processing (Rees et al., 1997), the authors concluded that their cerebellar activation was likely to reflect a ‘preparation for action’ role. In the trials analysed in the current experiment subjects were not required to make a motor response. However, as there is a known pattern of connectivity between parietal cortex and the cerebellum (reviewed in Schmahmann and Pandya, 1989), the cerebellar activation may reflect a hitherto-unappreciated example of attentional biasing to somatosensory stimuli.

The right medial frontal gyrus activation is likely to lie within the medial part of BA8. The functions of this area are largely unknown – it has been previously implicated in neuroimaging studies as disparate as the functional imaging of affective olfaction (Fullbright et al., 1998) and prospective memory (Okuda et al., 1998). However, in the context of my study it is interesting that its activations has been reported in a PET study of sustained vibrotactile attention (Johannsen et al., 1997) when subjects focused on the frequency of vibration to detect any changes. It may therefore be involved in attention to specific features of tactile stimuli (frequency in the Johannsen study, intensity in the present study). No tactile homologues of the ‘ventral’ stream (as defined by Mishkin, 1979) were activated in this contrast.

6.4.3.3 *Areas activated by tactile location discrimination task*

Areas specific to the location discrimination task conjunction analysis included bilateral posterior parietal regions, bilateral frontal eye fields, and cingulate cortex – similar regions to those implicated by previous studies of visuospatial attention (see review in Coull, 1998). The locations of these foci suggest that the bilateral superior parietal lobules (including BA7) mediate tactile spatial discrimination. While a previous study of tactile attention to different stimulus attributes (Burton et al., 1999) found that foci within the posterior parietal cortex were more anterior than those reported for visuospatial attention, this was not the case here. In addition,

neuroimaging studies of visuospatial attention performed since the study by Burton and colleagues (e.g. Bushara et al., 1999) have identified posterior parietal foci that were as anterior as those in the Burton study. Thus, as the current study lacked a visuospatial task in which this comparison could be made explicitly, it is impossible to say if multiple, modality-specific regions exist within the posterior parietal cortex for spatial computations, or if a single supramodal representation is used. In addition, the cytoarchitectonic identification of areas in human posterior parietal regions is currently contentious, and not as detailed as the studies performed in non-human primates (reviewed in Andersen et al., 1997). However, the superior parietal areas identified may be homologues of BA7b in the monkey, an area that is known to receive inputs from more anterior somatosensory areas (e.g. Andersen et al., 1990). Previous non-human primate studies examining the effects of attention to somatosensory stimuli on 7b neuron firing rate (Robinson and Burton, 1980a,b; Burton et al., 1997b) found that neurons in these areas modulated their firing rates when monkeys had to attend to or process tactile stimuli. Thus the results of this contrast agree with a 'dorsal' stream of somatic information from anterior parietal cortex (i.e. SI) to more posterior regions specialised for the processing or representation of tactile information in a spatial framework. The activation of the frontal eye fields is more ambiguous, as mentioned previously. This could reflect either differential amounts of eye movements between location discrimination and control conditions, or may represent covert shifting between two different locations in an 'internal' representation of the stimuli to be discriminated.

6.5 Conclusions

The current experiment was designed to see if it was possible to delineate the functional roles of somatosensory cortical areas by using selective attention paradigms similar to those employed in neuroimaging studies of the visual system (e.g. Corbetta et al., 1991). Specifically, I was interested in evaluating the model of Mishkin (1979), who proposed that a ventrally directed somatosensory pathway may mediate tactile object recognition and memory. This pathway was later demonstrated to include SI, SII, the insula, and the perirhinal cortex (Friedman et al., 1986). I did not observe activation in any of these areas when comparing activation with tactile ‘features’ over passive stimulation. The other proposed processing stream of tactile information is similar to the dorsal pathways of the visual system, projecting from anterior parietal cortex to posterior regions (likely to be the superior parietal lobule in humans). These areas were active when activation during tactile spatial discrimination was compared to activity during passive stimulus presentation. Therefore, while my results do not support the model of Mishkin (1979), they do suggest that separate aspects of tactile perception are processed in separate cortical areas.

6.5.1. Tactile Attention: Modulation of Activity in ‘Early’ or ‘Late’ Cortical Areas?

One of the more surprising findings of the current study was that most cortical regions identified in either the location or intensity discrimination conditions were not ‘classical’ somatosensory regions. Corbetta and colleagues (1991) found that attention to different visual features caused differential activation of the visual cortical areas proposed to be involved in processing those features. However, in the current study, I had proposed that intensity discrimination may activate more ‘ventral’ somatosensory regions such as the insula. These areas were not activated in the current analysis. However, the ‘dorsal’ regions of posterior cortex did display differential patterns of activation when location discrimination tasks were compared with the rest condition. This result suggests that, contrary to anatomical evidence, the somatosensory system may not use ventral cortical areas to encode object properties. However, rather than claiming that these areas are *not* activated, it may

be more useful to review ways in which the current paradigm may have *failed* to activate them.

The current paradigm was designed to examine areas that showed a mean difference in BOLD signal change over the entirety of a trial when compared to passive stimulus presentation. While other studies have claimed to be able to differentiate between ‘set’ and ‘stimulus-related’ attentional processes (e.g. Chawla et al., 1999), this was not possible in the current study. Thus the analyses carried out were biased towards the detection of regions mediating tactile attentional ‘set’ for each task, rather than attention to specific aspects of the stimuli *per se*. As an aside, attempting to differentiate between stimulus-driven and set attentional effects may be futile. The biasing of representations within early sensory cortices by attention can be mediated by ‘executive’ signals from other areas. This kind of modulatory strategy was suggested by Desimone and Duncan (1995) in their review of attentional mechanisms as mediated by signals from the prefrontal cortex. Thus it may be difficult and ultimately meaningless to differentiate between sensory areas in which stimuli are represented, and other areas whose contribution is essential for attention to produce perception and goal-directed behaviour. In addition, such ‘top-down’ control does not have to be interpreted literally. The topographic maps contained in SI, for example, (e.g. Ritter, 1990), may act as self-organising principles in which patterns of previous sensory input ‘tune’ sensory representations so that the map is maximally sensitive to future occurrences of the same stimulus.

A further reason for the lack of ventral cortex activation may be that, while ‘intensity’ is a tactile feature, the simple airpuffs may not have been of sufficient complexity to activate ventral somatosensory regions. A recent study by Reed and colleagues (2000), motivated by a similar question to that under discussion here, contrasted the evoked current fields in MEG when subjects discriminated either tactile patterns or different tactile locations. The field pattern for the location task was very similar to that seen in this study, involving mainly bilateral posterior parietal cortex. However, their ‘object’ task did demonstrate activation of temporal cortical regions. The discrepancy between the two studies may be explained by the different methods of analysis employed: Reed and colleagues displayed cortical field maps of *absolute* values in each contrast: thus both positive and negative field

changes were present. In the only previous PET study to address a similar question (Bonda et al., 1996), activation of ventral and temporal cortical areas was found when comparing activation in passive stimulation epochs *minus* activation during active tactile discrimination. The ventral regions found by Reed et al. (2000) may therefore be deactivated (or more active in the control period) during discrimination. In support of this hypothesis, when examining areas more active during control than intensity discrimination in the current experiment, temporal regions including the inferior temporal gyrus and bilateral perirhinal cortices showed significant changes. However, as the interpretation of decreases in the BOLD signal is currently uncertain, the interpretation of these results is ambiguous, and thus they are not discussed further. It is worth noting, however, that neurophysiological studies have suggested that activity in the inferior temporal regions is suppressed in monkeys during similar match-to-sample tasks to the ones used here (Miller et al., 1991; 1993). Thus, if the neurovascular signal is correctly reflecting a decrease in the mean neuronal activity of these areas, these results would be expected. Future studies combining non-neurovascular imaging methods such as MEG with fMRI should resolve this ambiguity.

The lack of attentional modulation in either SI or SII when comparing active processing of each task in isolation vs. passive stimulation is not surprising when compared to previous non-human primate neurophysiological and human neuroimaging studies of tactile attention. The majority of studies in non-human primates (e.g. Hsiao et al., 1993) compared activation in an attention task to an active distractor task, rather than requiring monkeys to specifically attend to single stimulus dimensions of a complex somatosensory stimulus. Similarly, the majority of human neuroimaging studies showing attentional modulation of SI (Roland, 1981; Drevets et al., 1995) in PET have done so in the *absence* of actual stimulation – the SI modulation was produced by subjects orienting to an expected stimulus that was not delivered during scanning. One of the few studies showing modulation of tactile areas was carried out by Burton and colleagues (1999). They demonstrated attentional modulation of SII between active processing and passive presentation of graded roughness stimuli. However, as SII appears to be specialised for roughness discrimination (Pruett et al., 2000), it is unclear whether this activation reflects

attentional modulation of a particular processing stream, or specific computations involved in the discrimination of roughness stimuli *per se*.

Finally, the findings of Steinmetz and colleagues (2000) suggest that other coding strategies (such as coherence in firing patterns) may be used by somatosensory areas, rather than mean increases of firing rates *per se*. The authors found that synchrony increased in 80% and decreased in 20% of neuron pairs in monkey SII when the animal had to attend to tactile stimuli. While synchrony of local circuit neurons may have an effect observable at the level of neuroimaging, it is currently unknown what effect (if any) these temporal coding strategies would have on a spatially averaged, indirect measure of neuronal activity such as the BOLD signal. For example, a recent study (Vanni et al., 1997) found fairly normal changes in synchrony in V5 in dyslexics when using MEG, in contrast to no activation found by a similar study using fMRI (Eden et al., 1996). Thus it may be possible to produce local synchrony changes without a concomitant difference in BOLD signal.

6.5.2 Task-Related Differences in Somatosensory Cortical Areas

The results of the current study support previous notions of differential activation patterns according to attentional strategies/task demands when processing tactile stimuli. While an exact differentiation between ‘dorsal’ and ‘ventral’ somatosensory processing systems was not found, the current results support previous studies in suggesting that the somatosensory system, like other mammalian cortical sensory systems, is organised in a hierarchical fashion which involves spatially disparate areas performing different computations. However, a number of the areas activated were not classical ‘somatosensory’ regions. In the next chapter the effect of ‘non-sensory’ regions on somatic perception is further explored.

7 Whose Arm Is It Anyway? : The ‘Action Space’ and Somesthesia

7.1 Perception for Action...or Action for Perception?

The earlier chapters of this thesis focused on the study of tactile perception in human subjects using non-invasive neuroimaging techniques. With few exceptions (Chapter six), the behavioural paradigms used did not require subjects to make overt responses. Even when different qualities of sensation were delivered (Chapter five), subjects did not have to differentiate between them.

To enhance perception, however, it is common for organisms to use active behaviour to ensure optimal sampling of environmental stimuli. Somesthetic stimuli are no exception. Humans naturally use their hands to acquire and extract information about the surface features (or *microgeometric* properties; Roland, 1987) of objects – i.e. their texture, contour, or consistency (Sathian, 1989). Similarly, tactile global form perception or *stereognosis* is facilitated by the active exploration of objects (‘haptic touch’; Iggo, 1982). Thus, motor behaviour can be used to maximise an organism’s ability to extract somesthetic information from the environment.¹

The relationship between action and perception is reciprocated. It is widely accepted that adequate afferent information is a necessary part of accurate motor behaviour. For example, maintenance of the thumb/forefinger ‘precision grip’ is crucially dependent on cutaneous afferent information (Westling and Johansson, 1984; Johansson and Westling, 1984). The importance of afferent information is reinforced by evidence from instances in which it is disrupted by trauma – like the case of deafferented patient G.O (Rothwell et al., 1982), who experienced difficulties in performing all but the most simple motor acts.

The data driving perception are not limited to the input from peripheral receptors, however. The concept of perception as a dynamic process can be traced back to the writings of von Helmholtz (1886) on ‘unconscious inference’. Most

¹ This point was often stressed by J.J. Gibson, one of the first researchers to argue that perceptual experiments needed more naturalistic contexts: ‘in general, experimenters have not realised that to apply a stimulus to an observer is not the same as for an observer to *obtain* a stimulus’ (Gibson, quoted in Stevens and Green, 1996).

modern writings on perception stress the necessary interplay between *bottom-up* stimulus-driven influences and *top-down* modulatory influences that originate within the nervous system. Top-down influences can be collectively thought of as internal contributions to the act of perception: thus attention, arousal, memory, and expectation all play their part. These influences need not solely originate from areas traditionally viewed as ‘sensory’ or ‘cognitive’ areas. For example, perception can be powerfully influenced by information transmitted from the motor system to sensory cortices. The concept of ‘efference copy’ was introduced by von Helmholtz (1886) to explain why voluntary movement of the head or eye muscles does not produce the perception of self-motion, even though the retinal co-ordinates of external objects change. Von Helmholtz suggested that a *copy* of one’s intended movement was used every time a voluntary action was planned, such that the sensory consequences of the action (*c.f.* Blakemore et al., 1998b) could be cancelled. While the reasons for this existence of this phenomenon are a matter of debate, experimental work has confirmed its existence (e.g. Blakemore et al., 1998a), and it is a common concept in current theories of motor control (Jordan and Wolpert, 1999).

However, while information from the motor system can influence the sensory experience of one’s body, the contents of this information are often implicit and not available for conscious report. Nevertheless, clinical and experimental observations suggest that this implicit information can influence subjective perception of the body. The information can take a number of different forms (Jeannerod, 1990): for example, the initial spatial configuration of the body before movement, the predicted goal of the movement, the sensory information generated by the movement (*reafference*), or the *predicted* sensory information (the consequences) of the movement. Input from other sensory modalities is also important. For example, vibration of the biceps brachialis tendon causes blindfolded subjects to perceive that their forearm is moving (Goodwin et al., 1971, 1972). Vision of the arm cancels the illusion. Thus, in this case, visual information overrides conflicting somesthetic information. It is rare but not unknown (Ernst et al., 2000) for tactile information to influence visual perception.

It is therefore apparent that the moment-to-moment experience of the body can be influenced by afferent sensory information and by the past, present and future states of the motor system. However, even with this great number of influences, our daily sensation is typically of a unitary self, rather than multiple, separate 'visual', 'proprioceptive', or 'movement' selves. Some researchers have suggested that this is because sensory sources of information from different modalities are combined in 'higher', multimodal areas (medial parietal cortex - Ferraina et al., 1997; premotor cortex - Graziano and Gross, 1998). In this fashion, information can be combined from different modalities and a single percept computed. While multiple sources of sensory information may be combined in this fashion, it is unlikely that *all* of the possible influences on the subjective perception of body position ultimately feed into a common location. As stated by Lackner and DiZio (2000) in a recent review, ' [while] multiple factors contribute to the computation of body orientation and configuration...specific sites where they are spatially and metrically represented have not been discovered'.

This has not prevented many authors studying the subjective sense of the spatial configuration of one's body. The term *body schema* was introduced by Head and Holmes (1911), who were the first to systematically study patients' perceptions of their bodies. They postulated that the spatial perception of one's body is updated 'on-line' by successive changes in position. Spatial perceptual disorders could thus arise from peripheral disruptions of incoming afferent information, or central damage to those brain areas involved in producing the perception of the body schema. For example, after the loss of a limb it is common for patients to report that they still feel the limb to be present, albeit in a perceptually impoverished manner. In an example of central damage altering body schema, neglect of the left side of the body is frequently seen after right parietal cortex stroke (reviewed in Bisiach and Vallar, 1988).

After Head and Holmes, the concept of 'schema' was generalised by the British psychologist F.C. Bartlett (1932) to encompass *all* internal representations of future actions. Schema were conceptualised as the generic products of the subject's previous experiences with similar tasks. From these, a model could be

formed to ensure that future occurrences of similar experiences were handled more efficiently. Schema could thus be continually updated and fine-tuned. Their contents were thought to be essentially unconscious, because their utility lay in their ‘how-to’ knowledge, rather than semantic, communicable information.

It is possible to view the body schema in a similar fashion: a dynamic model of the body, encompassing all afferent, re-afferent and efferent copy information. While under normal circumstances one or a combination of these factors drive perception to produce a single percept of the body, it is conceivable that after pathology one or more of these influences on the body schema may be perceived simultaneously, resulting in multiple conscious representations of motor effectors. In the remainder of this chapter I will present data from a subject (E.P.) who suffered a unilateral frontomedial lesion that produced unusual perceptual illusions (Hari et al., 1998). The expression of E.P.’s ‘body schema’ distortions suggest that the neuronal architecture underlying her percept is unlikely to be caused by interference or damage to areas that are primarily concerned with the processing of afferent sensory information. Rather, an argument will be advanced that these illusions are driven by the contents of previously executed motor programs influencing the patient’s perception of her body.

7.2 Materials and Methods

7.2.1 Patient Details – Lesion and Neurological Examination

The subject’s neurological details have been previously reported (Hari et al., 1998). All clinical details were collected during previous investigations. The subject was a 42 year old right-handed female native Finnish speaker with no previous psychiatric history. In January 1994 E.P. was admitted to hospital complaining of severe headache, acute global aphasia and left hemiparesis. Upon examination a subarachnoid hemorrhage was found, caused by an aneurysm in the left pericallosal artery. Small resections of the right cingulate gyrus and anterior corpus callosum had to be made during surgery to deal with this.

After the operation the subject was tired and feverish, and was slow to recover. Diagnosis of a right frontopolar infarction was confirmed after a CT scan in April 1994. A T1-weighted MRI using a Siemens MAGNETOM Vision (Siemens,

Erlangen, Germany) at 1.5T clearly showed a wedge-shaped infarction in the subject's right frontal gyrus (a subsequent T1-weighted scan of E.P. acquired at 2T is shown in figure 7.1). Neurological examination 36 months after the operation (January 1997) showed a well-oriented subject. There were no cranial nerve abnormalities, muscular strength and tendon reflexes were symmetrically normal, and the subject had a bilaterally negative Babinski reflex. Sensitivity to sharp pain and soft touch were slightly lower on the left than right face and limbs. Vibration, thermal sensitivity and position senses were bilaterally normal. Discrimination of touch on the fingers did not differ substantially between the left and right sides. Tactile naming of objects resulted in 15/15 correct responses with the right hand and 11/15 correct responses on the left.

Immediately after the operation, the subject's left hand displayed symptoms typical of callosal disconnection – intermanual conflict, a 'grasp reflex' (grasping objects and not letting them go), and the hand was described as having a 'will of its own' by the subject. In addition the subject experienced difficulties with tasks requiring bimanual co-ordination, and showed motor perseveration with rhythmic movements. Motor co-ordination was slightly inaccurate in the left hand during pointing behaviour. E.P.'s intelligence was average, with an uneven distribution: she was best at verbal reasoning tests and worst at abstract visualisation and mental rotation.

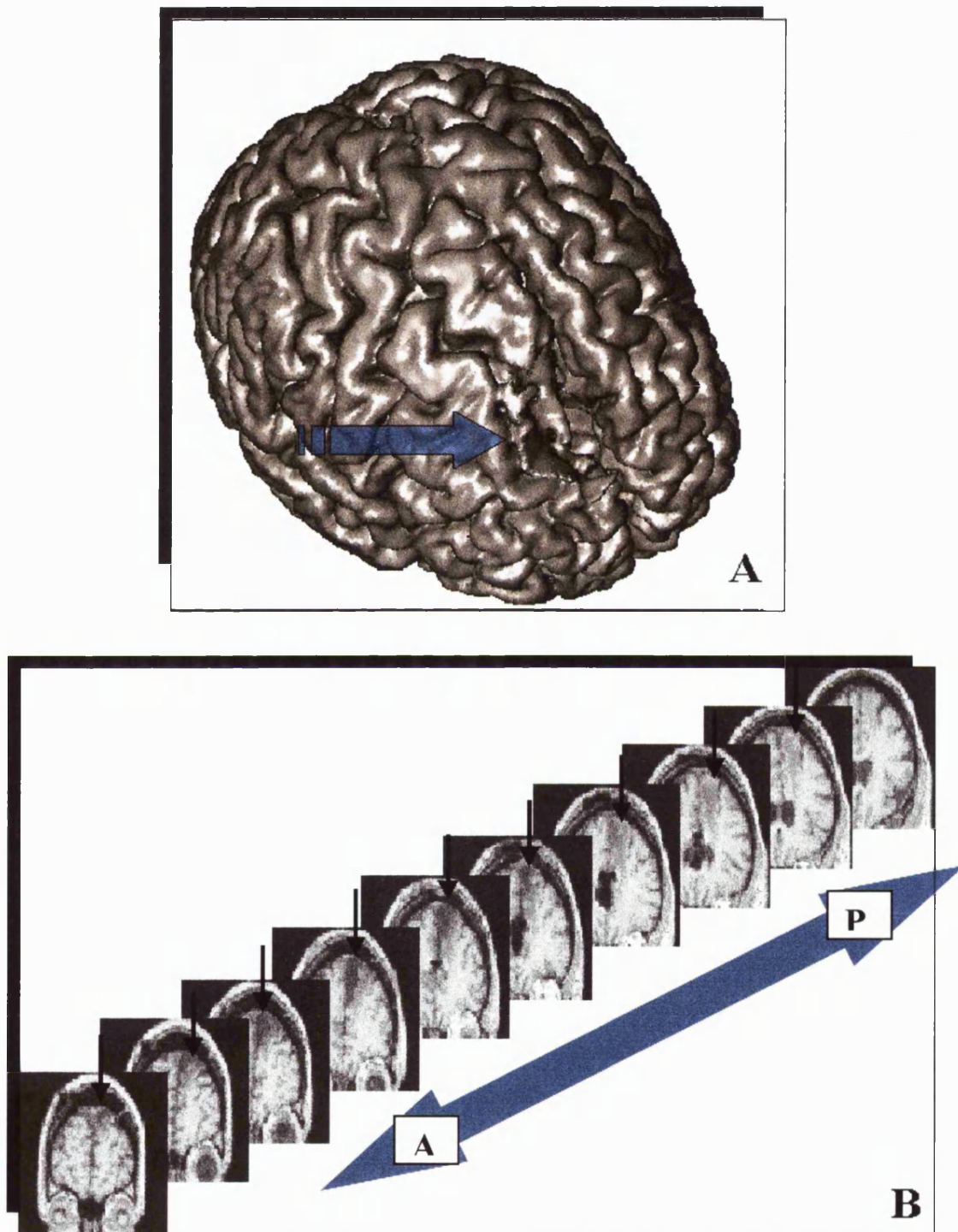


Figure 7.1. **A)** A three-dimensional rendering of E.P.'s brain constructed from her T1-weighted structural scan. The arrow indicates the region of the infarct in the right frontomedial region. **B)** E.P.'s lesion, shown in greater detail. Each individual picture is a 2mm thick coronal slice from E.P.'s structural scan. There is a 4mm gap between subsequent slices. The small arrows point to the infarcted area. The large arrow indicates the Anterior and Posterior direction.

7.2.2 Patient Details – Body Schema Distortions

Roughly three weeks after her operation E.P. reported distortions of her body schema which had begun immediately after her initial operation. E.P. frequently experienced a supernumerary, ‘ghost’ arm, and less often a supernumerary leg. These extra limbs were always experienced on the left side of E.P.’s body – the arm typically appeared medial to the left shoulder, and the leg appeared at the same place as the real left leg. The extra limbs did not replace E.P.’s perception of her real limbs – all three arms or legs were perceived simultaneously (but see below). These experiences have not diminished over time (the subject was scanned in June 1999).

Unlike many other published cases of supernumerary phantom sensations following central damage (Weinstein et al., 1954; Halligan et al., 1993; Sella et al., 1996) E.P. is aware that her experiences are abnormal, and shows insight into her condition. There is no denial of the symptoms and no signs of neglect. E.P.’s experience of her third arm is quite stereotypical and follows a similar pattern over each occurrence: after a delay (around 60-90s), the extra arm is experienced as occupying the spatial position previously occupied by the real left arm (the arm is felt, but not seen). The real left arm can be moved successively to a number of new positions in turn, and the ghost arm is perceived as ‘one step behind’, occupying the previous position of the real arm. Every time E.P. moves her real arm to a new position, perception of the ghost arm is cancelled, and returns after a delay. If E.P. does not move her left arm again, the ghost percept can continue for tens of minutes. Interestingly, the ghost arm only appears if E.P. *voluntarily* moves her arm to a new position: passive movement does not elicit the ghost. If the phantom percept continues for long enough (over a period of tens of minutes), E.P. begins to *only* perceive the phantom arm – her perception of her real arm begins to fade. This illusory percept has persisted since E.P.’s infarct, while her other symptoms (e.g. intermanual conflict) have faded.

The percept is realistic enough to cause E.P. confusion: for example, when shopping after her operation she felt she had accidentally taken bags from other people, because the third arm made her feel as though she was carrying three bags. While this can cause her some embarrassment, E.P. has never attempted to

rationalise or ignore the ghost's presence. Perception of the ghost arm and leg are cancelled by vision of the normal left arm/leg. E.P.'s descriptions of her 'ghost limb' percepts are intriguing. While otherwise neurologically unremarkable, she experiences an illusory arm and leg that appear to 'echo' the previous position of each limb. The extremely repeatable nature of the illusion suggests that it is possible to study the neural correlates of E.P.'s experience.

7.2.3 Patient Details – Previous Investigations

A previous study (Hari et al., 1998) used MEG to examine E.P. This study found a significant decrease in the height of right median-nerve somatosensory evoked fields (SEFs) in left SII when the ghost arm was present. The authors concluded that this activity was an objective correlate of the ghost sensation, a conclusion consistent with SII's postulated role in sensorimotor integration (Huttunen et al., 1996; Lin et al., 2000). However, the authors were unable to directly contrast, 'context-free', the absence or presence of the ghost arm. The current experiment was designed to examine this question, using fMRI.

7.2.4 Experimental Details

7.2.4.1 *On the Collinearity of Experimental Factors in fMRI*

The previous MEG experiment contrasted differences in an evoked measure of somatosensory function (SEFs) during the absence and presence of the ghost arm – in effect, the *interaction* of the ghost percept with another experimental factor. The experimental question I wanted to address was simpler: are there any cortical areas in E.P.'s brain whose neurovascular activity correlates with E.P.'s perception of the ghost arm? This question can be thought of as a simple subtraction between periods of time during which E.P. experiences her phantom versus periods when it is absent. A categorical comparison of this form (*phantom arm 'on' – phantom arm 'off'*) is made easier due to E.P.'s ability to 'turn off' the phantom every time she moves her left arm to a new position. However, while the time between its appearances is very repeatable (usually between 60-90s), E.P. has no control over *exactly* when the phantom appears, although she is able to signal its presence with her right arm. So, in the current experiment, any period where E.P. experiences her phantom arm is, by necessity, 'bookended' by a movement of her right hand (to signal its presence) and her left arm (to cancel the

percept). This is common when using fMRI to study delayed-response paradigms, like those used in working memory studies. These kinds of experiments typically consist of an initial presentation of a ‘target’ stimulus, followed by a variable delay, finally followed by a ‘probe’ stimulus that signals the subject to make a motor response based on some comparison between the previous stimuli. From the perspective of experimental design, the ‘delay’ or working memory component of these studies is formally comparable to the tonic ‘phantom on’ or off periods of the current study.

Experiments of this sort are comparatively easy to evaluate when examining similar questions in non-human primates (e.g. Fuster et al., 1982) - investigators usually have specific hypotheses relating to each component of the trial, so that they are interested in examining which areas correlate exclusively with ‘target’, ‘delay’ or ‘probe’. In fMRI, however, the smoothing of the hrf imposes collinearity between the different components of the task. The design matrix formed by a multiple linear regression model of the experiment (as in SPM) will contain some non-orthogonal covariates. While it is possible to use careful experimental design to address these difficulties (e.g. Toni et al., 1999), this device does not categorically remove the problem. However, it is possible to circumvent these ambiguities by testing only the orthogonal components of the model’s regressors. In other words, the model can still be evaluated – as long as the regressors are adjusted so that ‘redundant’ parts (those shared with other regressors) do not enter into the inference procedure. This procedure was adopted here.

7.2.4.2 Experimental Setup and Scanning Details

E.P. was familiarised with the behavioural paradigm (Figure 7.2) outside the scanner. During scanning, E.P. lay supine on the scanner bed with her eyes closed and her arms by her side, a position that robustly elicited E.P.’s phantom arm after a variable delay (see results section). As voluntary movement of E.P.’s real left arm abolished the phantom, and the sensation itself arose spontaneously but regularly, it was possible to manipulate the occurrence of the phantom in a systematic manner.

When E.P. sensed the presence of the phantom, she pressed a button on a MRI compatible button box with her right index finger (Figure 7.2, first event in condition A). After a variable delay (between 21-23.5s, mean 22.3s) E.P. received an auditory command in Finnish to move her left arm (first event in condition B) which caused the phantom perception to disappear. The subject was trained prior to entering the scanner so that her movement would cause as little movement of her torso as possible, and to ensure that the movement was stereotypical and thus repeatable. The period between E.P. signaling the presence of her phantom arm and moving her left arm was designated the 'phantom on' period (condition C). During this period, E.P. consistently perceived her phantom left arm. This was confirmed by questioning E.P. after each scanning session.

After 10s, the subject received a command in Finnish to press the button box as before (second event, condition A), and after a further variable delay (as above) to move her left arm (second event, condition B). The period between E.P. pressing the button box and moving her arm was designated as the 'phantom off' period. The length of this period (between 21-23.5s, similar to the length of the 'phantom on' condition) was chosen as, even though E.P. is lying at rest, this time is too brief for the phantom sensation to develop. The variable length of each 'phantom on' and 'off' period ensured that any anticipatory response by E.P. to the end of each block was minimised, and in addition increased the effective sampling frequency of the hrf (Josephs et al., 1997). A complete cycle of the paradigm consisted of a 'phantom on' followed by a 'phantom off' period. Six cycles of the paradigm were repeated over each session.

7.2.4.3 *Scanning Parameters*

Five experimental sessions were acquired; the data from session two were not analysed as the subject dropped the button box and was unable to correctly signal the presence of the phantom arm. Because it took E.P.'s arm a variable amount of time to be perceived, the length of each session differed (session 1 - 350 scans; 3 - 300 scans; 4 - 295 scans; 5 - 315 scans). The first 4 scans of each session were removed prior to analysis to account for T1 equilibrium effects. E.P. remained in the scanner bore between sessions, which were typically separated by a gap of 10 minutes.

The data were acquired on a Siemens MAGNETOM Vision scanner (Siemens, Erlangen, Germany) at 2T. Each fMRI volume scan consisted of 48 transverse slices (inplane matrix 64x64; voxel size 3x3x2.1mm with a 1.05mm gap between adjacent slices; TE=30ms; TR=2.83s). The scans were acquired in an oblique orientation (roughly 20° above the horizontal, tilted anterior above posterior). The TE of 30ms was used to reduce susceptibility-induced signal loss around the region of E.P.'s aneurysm clip. A T1-weighted high-resolution MRI of the subject (TE = 4.1ms; 1 x 1 x 1.5mm resolution) was acquired to facilitate anatomical localisation of the functional data. Auditory stimuli were delivered via a custom-built sound delivery system, with headphones designed to attenuate scanner noise (Palmer et al., 1998).

7.2.4.4 Image Preprocessing

Data preprocessing was carried out using SPM99 (Wellcome Department of Cognitive Neurology, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>). All functional volumes were realigned using the first volume from the first session as a reference (Friston et al., 1995). To correct for differences in slice times within each volume, the data within each slice were interpolated in time to approximate a common acquisition time, using the middle slice as a reference (Henson et al., 1999). The data were resampled at 2x2x2mm prior to smoothing with an 8mm FWHM Gaussian kernel. The subject's T1 structural scan was coregistered to the mean functional volume by maximising the mutual information between the two volumes (Collignon et al., 1995). The subject's functional data were not normalised to a standard anatomical co-ordinate system, as the combination of her lesion and signal drop-out from her arterial clamp complicated this process.

7.2.4.5 Data Analysis

Data analysis was carried out using SPM99 as before. Functional volumes from all sessions were treated as a time series, and experimental effects estimated using a multi-session design matrix that included separate session mean terms. Each session contained six experimental effects of interest modeled as 'event' or 'tonic' responses. The four 'events' comprised E.P.'s right index button presses and left arm movement conditions, separated into four conditions by their occurrence in the context of the 'phantom on' or 'phantom off' conditions. The expected

haemodynamic response to each event was modeled by convolving transient ‘delta’ functions indexing each event with a synthetic haemodynamic response function (Friston et al., 1994) and its first-order temporal derivative. The inclusion of the temporal derivative component has previously been shown to increase sensitivity in event-related analyses (Hopfinger et al., 2000).

The two ‘tonic’ conditions encompassed the ‘phantom on’ and ‘phantom off’ responses. Each of these was modeled using a box-car function convolved with the same synthetic haemodynamic response function as above. In addition to the six experimental effects, each single session partition of the design matrix contained six covariates representing the estimated movement parameters for each scan (obtained from the realignment parameters). To remove low-frequency noise the data were high-pass filtered using a set of discrete cosine basis functions with a cutoff period of 240s. Temporal autocorrelation was dealt with using the method of Worsley and Friston (1995) by temporally smoothing the session time series with a Gaussian kernel of 3s- FWHM.

Linear contrasts of the covariates were evaluated for the main effects of each ‘event’ response and for the contrast ‘phantom on- phantom off’. Results were displayed as a voxelwise statistical parametric map of t or F values. Voxels that survived a threshold of $p < 0.05$ corrected for multiple comparisons across the entire volume were reported as significant. A cluster threshold of three contiguous voxels ($k=3$) was used.

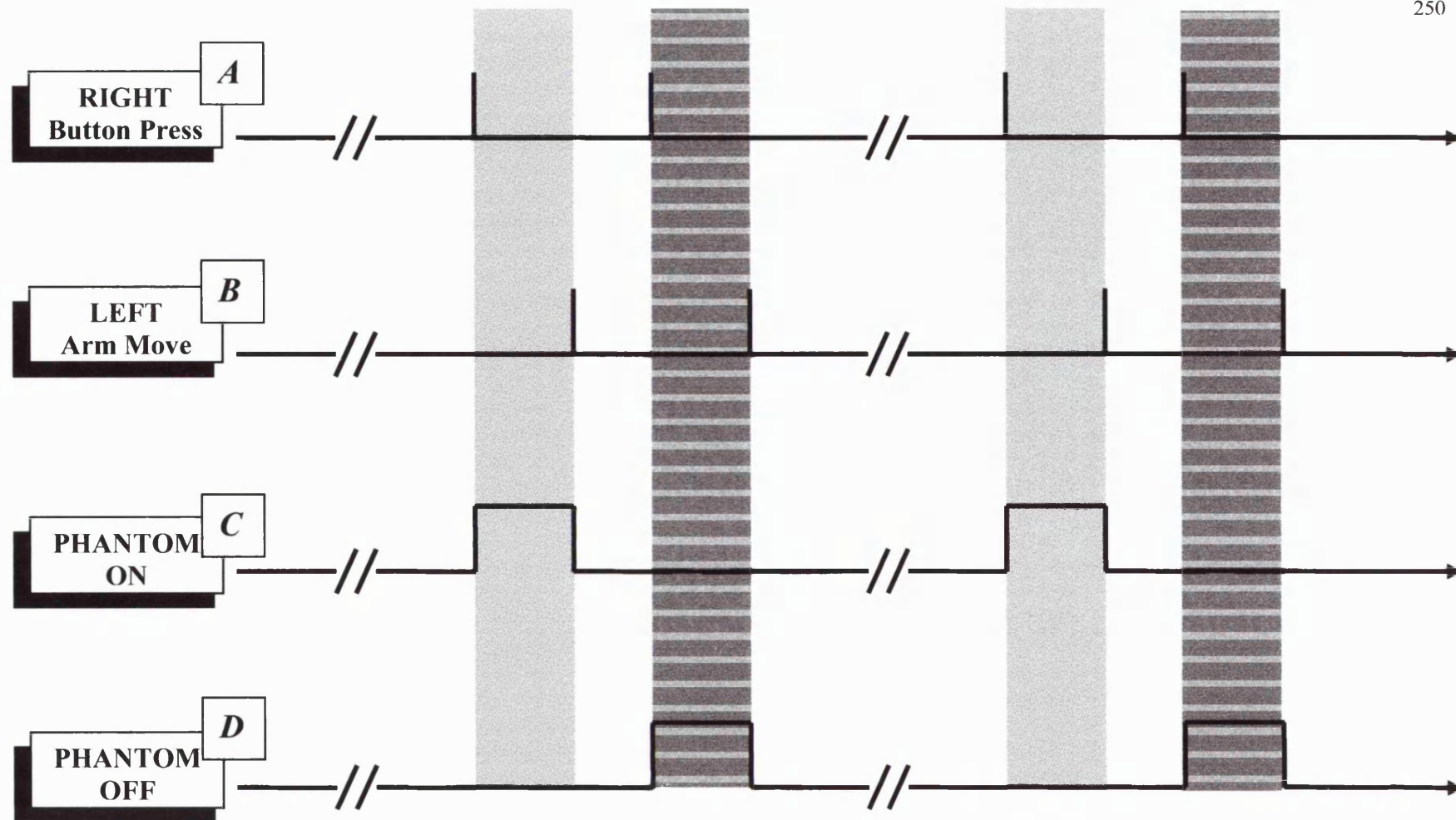


Figure 7.2. Schematic representation of two cycles of the experimental paradigm. Each timeline is a separate experimental condition (in the analysis the right button press and left arm move conditions were each split into two regressors, depending on whether they had occurred in the context of a 'phantom on' or 'off' condition. Here they are represented by a single timeline each for the sake of clarity. The time at which each experimental condition occurred is indicated by an increase in height from the pre-stimulus 'baseline'. E.P. indicates the presence of the phantom with a right index finger button press, which is also the beginning of the 'phantom on' period. After a delay, during which E.P. perceives the phantom's presence, E.P. was instructed to move her left arm, abolishing the phantom. After a delay of 10s, E.P. was instructed to press the button box again (mimicking her motor response to signal 'phantom on'), and after a delay during which E.P. did not experience the phantom, she is instructed to move her left arm again (thus mimicking the motor response that ends the 'phantom on period'). This was repeated six times in each session.

7.3 Results

As the subject's functional and structural data was not normalised to a standardised anatomical template (i.e. as defined by Talairach and Tourneaux, 1988), all locations of 'activated' voxels are discussed with reference to their anatomical location in E.P.'s brain. The length of time required before E.P. reported her perception of the phantom from rest (i.e. the time between cycles of the experiment, Figure 7.2.) was variable (Session 1- mean $109.20 \pm \text{st.dev. } 20.82\text{s}$; Session 3 - $81.88 \pm 6.12\text{s}$; Session 4 - $77.62 \pm 24.32\text{s}$; Session 5 - $90.23 \pm 9.09\text{s}$), but comparable to times previously reported by Hari and colleagues (1998).

7.3.1 Main effects of 'Event' Conditions

The three-dimensionally rendered brain in Figure 7.3. shows voxels that exhibited statistically significant ($p < 0.05$ corrected for multiple comparisons across the image volume) increases in BOLD signal during E.P.'s right index finger press signaling the presence of the phantom arm across all sessions. Large clusters can be seen in the left precentral gyrus (cluster size 354 voxels; $F = 11.52$) and left medial wall (cluster size 53 voxels; $F = 7.97$). This pattern of evoked activity is similar to results from previous studies using fMRI to examine the neurovascular correlates of simple motor actions (e.g. Rao et al., 1993.). The activated area of the left precentral gyrus corresponds to the 'hand knob' (Yousry et al., 1997) of primary motor cortex (M1). The medial wall cluster's location (the Y co-ordinate of the peak cluster voxel is -8) is consistent with the location of human SMA 'proper' as lying posterior to the VAC line (Zilles et al., 1995), at which $Y = 0$. Although no non-linear transformations were applied to the image data to normalise it to the space of Talairach and Tourneaux (1988), E.P.'s brain was linearly transformed by hand to render its axes consistent with those defined in the atlas.

The graphs in Figure 7.3 represent the evoked activity at the peak voxel of the SMA and M1 clusters across each of the four simple movement conditions, plotted as a function of peri-stimulus time (each of the conditions modeled by events). Conditions 'A' and 'C' represent right-button presses and conditions 'B' and 'D' left arm movements. The voxels display differential evoked activity that is dependent on the movement type – significant responses to conditions A and C,

and non-significant responses to B and D. Although the evoked activity associated with these simple movements was not my prime concern in the current study, these results serve as an 'internal control' of the validity of the BOLD measure as an indicator of neurovascular change in E.P.'s brain.

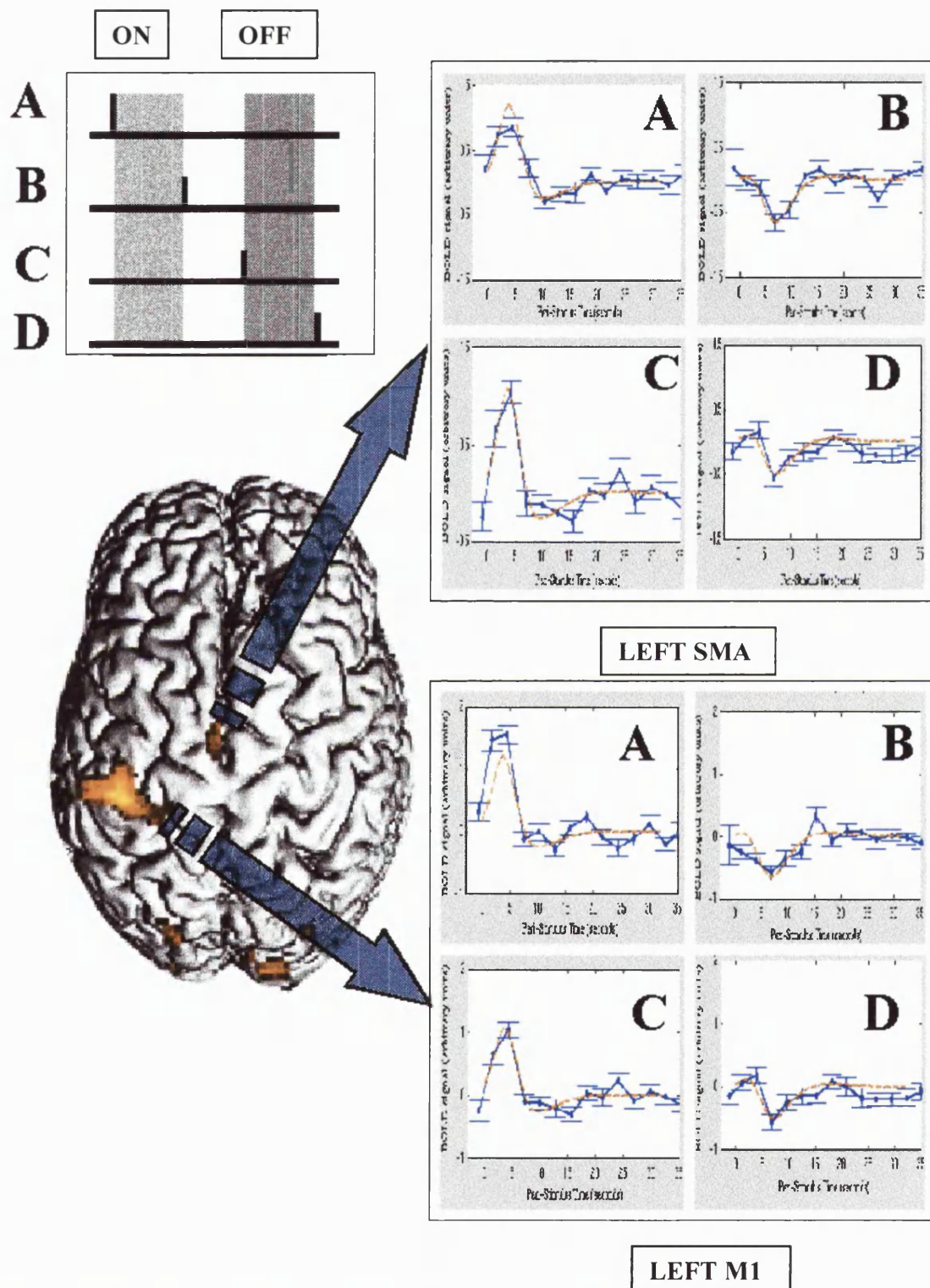


Figure 7.3. Simple movement-related effects in E.P.'s brain. The two activated clusters are left MA and left primary motor cortex (M1) respectively. The plots of BOLD activity on the right correspond to the main effects during each of the experimental conditions (A-D; Figure 7.2.). Activity is plotted as a function of peristimulus time – the red trace is the fitted response and the blue the adjusted data.

7.3.2 Contrast of ‘Tonic’ Conditions: ‘Phantom On’ – ‘Phantom Off’

The results of the ‘phantom on’ – ‘phantom off’ contrast are shown in Figure 7.4. Only the orthogonal components of both regressors (with respect to the rest of the experimental model) were tested. The contrast therefore identifies voxels where there is a statistically significant positive difference ($p < 0.05$ corrected for multiple comparisons) between the parameter estimates of the ‘phantom on’ covariate and the ‘phantom off’ covariate, *after* the variance ‘explained’ by the remainder of the model has been accounted for. A similar procedure was used in section 7.3.1 (each ‘event’ covariate was orthogonalised with respect to the rest of the experimental model).

Only a single cluster of activated voxels survived correction for multiple comparisons – a cluster on the right medial wall (cluster size 9 voxels, $T = 5.11$, $p < 0.012$) that I identify as lying in the anterior part of the supplementary motor area proper (‘SMA proper’). The fitted response and adjusted data plotted as a function of peri-stimulus time for this peak voxel are shown in the bottom half of Figure 7.4. It is clear from this figure that there is a sustained difference between the evoked neurovascular response in this voxel over the periods in which E.P. experiences the phantom (red data) compared to those where she does not (blue data). Furthermore, as only the orthogonal components of this contrast were tested, this difference is unlikely to have been caused by a differential response in SMA’s response to any of the other experimental components (the simple movements) differentiating the two conditions.

The location of the cluster is harder to confirm, as the identification of areas within the medial wall of the frontal lobe is a subject of debate. A number of progressively more detailed classification schemes have been applied to this portion of cortex. Brodmann originally defined this area as Brodmann area 6² using cytoarchitectonic criteria. Early cortical stimulation studies (Penfield and Welch, 1951; Woolsey et al., 1952) defined the region physiologically as a single area, because it contained a complete somatopical map of body movements. Later studies suggested that this was an oversimplification, and it is now widely

accepted that the SMA can be anatomically and functionally segregated into two separate areas according to definitions derived from comparative neuroanatomy (reviewed in Rizzolatti et al., 1998). Drawing on comparisons with the cortical fields of the macaque, they suggested that the SMA contained two areas homologous to macaque F3 ('SMA proper') and macaque F6 ('preSMA'). Subsequent classification schemes have attempted to demarcate the internal anatomy of the SMA further (Vorobiev et al., 1998). While the exact number of separate cortical areas within the medial wall is still a matter of controversy, it is less controversial to note that the SMA appears to display a gradient of specialisation along its rostro-caudal axis.

As discussed in previous chapters, the criteria for defining a particular collection of neurons as a 'cortical field' (Kaas, 1983) or 'area' can differ, suggesting that a truly pluralistic criteria may be the one with the greatest utility. For example, Zilles et al. (1995) claim that a combination of tract-tracing, immunocytochemical and cytoarchitectonic data will provide the best definition of an area. However, in the current study the only information available is defined at a gross anatomical level. This does not necessarily limit the anatomical resolution of the study, as previous work has shown that there is a good approximation of microstructure and macroanatomy in some areas of the medial wall. Most investigators agree in principle with the classification scheme of Picard and Strick (1996) that defines four separate areas: anterior SMA (pre-SMA), posterior SMA (SMA 'proper'), rostral cingulate zone (RCZ) and caudal cingulate zone (CCZ). It has been common for previous studies to demarcate SMA and pre-SMA using a vertical line drawn through the anterior commissure (VCA line) perpendicular to a line drawn through the anterior and posterior commissures (AC-PC) line, *after* the brain has been spatially normalised into the space of Talairach and Tournoux (1988). Structural abnormalities in E.P.'s brain prevented a successful non-linear, shape-based 'warp' of her brain into Talairach space. However, it was possible to linearly transform her brain such that the VCA and PCA lines were comparable with those defined by Talairach and Tournoux

² However, even at the time of Brodmann some investigators thought BA6 was composed of separate cortical areas – for example, the atlas of Vogt and Vogt (1919) defined four non-primary

(1988). Therefore landmarks used in previous studies were used to identify the area of the medial wall activated in the ‘phantom on-phantom off’ contrast.

The peak activation in the ‘phantom on-phantom off’ contrast is located posterior to the VAC line, in a position consistent with SMA-proper (Fig. 4). The lateralisation of the cluster is harder to determine, as with most medial wall activations whose maxima lie close to the sagittal midline, but the peak voxel appears to lie in the right SMA. Reducing the significance threshold by a factor of ten (a critical t threshold of 4.09) resulted in near equal spread of the cluster to the right and left hemispheres, and a slight expansion in the anterior direction. I therefore conclude that the activated cluster lies predominantly in the right SMA area proper, with some spread to the left SMA.

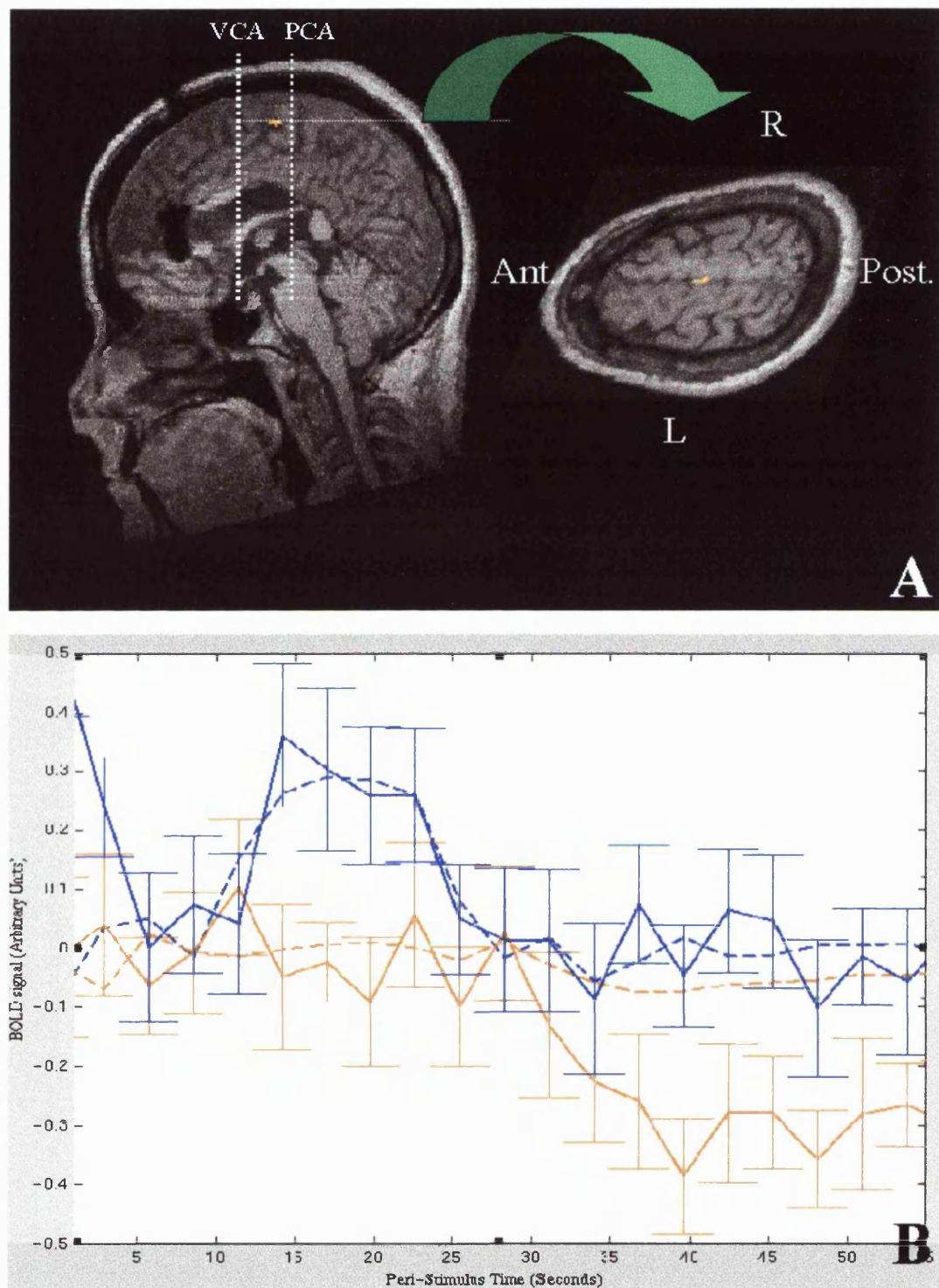


Figure 7.4. **A.** Sagittal slice (2mm thick) of E.P.'s T1 scan showing location of SMA cluster in detail. **B.** BOLD signal change at peak voxel of SMA cluster. The blue trace is activity during 'phantom on' periods. The red trace is activity during 'phantom off'. The error bars are the SEM around each time point. The traces are shown as a function of peri-stimulus time (as in Figure 7.3).

7.4 Discussion

The findings of this fMRI study suggest that activity within areas traditionally classified as part of the motor system can nevertheless influence conscious perception of the body. When E.P. cannot see her left arm, she gradually perceives a 'third arm' that is experienced as occupying the previous position of her real left arm. This percept can continue indefinitely. The specificity of E.P.'s illusion suggests that action or sensory-related signals that were previously responsible for her perception of the arm in its last position are responsible for her ghost arm. However, it is unlikely that E.P.'s illusion is driven by proprioceptive influences, as her ghost arm is only experienced after a new volitional movement. Furthermore, E.P. remains conscious of her real left arm even when experiencing her phantom arm. Thus, the experience of the ghost arm seems to rely more on action than perception, perhaps represented by sustained activation in the left SMA.

7.4.1 The SMA and 'Goal-Directed' Movements

The SMA is a functionally complex area, involved in many aspects of motor control (Tanji, 1996). As well as reciprocal connections to M1, in the monkey the SMA proper (F3; Luppino et al., 1991) receives afferent projections from the cingulate motor areas (CMA), the pre-SMA (F6) and the parietal area PEci (initially defined by Pandya and Seltzer, 1982). Area PEci is the main input to F3 in monkeys, and contains a complete somatopical map of the body (Murray and Coulter, 1981). As befits an area with such a diverse pattern of corticocortical connections, there have been a number of specific hypotheses concerning the function of the SMA. Most of these hypotheses have focused on the role of the SMA as a 'supramotor' area (Tanji and Shima, 1996). Prominent amongst these have been the ideas that the SMA proper is preferentially involved in i) the internal generation of movement in the absence of external cues (Thaler et al., 1995; Chen et al., 1995) and ii) the generation of planned sequences of movements (Tanji and Shima, 1996). In addition, functional imaging studies of the SMA have demonstrated its activation during simple sensory stimulation in the absence of movement (e.g. Korvenoja et al., 1999). While it is possible that the activation of SMA seen in the present study may be indicative of any of these

underlying roles, the specificity of E.P.'s percept argues for a distinct expression of one of the SMA's functions.

According to some computational models of motor control, internal representations of future motor actions can be used as feed-forward controllers during movement execution (e.g. Jordan and Wolpert, 1999). For example, one model of saccadic eye movement generation (Robinson, 1975) has suggested that the route to a particular position is computed in a dynamic fashion by comparing the current position of the eyes with their intended target position (or *goal state*). The encoding of the endpoint of a sequence is consistent with the proposed functional role of the SMA in the construction of an internal representation of subsequent movements, in particular the goal of the action. Studies performed on patients with medial wall lesions support this view. Laplane and colleagues (1977) reported observations on three patients after medial wall damage that included the SMA. Amongst other difficulties (e.g. partial mutism), these patients showed deficits in spontaneous movements contralateral to the lesion that could be ameliorated by 'strong' spoken commands by the examiner. Laplane et al. proposed that SMA damage in these patients interfered with the generation of actions that relied upon internal context for their execution. This evidence suggests that the patients had a reduced capacity for movement because they lacked the ability to generate a goal that the motor system could use to compute subsequent movements.

As well as evidence for the role of the SMA in the internal representation of future movements, there is also evidence that the *origin* of a movement may be represented by medial wall structures. Using single-cell recording techniques in monkeys, Clower and Alexander (1998) examined pre-SMA and SMA neurons during a sequential movement task. They found that SMA neurons selectively encoded specific spatial features of simple joystick movements, such as the origin and endpoint of the movement. This activity was found across each of the 'epochs' of the task that the authors examined, including the period in which the monkey moved the joystick to the new position. This suggests that under normal physiological conditions the origin of a movement is still represented in some form during and even after the movement is executed.

7.4.2 Physiological Interpretation of Sustained SMA Activity

If the origin of a movement remains represented by the motor system even after a movement has been completed, E.P.'s phantom may be caused by an unmasking of this information. While the long delay before E.P.'s phantom is experienced is hard to explain, there have been previous reports (Wolpert et al., 1998) of patients with deficits in the perceived position of their arm that are expressed after similar delays. While Wolpert et al.'s patient suffered from a perceptual deficit that can be viewed as a gradual corruption of a previously accurate estimate of the position of her arm, E.P.'s percept seems to be driven by the influence of a previously implicit computation of the motor system that reappears over time.

While this explanation is consistent with the behavioural expression of E.P.'s ghost arm, it is more difficult to describe in neurophysiological terms how a sustained representation may influence perception. However, there is no reason to believe that the mechanisms underlying E.P.'s percept are any different to those underlying other 'positive' perceptual illusions. For example, fMRI studies of the 'visual motion after effect' have found activation of area V5/MT (Zeki et al., 1993; Tootell et al., 1995). This is a significant observation as this area is thought to process afferent-driven visual motion (Zeki, 1974). While the SMA is not traditionally regarded as a sensory area, this does not mean that it cannot influence conscious perception of limb position. Using PET, Naito and colleagues (1999) found activation of the SMA, CMA, premotor cortex and M1 during subjects' perception of a kinesthetic illusion. Activation of the SMA and other motor areas can therefore influence subjects' perception of the limbs in space.

It is arguable that other aspects of the present paradigm may be responsible for sustained activity in SMA, independently of E.P.'s perception of her ghost arm. Previous functional imaging studies have described sustained activity in the medial wall during working memory tasks (e.g. Paulesu et al., 1993; Coull et al., 1996; Courtney et al., 1996; Fiez et al., 1996; Smith et al., 1996; D'Esposito et al., 1998; Petit et al., 1998). While the interpretation of this activity varies between investigators and paradigms used, it is generally taken to represent a form of motor preparation, as during the delay period in working memory experiments subjects are aware that they will be required to respond in some manner upon

presentation of a subsequent cue. The Talairach co-ordinates of the maxima from these studies place the peak activations within the pre-SMA, as the maxima are anterior to the VCA line (Petit et al., 1998).

It is unlikely that the sustained SMA proper activity seen in this study can be attributed to motor preparation, for two reasons. First, the anatomical location of the medial wall cluster is too posterior to be located within the pre-SMA. Second, it is unlikely that E.P. experienced any differences in motor preparation or in the selection of motor responses from memory (Petit et al., 1998) between the two delay periods. E.P.'s left arm movements in both were stereotypical and followed a similar pattern – a brief movement after a vocal cue in Finnish. This cue was identical in both delay periods.

A further possible interpretation of the difference in sustained SMA activation is the difference of context between the transient right index finger movements (the button presses) that precedes both 'tonic' periods. In the movement before the 'phantom on' period, E.P.'s movement was self-initiated (timed by her perception of the onset of the ghost arm). In the other 'event', E.P. was instructed to move her right index finger by an external cue, an instruction in Finnish. It could therefore be argued that the differences in sustained SMA activation observed reflect the internal or external nature of the instructions given to E.P. (e.g. Deiber et al., 1999). However, the multiple regression model used for analysis meant that differences between 'phantom on' and 'phantom off' tonic periods were analysed after variance that could be explained by either of the transient regressors (the modeled responses to the right hand index finger movements) had been removed. My interpretation of the sustained activity is that it reflects condition-explicit changes in the BOLD signal of the right SMA that are specific to E.P.'s percept.

7.4.3 The Influence of Motor Representations on Subjective Perception

There is a great deal of evidence to suggest that normal subjects are usually unaware of many aspects of their own actions, including the goal state (e.g. Fourneret and Jeannerod, 1998). However, under certain circumstances these previously implicit representations may become explicit and be able to influence conscious perception of the body. Focusing on the desired goal of an action,

Jeannerod (1990) has suggested that neurons encoding the 'final configuration' of the body would continue firing 'until the final goal has been reached'. If the goal was not reached, 'the sustained discharge would be interpreted centrally as a pure representational activity and give rise to mental imagery' (Jeannerod, 1990). In E.P.'s case, it may be that the alterations in cerebral connectivity arising from her left frontomesial lesion result in the simultaneous expression of two positions of the arm, one representing where the arm was previously (its origin), and one representing its current position (its goal). Upon making a new volitional movement, the current position of the arm becomes the origin of the movement, and thus after a delay upon completion of the new movement the ghost arm appears in the previously vacated position. There is no obvious explanation from my data why the origin of the movement is retained and re-expressed after this delay, or why proprioception is not sufficient to cancel it, yet vision of the limb is. However, it is interesting to speculate that this representation results from a loss of the normal influence of the cingulate motor areas on the SMA, as E.P.'s lesion includes these regions. Just as utilization behaviour (a behaviour observed after frontal lesions in which visual presentation of objects compels patients to grasp/use them; Lhermitte, 1983) reflects the inability to suppress effects of the external world (the 'affordances' of objects) on the motor system, E.P.'s phantom percept may be an example of an inability to suppress internal representations on perception.

7.5 Conclusions

The data presented in this chapter demonstrate that sustained activity in a traditionally 'motor' area of the brain (the SMA) correlates with E.P.'s perception of a third, 'phantom', arm that she perceives in addition to her real left arm. The classic view of mechanisms underlying subjective perception of the body in space is that they mainly involve areas that process primary somatic afferent signals. The incompleteness of this view has been challenged by a number of investigators working in quite separate disciplines. For example, position sense or body schema was once thought to depend almost completely on the activity of joint receptors and the central areas that process their signals. However, afferent signals from muscle were later shown to be important (Goodwin et al., 1972). When reviewing his

work on position sense and somesthesia Lackner (1988) concluded that '...observations indicate that more complex sensory interactions are involved in the determination of position sense than can be accounted for solely by isolated static topographic mappings of somatosensation'. He concluded that 'the perceptual representation of the shape of the body is highly labile' (1988).

Recently, a role for the influence of the contents of the motor system on perception has been proposed. The evidence reviewed in this chapter, together with my data from E.P. suggest that the dichotomy between an 'acting brain' and a 'knowing brain' may be an oversimplification (as suggested by Gallese, 1999). While my results say less about the mechanisms by which body schema are constructed, they demonstrate that a seemingly unitary percept in both time and space can be generated from a combination of quite disparate sources of information about the past, present and future states of an organism.

Most investigators are content to discuss the afferent representation of the body in somatosensory cortex as a somatosensory 'map' which represents a perceptual 'space', the body surface. The contents of this map represent the present state of the peripheral surface of the body, specified in terms of afferent somesthetic information. The present results suggest that, while a perceptual space such as the somatosensory map can be used to influence the subjective position of the limbs, an 'action space', specified in terms of the contents of the motor system, can be used to generate a similar mapping.

8 Discussion and Conclusions: fMRI of the Human Somatosensory System

8.1 General Discussion

This thesis concentrated on the study of the human somatosensory system with functional magnetic resonance imaging (fMRI). The results presented herein allow a number of conclusions to be made, whilst acknowledging that a great deal of exciting questions remain to be answered.

8.1.1 Somatopy, or Not Somatopy? : Spatial Order in SI

The existence of an ordered topographical map of the periphery in the primary somatosensory cortex (SI) has been recognised since the early intracortical stimulation studies of Penfield and Boldrey (1937). Changes in this order have been demonstrated to correlate with changes in somesthetic perception observed after peripheral injury to the limbs using magnetoencephalography (MEG - e.g. Mogilner et al., 1993; Ramachandran, 1993). However, MEG can only indirectly show expansions or contractions of SI representations through difference in dipole strengths. The use of fMRI is advantageous as the spatial arrangement of SI can be observed in greater detail. However, before using fMRI to characterise changes within SI, the technique's ability to image a stable SI map must be proven. I addressed this question in Chapters three, four and five.

In my initial studies, presented in Chapter Three, I found it difficult to elicit robust patterns of BOLD signal change in the region of the postcentral gyrus (PoG) where human SI is located. I addressed this question explicitly by presenting parametrically varying frequencies of airpuff stimulation in the experiment in Chapter Five. While these results showed greater signal change around SI, they did not reveal a stable pattern of somatopy. At the time of writing, two papers (Maldjian et al., 1999 [vibrotactile]; Kurth et al., 2000 [electrical]) have shown a somatopical pattern of activation for all five digits within SI using fMRI. An equal number of papers have reported difficulties in detecting somatopy within SI (Kurth et al., 1997; Gelnar et al., 1998). Thus this issue is still contentious. The existence of so many studies with contrary findings begs the

questions - why does fMRI not reliably detect SI somatopy? There does not appear to be any single element of experimental design (e.g. scanner field strength, experimental design or stimulation method) that separates successful SI mapping studies from unsuccessful ones. One possibility is the fact that some studies that have successfully shown somatotopical order in SI (Kurth et al., 1998; 2000) have used electrical stimulation. These stimuli produce action potential ‘volleys’ of greater magnitude in peripheral nerves than airpuff stimuli. Yet although electrical stimuli are useful as non-specific probes of the somatosensory cortex for clinical purposes, they are artificial. In this thesis I concentrated on using naturalistic stimuli. While it requires some effort to design, construct, and calibrate these systems, they are essential for proper physiological studies of the somatosensory system. It is interesting to consider the comments of Regan and Spekreijse (1986) in this context. In their review of visual evoked potentials (1986), they noted that real advances in this field were only made when researchers began to use complex, textured stimuli, which were complicated to design and use. Before this simple photic flash stimuli were commonly employed, which could be easily used yet were artificial (in a similar manner to electrical nerve stimulation?). Thus the effort invested in the development of ecologically valid stimuli (such as the vibrotactile stimuli used by Francis et al., 2000) in neuroimaging studies of somesthesia may well pay future dividends.

In addition to a lack of an identifiable pattern of digit somatopy, I found that the simple activation paradigms used in Chapters three and five were more likely to activate the crown of the postcentral gyrus, rather than the anterior bank. Roughly, these areas correspond to BA1 (crown) and BA3b (bank). This finding was also unexpected. Given the known neurophysiological profiles of these areas from studies in non-human primates (e.g. Burton and Sinclair, 1996), there is no reason why BA1 should be more consistently activated using the simple activation paradigms in my studies. Other studies have demonstrated similar findings. Careful inspection of the results of Kurth et al. (1998), Geyer et al. (1998), and Francis et al. (2000), amongst others, show that the crown of the postcentral gyrus is activated more consistently than the bank.

This result might be a demonstration of a difference between non-human primates and man. In the monkey, the two adjacent strips of cortex (BA3b and BA1) are positioned such that, while the digits occupy a similar mediolateral position, the tips of the digits are oriented such that they lie anterior in BA3b and posterior in BA1. Preliminary fMRI data (Christopher Moore, personal communication) suggests that this arrangement may be reversed in the anterior/posterior direction in humans. The digit tips would thus lie posterior in BA3b and anterior in BA1 – on the BA3b/BA1 border. If true, digit stimulation would not produce two separate foci in BA3b and BA1. Instead a larger, single focus made up of combined signals from both representations would result. This may explain why the studies mentioned above and those of Chapters three and five typically found more robust activation on the crown of the postcentral gyrus, characteristically where BA1 or the BA3b/BA1 border would be expected to lie. If true, this would represent a striking example of what Crick and Jones (1993) have called the ‘backwardness of human neuroanatomy’ – its reliance on non-human primate data.

However, there is currently no empirical evidence for this speculation, nor is there any convincing reason for why this shift in BA1 and BA3b topography may have occurred between monkeys and man. Yet the discovery of two subdivisions of human primary motor cortex (BA4a and BA4p; Geyer et al., 1996), not present in most non-human primates, demonstrates that there is a precedent for species-specific differences in primary cortex.

8.1.2 ‘Higher Order’ Studies of Somesthesia

The experiments presented in Chapters Six and Seven focused on more ‘cognitive’ somesthetic fMRI experiments. In Chapter Six, a selective attention paradigm was used to examine task-specific processing of somesthetic stimuli. This study found that using spatial criteria to perform a tactile discrimination task activated regions of posterior parietal cortex that were previously shown to be active in similar visuospatial imaging experiments (i.e. Corbetta et al., 1998). In Chapter Seven, BOLD activity in the supplementary motor area correlated with a

patient's proprioceptive illusion (a 'third arm'). The result demonstrates the influence that 'motor' regions can have on somatic perception.

Both studies demonstrate that somatic perception is not the sole domain of somatosensory cortex. There may be a number of reasons why tactile imaging tasks 'recruit' other brain areas. The PET study of Sathian and colleagues (1997) found that a single focus near the parieto-occipital fissure was more activated when subjects performed a tactile orientation task than when subjects performed a feature detection task on the same stimuli. The authors concluded that visual cortical areas might be useful when tactile discrimination tasks involve the processing of macro-geometric features such as orientation and object shape. In a follow-up study they demonstrated the specificity of activation in the parieto-occipital area for their orientation task (Zangaladze et al., 1999). By giving subjects short pulses of transcranial magnetic stimulation (TMS) over a region near their PET focus from the 1997 study during an orientation discrimination task, they found that they could specifically disrupt task performance. However, TMS over this area did *not* interfere with performance on a grating width discrimination task. Thus activity in this area appears to be specific to tactile orientation discrimination. A recent study by Amedi et al. (2000) demonstrated that other 'visual' areas are activated by supposedly 'tactile' tasks. Using fMRI, they found activation of an area adjacent to the lateral occipital complex (LOC), an area previously shown to activate preferentially when subjects viewed visual objects compared to visual textures. In addition, this 'tactile' area adjacent to LOC showed significantly less activation when presented with tactile textures, and negligible activation in visual imagery and motor response control conditions, meaning that it appears to be specialised specifically for tactile shape perception.

Does the involvement of visual areas in tactile tasks reflect tactile processing or visual processing? It is difficult to answer this question unequivocally. The visual system is very good at representing simple orientation patterns of the sort found used by Sathian and colleagues (1997). In the study by Amedi et al. (2000) subjects had to perform objects recognition using haptic exploration. Again, the representations constructed by subjects may have been primarily visual. Thus

there are two possible explanations. First, the areas activated by tactile tasks may be truly visual cortex, and their activation may merely reflect subjects relying on visual representations to solve them. Or, secondly, these areas may only have been classified as ‘visual’ cortex because visual tasks are used in most neuroimaging studies of cognitive neuroscience. Future studies that employ matched visual and tactile tasks in the same study will help in elucidating the functions of these areas.

8.1.3 Don’t Get Touchy: Speculations on the Difficulty of Tactile fMRI

It is tacitly accepted, though rarely admitted, that neuroimaging studies of the somatosensory system are less likely to produce results than those of other modalities. There may be a number of reasons for this. In his review of perceptual learning, Goldstone (1998) notes that ‘attentional weighting’ is a method by which perception can be adapted to different tasks: by ‘...increasing the attention paid to perceptual dimensions and features that are important, and/or by decreasing attention to irrelevant dimensions and features’. Most simple sensory stimulation paradigms rely on subjects attending to the stimulus, or to a particular dimension of the stimulus. However, a simple task may prove difficult if subjects have little experience of what the dimension actually *is*. The dimensions of tactile experience may be sufficiently novel to prevent their efficient representation. By way of contrast, normal subjects are skilled in using visual concepts such as ‘colour’ to categorise visual experiences. While tactile stimuli can be ‘parsed’ into different features (Burton et al., 1999), it may take subjects some practice to do so competently.

Training or perceptual learning may help to ameliorate these problems. After training humans can show remarkable increases in their tactile abilities (e.g. Sathian and Zangaladze, 1997), even performing as well as trained blind Braille readers (Grant et al., 2000). Thus, my hypothesis would be that subjects trained in tactile attention would on average activate somatosensory cortical areas with greater efficacy than untrained subjects (or in the same subjects before training). fMRI is an ideal measure to use to address these questions.

8.2 Concluding Remarks

Our tactile lives and memories are extremely sparse – there are few adjectives that one can use to describe tactile experience. If more is known about how stimuli are transduced by the skin, these principles can be employed to utilize the skin as an information-processing channel to replace vision in the blind (e.g. Tan and Rabinowitz, 1996). In addition, while primate sensory systems share a number of common features (the use of feedback loops between ‘stages’ in sensory processing, an increase in receptive field size as one progresses further from the periphery etc.), they differ in the number of areas and in their intrinsic and extrinsic connectivity. Thus each system is equally worthy of study.

In his book ‘Pride and a Daily Marathon’ (Cole, 1995), the clinical neurophysiologist Jonathan Cole describes the daily challenges faced by one of his patients (Ian Waterman) who lost both light touch and proprioception below neck level when he was 19. In addition to the obvious effects on movement and perception, Mr. Waterman found that one of his greatest problems was conveying a sense of his predicament to other people. It is easy to imagine how blindness or deafness can be a serious handicap, yet almost impossible to truly communicate the severe disability that results from the loss of touch and proprioception. One suspects that Proust would not have written ‘*A la recherche du temps perdu*’ (1913) if he had only the *touch* of a Madeleines cake to inspire him. The systematic study of somesthesia using non-invasive imaging suggests that, for the future Prousts of the 21st century, this may not remain true for long.

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Appendix 1 – Chapter Four Tabular Data

Table 1a. Local maxima for the motor fixed effects analysis.

Area	Cluster size(k) ¹	Z Score ²	Talairach Co-ordinates		
			X	Y	Z
Left precentral gyrus (SM1)	5958	9.77	-38	-10	52
Left precentral gyrus (SM1)		9.63	-62	-20	38
Left postcentral gyrus (SM1)		9.51	-60	-18	46
Right cerebellum, anterior lobe	1709	9.50	20	-54	-18
Right cerebellum, anterior lobe		9.19	2	-54	-24
Right cerebellum, anterior lobe		9.14	8	-58	-20
Left supplementary motor area (SMA)	927	9.39	-2	-2	52
Right SMA		8.75	8	2	58
Right SMA		8.50	4	8	66
Left inferior frontal gyrus	227	9.23	62	6	16
Left inferior frontal gyrus		6.98	62	4	4
Right postcentral gyrus (SM1)	197	9.07	58	-12	50
Right precentral gyrus (SM1)		8.29	52	-6	38
Right precentral gyrus (SM1)		7.71	62	-2	38
Left inferior thalamus	466	8.84	-12	-18	2
Left ventral midbrain		6.15	-8	-12	-14
Left midbrain		5.90	-8	-20	-12
Right lateral premotor cortex	70	8.80	38	-8	50
Right inferior frontal gyrus	62	8.60	64	0	16
Right inferior parietal lobule	604	8.54	50	-28	24
Right transverse temporal gyrus		8.36	52	-18	12

Right superior temporal gyrus		7.99	68 -26 16
Left posterior cingulate gyrus	100	8.32	-8 -26 42
Left posterior cingulate gyrus		7.11	-2 -22 48
Right inferior frontal operculum	228	8.23	0 6 4
Right insula		6.12	0 6 10
Left cerebellum, anterior lobe	66	7.85	20 -56 -20
Right cerebellum, anterior lobe	98	7.73	2 -58 -48
Right cerebellar tonsil		7.43	6 -70 -40
Left posterior postcentral gyrus	67	7.63	18 -46 64
Left superior frontal gyrus	79	7.49	28 42 26
Left superior thalamus	46	7.40	18 -10 18
Left thalamus		5.73	-12 -6 12
Left medial frontal gyrus	223	7.27	-38 58 -2
Left medial frontal gyrus		7.27	-30 62 4
Left inferior frontal gyrus		7.20	-34 54 -8
Third ventricle	22	7.27	6 -42 -6
Right putamen	171	7.26	8 6 -2
Right putamen		6.68	0 6 -12
Right anterior cingulate gyrus	27	6.74	14 8 42
Right postcentral gyrus	7	6.74	40 -30 58
Right thalamus	40	6.70	14 -14 2
Right inferior frontal gyrus	18	6.46	30 60 -2
White matter, subcortical	33	6.46	16 0 12
White matter, subcortical		5.13	12 6 2
Right posterior cingulate	19	6.43	12 -24 46
Right cerebellum	18	5.94	48 -50 -38
Right thalamus	16	5.79	20 0 -6
Left cerebellum	12	5.76	-36 -64 -26
Left superior frontal gyrus	5	5.64	-28 28 56
Right thalamus	9	5.55	8 -4 -4
Right cerebellum	12	5.51	40 -62 -50
Left superior frontal gyrus	8	5.42	-22 38 48
Right caudate nucleus	9	5.30	20 -6 20

¹ Only clusters with $k \geq 5$ are listed. Where multiple foci exist for a cluster, the three most significant are reported.

² All foci reported survive a statistical threshold of $p < 0.05$ corrected for multiple comparisons across the entire image volumes.

SM1 = Primary somatomotor cortex.

SMA = Supplementary motor cortex.

Table 1b. Local maxima for the motor random effects analysis.

Area	Cluster size(k)	Z Score	Talairach Co-ordinates		
			X	Y	Z
Left precentral gyrus (SM1)	4253	8.76	-36	-10	52
Left precentral gyrus (SM1)		8.45	-60	-18	38
Left frontal operculum		8.37	-48	4	0
Right cerebellum, anterior lobe	951	8.04	18	-52	-18
Right cerebellum, anterior lobe		7.55	30	-52	-26
Right cerebellum, anterior lobe		7.34	36	-62	-24

Left inferior frontal gyrus	151	8.00	-62	8	16
Left inferior precentral gyrus		6.96	-60	-2	16
Left supplementary motor area (SMA)	545	7.62	-8	-2	48
SMA		7.34	0	2	56
Right superior SMA		7.15	4	10	66
Left Thalamus	173	7.44	-12	-20	2
Left midbrain (red nucleus)		5.47	-12	-14	-10
Right postcentral gyrus (SM1)	104	7.40	58	-12	50
Right inferior precentral gyrus		6.93	50	-4	36
Right inferior precentral gyrus		5.75	60	-2	40
Left supramarginal gyrus	44	7.27	-58	-44	18
Right lateral premotor cortex	46	7.19	38	-8	52
Right frontal operculum	104	7.10	50	6	4
Right parietal operculum	256	7.07	50	-28	26
Right transverse temporal gyrus		6.94	48	-18	14
Right transverse temporal gyrus		6.16	68	-26	16
Left posterior cingulate gyrus	39	6.88	-8	-24	44
Right inferior frontal gyrus	32	6.71	64	0	16
Right inferior postcentral gyrus	25	6.56	62	-12	12
Cerebellar vermis	25	6.22	6	-70	-40
Left superior frontal gyrus	21	6.04	-28	42	26
Right cerebellar tonsil	8	5.88	12	-56	-48
Left superior thalamus	12	5.81	-20	-12	18
Left posterior postcentral gyrus	14	5.73	-18	-46	64
Left cerebellum, anterior lobe	10	5.68	-20	-56	-20
Right putamen	20	5.57	28	8	-2

SM1 = Primary somatomotor cortex.

SMA = Supplementary motor cortex.

Table 2a. Local maxima for the cognitive fixed effects analysis.

Area	Cluster size(k) ¹	Z Score ²	Talairach Co-ordinates		
			X	Y	Z
Right inferior parietal lobule	888	9.27	50	-30	44
Right inferior parietal lobule		8.63	34	-44	44
Right supramarginal gyrus		7.95	66	-24	40
Left medial precentral gyrus (FEF)	1716	9.26	-24	0	50
Left lateral precentral gyrus		8.96	-50	4	46
Left middle frontal gyrus		8.51	-54	10	26
Left precuneus	1812	9.17	-10	-66	44
Left superior parietal lobule		8.86	-42	-36	50
Left superior parietal lobule		8.77	-18	-62	64
Right medial precentral gyrus (FEF)	776	9.17	26	-4	58
Right superior frontal gyrus		8.70	20	6	60
Right superior frontal gyrus		7.68	12	14	66
Right superior parietal lobule	876	8.99	20	-66	58
Right superior parietal lobule		8.74	26	-70	50
Right superior parietal lobule		8.42	22	-58	62
Right anterior precentral gyrus	238	8.84	62	4	28
Left middle frontal gyrus	454	8.63	-34	36	22
Left middle frontal gyrus		8.22	-48	40	24
Left middle frontal gyrus		7.11	-30	46	34
Right lateral premotor cortex	85	8.39	56	0	46
Left supplementary motor area	421	8.30	-2	18	50
Right inferior frontal gyrus	406	8.30	56	16	-2

Right inferior frontal gyrus		7.44	48	26	-8
Right superior temporal gyrus		7.44	-34	16	6
Left inferior frontal gyrus	414	8.24	-56	12	0
Left inferior frontal gyrus		8.09	-42	22	8
Left insula		7.23	-34	16	6
Right cerebellum, anterior lobe	190	8.00	30	-62	30
Right cerebellum, anterior lobe		7.32	34	-54	36
Right cerebellum, anterior lobe		5.86	40	-60	36
Left temporo-occipital sulcus	41	7.96	-52	-52	18
Right inferior parietal lobule	44	7.92	68	-38	24
Right inferior parietal lobule		5.48	68	-30	32
Right inferior parietal lobule		5.33	64	-44	34
Right middle frontal gyrus	311	7.91	44	40	32
Right middle frontal gyrus		7.81	44	42	20
Right middle frontal gyrus		7.80	34	36	18
Right anterior cingulate gyrus	37	7.75	12	12	38
Left inferior parietal lobule	80	7.67	-62	-36	32
Right middle temporal gyrus	72	7.65	58	-20	6
Right superior temporal gyrus	67	7.62	48	-32	2
Right middle occipital gyrus	27	7.21	50	-74	12
Left precentral gyrus	11	6.99	-54	-8	14
Left middle frontal gyrus	28	6.99	-30	56	26
Left superior temporal gyrus	43	6.96	-54	-40	4
Left inferior frontal gyrus	16	6.67	-54	34	8
Right cerebellum	16	6.58	36	-38	42
Right calcarine cortex (V1)	17	6.45	12	-78	8
Right insula	11	6.39	40	6	0
Left cerebellum	30	6.36	-22	-56	34
Left anterior cingulate	9	6.35	-12	16	32
Left inferior frontal gyrus	23	6.02	-36	58	2
Left inferior frontal gyrus		5.53	-32	62	4
Right insula	11	5.90	42	16	4
Left calcarine cortex (V1)	17	5.80	-6	-72	20
Right middle frontal gyrus	7	5.77	40	30	24
Left calcarine cortex (V1)	6	5.50	-4	-9	0
Left hemisphere, white matter.	9	5.44	-22	54	0
Right superior frontal gyrus	5	5.24	16	38	54

FEF = Frontal eye fields.

V1 = Primary visual cortex.

Table 2b Local maxima for the cognitive random effects analysis.

Area	Cluster size (<i>k</i>)	Z Score	Talairach		
			Co-ordinates		
			X	Y	Z
Left superior parietal lobule	690	8.13	-40	-36	48
Left posterior postcentral gyrus		7.44	-48	-28	40
Left superior parietal lobule		7.28	-30	-48	42
Left medial precentral gyrus (FEF)	1134	8.07	-26	-2	50
Left middle frontal gyrus		8.06	-50	8	44
Left ventral precentral gyrus		7.74	-52	10	26
Left superior parietal lobule	156	7.87	-18	-64	64
Left superior parietal lobule		6.58	-26	-62	60

Left superior parietal gyrus		5.59	-34 -60 60
Right inferior parietal lobule	460	7.87	48 -30 44
Right inferior parietal lobule		7.50	56 -32 44
Right supramarginal gyrus		6.84	64 -24 40
Right superior parietal lobule	540	7.75	18 -64 58
Right superior parietal lobule		6.97	22 -56 62
Right superior parietal lobule		6.93	26 -64 34
Right medial precentral gyrus (FEF)	569	7.73	28 -2 60
Right superior frontal gyrus		7.62	20 6 62
Right superior frontal gyrus		6.47	12 12 68
Left precuneus	157	7.72	-8 -66 42
Right anterior precentral gyrus	173	7.56	62 6 28
Left middle frontal gyrus	276	7.38	-34 38 24
Left middle frontal gyrus		6.81	-50 36 24
Right cerebellum, anterior lobe	78	7.24	30 -62 -30
Right cerebellum, anterior lobe		6.56	32 -56 -36
Right inferior parietal lobule	22	7.03	68 -38 24
Right middle temporal gyrus	55	6.95	60 -20 -8
Right lateral premotor cortex	41	6.94	54 2 44
Left inferior frontal gyrus	139	6.92	-42 22 -8
Left inferior frontal gyrus		6.80	-56 12 0
Right inferior frontal gyrus	122	6.89	56 16 -2
Left temporal-occipital sulcus	18	6.77	-52 -52 -18
Left supplementary motor area (SMA)	201	6.71	-2 18 48
Left supplementary motor area (SMA)		6.66	-6 10 54
Left supplementary motor area (SMA)		6.64	0 16 58
Right anterior cingulate gyrus	15	6.66	14 12 38
Right middle frontal gyrus	98	6.53	38 38 34
Right middle frontal gyrus		5.93	44 40 20
Right middle frontal gyrus		5.66	34 44 38
Left inferior parietal lobule	33	6.26	-64 -38 26
Right middle frontal gyrus	19	6.26	34 36 18
Right superior temporal gyrus	26	6.01	46 -30 -4
Left middle frontal gyrus	7	5.98	-30 54 28
Right superior temporal gyrus	16	5.90	54 18 -20
Right inferior frontal gyrus	16	5.79	50 26 -8
Left superior frontal gyrus	7	5.73	-10 12 70

FEF = Frontal eye fields

SMA = Supplementary motor area.

Table 3a Local maxima for the visual fixed effects analysis.

Area	Cluster size (<i>k</i>)	Z Score	Talairach		
			X	Y	Z
Right calcarine cortex (V1)	11002	9.72	14	-86	2
Right calcarine cortex (V1)		9.63	6	-74	-4
Left calcarine cortex (V1)		9.57	-8	-82	0
Right superior temporal gyrus	80	7.96	42	-28	18
Right precuneus	54	7.93	8	-80	44
Left lateral geniculate nucleus	91	7.92	-18	-26	-4
Right superior temporal gyrus	51	7.81	70	-32	14
Left inferior parietal lobule	152	7.79	-32	-38	54
Left superior parietal lobule	130	7.75	-28	-54	54