

Neuropsychological and neuroimaging investigations of an inherited disorder of speech and language

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"I am not yet so lost in lexicography, as to forget that words are the daughters of earth, and that things are the sons of heaven. Language is only the instrument of science, and words are but the signs of ideas: I wish, however, that the instruments might be less apt to decay, and that signs might be permanent, like the things which they denote."

Samuel Johnson

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Abstract

A disorder of speech and language affects half of the members of the KE family, and cosegregates with a genetic abnormality on chromosome 7 (Fisher *et al.* 1998). Members of this family were investigated neuropsychologically and with functional and structural imaging.

Neuropsychological investigations revealed that affected family members (n=13) were impaired relative to unaffected members (n=12) on several tests assessing language, nonverbal intelligence and praxis. The two groups could be successfully discriminated, however, solely on the basis of a measure of articulation. It is suggested that the core deficit is one affecting articulation, and that, in a developmental context, this might give rise to secondary deficits in other cognitive domains. The pattern of impairment in affected members was contrasted with that in patients with acquired aphasia (n=11), who were also impaired in articulation. The deficit in articulation might also explain the findings in four affected members of a significant difference in implicit processing of regular versus irregular verbs and of an impairment in processing sentences containing auxiliary verbs. Investigation of auditory processing in this family did not reveal any significant impairment.

A positron emission tomography study of two affected family members revealed several regions of the left hemisphere that were functionally either overactive or underactive during word repetition, including the caudate nucleus and other motor regions and areas involved in speech production. Analysis of magnetic resonance imaging scans, acquired in ten affected and seven unaffected family members, showed that the former had abnormal amounts of grey matter in a number of brain areas, including the caudate nucleus bilaterally. Further analysis of the scans confirmed that this structure was abnormally small bilaterally in the affected family members, and it was proposed that this abnormality is responsible, at least in part, for their core deficit.

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Aims and Structure of Thesis

There are four parts to this thesis: an introduction, neuropsychological studies, neuroimaging studies and a discussion. In Part One, the first chapter provides an overview of research on developmental disorders of speech and language, the background against which the KE family have been investigated. The disorder of speech and language shared by the affected members of the KE family has a genetic aetiology. The size of this family and the availability of affected and unaffected individuals who share the same environment provides a unique opportunity to investigate this disorder at both behavioural and neural levels. The KE family is described in detail in Chapter 2, along with an overview of previously published studies.

The neuropsychological investigations are reported in three chapters constituting Part Two. They represent one of the aims of this thesis, which is to characterise the functional deficits common to the affected members of the KE family. To this end, the performance of the KE family on a number of tests of language, praxis and nonverbal intelligence is described in the first of these chapters. The affected family members are compared with a group of adult patients with aphasia acquired after a stroke involving the left hemisphere. Comparison of the profiles in these two language-impaired populations is aimed at revealing possible common neurobiological correlates. The second chapter of Part Two examines the deficit in the KE family from a psycholinguistic viewpoint. The results of tests of on-line processing of morphology and syntax are described for four affected family members. In the final chapter of Part Two, the question of whether an auditory perceptual deficit is present in the affected family members is addressed. Such a deficit is presumed to cause language impairment and has also been related to an altered pattern of hemispheric dominance. To test this suggestion more systematically, results of a test of dichotic listening for digits, used as a measure of hemispheric dominance for speech and language, are also described.

Part Three consists of three chapters, which address the second aim of this thesis. This is to investigate the presence of structural and functional brain abnormalities associated with the disorder in the KE family. The first chapter of Part Three presents a functional (positron emission tomography, PET) imaging study of the KE family. These results have important implications for the two structural imaging studies described in the second and third chapters of Part Three. The

second chapter describes a voxel-based morphometry study of structural magnetic resonance imaging brain scans, which is a novel approach to morphometric analysis of the whole brain, and is used to identify regional differences in the relative amounts of grey matter. The third chapter describes a more traditional method of image analysis, region-of-interest pixel counting, which measures in greater detail the size and shape of one brain region, the caudate nucleus. This nucleus was revealed to be functionally abnormal by the PET study and structurally abnormal by the first morphometric study.

Finally, in Part Four, the relationship between the neuropsychological and the neuroimaging results is discussed and directions for future studies are suggested.

Part One : Introduction

1. The study of developmental disorders of speech and language

This thesis reports the results of neuropsychological and neuroimaging investigations of the KE family. Almost half the members of the KE family are affected by a developmental disorder that severely affects speech and language and persists into adulthood. Developmental disorders of speech and language (DDSL) occur in about 7% of children (Tomblin *et al.* 1997), in the absence of factors associated with a failure of language development, such as deafness, mental deficiency, motor disability, emotional disturbance, social deprivation or neurological deficits. These disorders of speech and language are striking, not least because most children acquire language apparently with little effort. Although there is mounting evidence for a genetic aetiology in DDSL, the KE family provide a dramatic example of a single genetic abnormality resulting in a severe and persistent difficulty in language acquisition. It is presumed that genes cause DDSL via influences on brain development. It is even more striking, therefore, that these disorders occur in the absence of a frank neurological deficit. In fact, children with unilateral brain damage, in some cases affecting the whole of one hemisphere, do not show deficits in speech and language that resemble those seen in DDSL. The nature of the abnormalities in brain development that result in DDSL, therefore, is intriguing.

Genetic, neurobiological, cognitive and behavioural studies of populations with DDSL aim to explain the abnormal development of speech and language at one or more of these levels. There is no prospect of animal models to aid our understanding of language development because language is a uniquely human ability. The ultimate aim of studies of groups of children with DDSL, therefore, is to further understand the normal development of language.

This chapter presents an overview of research on DDSL providing a background against which the KE family has been investigated. It is divided into sections describing the behavioural, genetic and neurobiological correlates of DDSL. Before these sections, a brief, historical account of the research that has led to the current diagnostic category of specific language impairment (SLI) is provided. This is followed by descriptions of the characteristics of the language impairment of children with SLI, the diagnostic criteria used in current research, and the subtypes of SLI.

1.1 Developmental disorders of speech and language

1.1.1 Historical perspective

The study of children with DDSL dates from the early part of the last century (see Weiner, 1986, for a review). Attention was drawn to DDSL by Gall in 1822. He described a group of children “who do not speak to the same degree as other children although they understand well or are far from being idiotic” (cited Leonard, 1998). A number of case reports describing children with seemingly normal intelligence and understanding but with severe speech difficulties followed Gall’s report. These disorders were referred to as “congenital aphasia” (Väisse, 1866) and “hearing mutism” (Coën, 1886). Later, the emphasis of research gradually widened to include children with moderately impaired language production and also those with language comprehension deficits, rather than only those with severely limited production. In the early twentieth century efforts were made to subcategorize the disorder into pure production impairments or combined production and comprehension deficits. At this time, the grammatical deficits of children with DDSL also first received attention.

By the middle of the twentieth century, the preferred term used to describe children who develop normally in every aspect except language was “developmental aphasia” (Benton, 1964; Eisenson, 1968). Later, the term “dysphasia” replaced “aphasia” because the latter strictly refers to absence of language (Eisenson, 1972). Thus, “developmental dysphasia” became a common label (Tallal, Stark & Curtiss, 1976). “Aphasia” and “dysphasia”, however, are typically associated with acquired disorders of language following stroke. To convey the absence of frank brain damage, more neutral terms were adopted, such as “language disorder” and “language impairment”. These changes also represented attempts to develop exclusionary criteria for the diagnosis of language disorders, such that children with brain damage were considered as a separate category. As a result of these changes, and in an attempt to avoid unintended implications regarding the nature of the disability, an array of confusing labels has been used over the last thirty years: “infantile speech”, “aphasoid” (Lowe & Campbell 1965), “dyslogia” (Eisenson, 1969), “developmental language disorder” (Aram & Nation 1975), “specific language deficit” (Stark & Tallal, 1981), “specific language impairment” (SLI; Leonard, 1981; Johnston *et al.* 1981) and “language/learning impaired” (Tallal, Ross & Curtiss, 1989).

The current and most widely adopted term used to refer to DDSL is SLI. The definition of SLI is important in introducing a degree of homogeneity among

research populations. In fact, the diversity of labels used historically suggests that studies predating the accepted criteria of SLI should be considered with caution because they may not be describing the same disorder.

1.1.2 Characterising SLI

Children with SLI have limited language ability. There are certain areas of language that are particularly problematic for children with SLI, but within the population as a whole, there is significant heterogeneity in terms of the deficits in different aspects of language in each individual. Typically, these children produce immature speech, frequently omitting grammatical morphemes (grammatical suffixes and function words), but also erroneously adding morphemes to produce over-regularisations, such as “drawed” for “drew” (see Leonard, 1998 and Bishop, 1997, for examples of language produced by children with SLI). Vocabulary may be limited and the child may have word-finding difficulties. Phonological production is also frequently delayed or deviant. Reading problems may emerge during school years. These language problems persist throughout development, although an individual with SLI may demonstrate different profiles of impairment at different ages (Bishop, 1997). The use of appropriate language tests can reveal deficits relative to age-matched controls even when the language deficit may appear to have resolved (Bishop, North & Donlan, 1996). The most commonly observed profile is one of greater weakness in morphosyntax and phonology compared to other areas such as lexical development and pragmatic use of language. Language comprehension is often impaired relative to chronological age levels, but less so than language production. Significantly more males than females are diagnosed with SLI (Tallal, Ross & Curtiss, 1989). Also, children with SLI are more likely than others to have relatives who have a language impairment (see Section 1.3).

1.1.3 Diagnostic criteria for SLI

Diagnosis of SLI is controversial but most researchers have adopted specific criteria to reduce the heterogeneity of study groups. Although these criteria can differ, they are generally variations of those specified by the World Health Organisation (WHO; International Classification of Diseases, ICD-10, 1993):

- Language skills, measured using standardised tests, are two standard deviations below those for the child’s age-group.
- Language skills are at least one standard deviation below nonverbal intelligence.

- There are no neurological, sensory, or physical impairments that directly affect use of spoken language, nor is there a pervasive developmental disorder.
- A distinction is made between receptive language disorder, where comprehension is more than two standard deviations below age level, and expressive language disorder, where only expressive language is severely affected.

The American Psychiatric Association's Diagnostic and Statistical Manual (DSM-IV; 1994) also has diagnostic criteria for "developmental language disorder", similar to those of ICD-10, but it includes the additional requirement that language difficulties interfere with academic or occupational achievement, or with social communication.

Assessing language ability

Language ability is usually assessed using standardised clinical tests. These tests examine language function in a number of areas, typically covering both receptive and expressive, lexical and grammatical abilities. A commonly used method of diagnosing SLI is to adopt a statistical cut-off of more than two standard deviations (SD) below the mean for chronological age (as in ICD-10 criteria). One of the disadvantages of this method, however, is that it results in a fixed prevalence of the disorder in the normal population. A preferred method may be to first clinically diagnose the language disorder when it interferes with academic achievement or social communication (i.e. according to DSM-IV criteria) and then to assess the magnitude and profile of the impairments using standardised tests and the two SD cut-off. The problem with this method, however, is that clinical opinion will vary. Another alternative is to use age-equivalent scores and to diagnose language impairment as a discrepancy between chronological age and "language age" (Stark & Tallal, 1981). An age-equivalent of two years on a language test in a four-year-old child, however, is potentially more serious than an age equivalent of seven years in a nine-year-old child, and this method does not allow for such differences (see Bishop, 1997, for a discussion of further problems with this method). At present, there is no agreement as to the best method for establishing the severity of a language deficit.

Language development and nonverbal intelligence

A discrepancy between nonverbal cognitive ability and language is considered a fundamental criterion for the diagnosis of SLI (see ICD-10 criteria above). Many researchers also require that nonverbal intelligence must be at least

average, defined as an intelligence quotient (IQ) not less than one SD below the mean. This requirement excludes children with global developmental delay who cannot be considered to have a specific language deficit.

There are a number of controversies surrounding the use of this criterion. For example, the use of different tests to assess nonverbal intelligence could result in overlapping, but nonidentical, classification of the same population. In addition, these tests have an error of measurement so that use of exact cut-off scores may be over-exclusive (these problems apply to language assessment as well). Another problem is that some individuals with low IQ, specifically those with Williams syndrome, can have apparently normal language function (Bellugi *et al.* 1988; but see Karmiloff Smith *et al.* 1998). Such evidence suggests that the use of average nonverbal IQ as a criterion for SLI is unnecessary.

Lastly, impairments in language may adversely affect the development of other aspects of cognition. Follow-up studies of children with SLI, who at the time of diagnosis had normal nonverbal IQs, have shown that these can decline (Tallal *et al.* 1991; Tomblin, Freese & Records, 1992; Bishop & Adams, 1990). As a result of this decline, many of the children no longer fulfil the more strict criteria for SLI.

Language development and neurological impairments

Although some neurological disorders, such as epilepsy and stroke, are associated with language impairment in childhood, the diagnostic category of SLI typically excludes those children whose language impairment results from an acquired neurological insult. Historically, these children may have been included in studies of DDSL, but the current view is that they are a separate group from those with SLI.

In general, children with either congenital or acquired unilateral focal lesions do not show persistent speech and language problems that either resemble those seen in SLI or can be characterised as dysphasia (Hécaen, 1976). The absence of such impairments is attributed to the remarkable plasticity and reorganisational capacity of the immature brain that can subserve speech and language functions provided the necessary neuronal substrate is intact on one side (see Vargha Khadem *et al.* 1991; Vargha Khadem & Polkey, 1992). In contrast to those with unilateral lesions, children with acquired bilateral pathology show chronic and severe speech and language deficits (Landau, Goldstein & Kleffner, 1960; Vargha Khadem, Watters & O'Gorman, 1985). These deficits may be similar to those seen in SLI and the KE family. Also, some children with a particular kind of epilepsy (Landau-Kleffner

Syndrome; Landau & Kleffner, 1957; Paetau *et al.* 1991) exhibit severe interference with language use and subsequent restriction in language development (i.e. verbal auditory agnosia; Rapin, Mattis & Rowan, 1977). In these children also, pathology is often bilateral and associated with epileptic foci in posterior temporal cortex.

Language development and sensory, physical or social impairments

Children with sensory impairments, particularly those with auditory deficits, would be expected to have language learning difficulties. Most investigators examine a child's hearing with pure tone audiometry before diagnosing SLI; similarly, children who have had recent bouts of otitis media with effusion (OME), which causes temporary hearing loss, will be excluded from research studies on SLI. Although OME responds well to treatment, it often recurs leading to periods of impaired hearing, which can affect spoken language. Children with SLI are no more prone to OME than those without language problems (Bishop & Edmundson, 1986), thus excluding this disease as a causative factor.

Children with abnormal oral structure, such as cleft palate, are excluded from the category of SLI because it is assumed that the physical abnormality interferes with the production of language. Abnormal oral function is often an exclusionary criterion for the same reason; it is diagnosed if the child has difficulty producing simple movements of the tongue and of the lips.

Finally, SLI excludes children who fail to communicate because of impaired social interactions. Such impairments are typically associated with pervasive developmental disorder and autism, which is characterised by poor eye contact and gesture, restricted play and social interaction and stereotyped behaviour. Abnormal social interactions may be associated with other psychiatric disorders, such as schizophrenia, although this is rare in childhood.

1.1.4 Subtypes of SLI

Language is a complex behaviour; it is not surprising, therefore, that its development can be impaired in a number of different ways. A simple dichotomy within the language domain is that between receptive and expressive forms, and this has led to a common distinction in research studies as early as the beginning of this century. Both ICD-10 and DSM-IV criteria distinguish between these two types of language impairment in SLI. In expressive language disorders it is usually only the expressive form that is impaired, while both expression and comprehension are impaired in receptive language disorders. Problems with both aspects of language can be identified in most children with SLI, however, if appropriate tests are used. A

simple dichotomy is inadequate, therefore, and classification systems, which attempt to distinguish between subtypes based on linguistic processes, have been developed.

One of the most widely used classifications of SLI is that of Rapin & Allen, (1989; see Table 1.1). These investigators reported successful classification using this system for the members of a group of pre-school children with language disorders, with the exception of a few cases who had severely disordered autistic behaviour. However, Bishop & Edmundson (1987) noted that the impairment of a child with SLI can change with age, manifesting itself in different ways at different points in development. Also, even though studies of SLI attempt to identify the underlying processes of the disorder, the existence of subtypes suggests that a common aetiology is unlikely. Currently, most studies do not treat subtypes separately. Further work is now needed to refine and validate these classifications, and to specify separate diagnostic criteria for each subtype.

Table 1.1 *The six language disorder subtypes of Rapin & Allen (1989)*

| <i>Subtype</i> | <i>Description</i> |
|----------------------------------|--|
| Verbal auditory agnosia | Also known as word deafness. The child appears to lack any comprehension of speech but has normal hearing. |
| Semantic-pragmatic deficit | Speech is fluent and well-formed but is typically echolalic or stereotyped. Content of language is often non-specific and comprehension is usually literal. |
| Lexical-syntactic deficit | The child has severe word-finding difficulty and usually replaces the target word with a paraphasia, although speech sounds are normal. The child may also have difficulty understanding grammar. |
| Phonological-syntactic deficit | Speech is dysfluent and short utterances are produced often simplified by omission of morphemes, phonological contrasts and function words. Comprehension is usually less impaired than language production. |
| Phonological programming deficit | Speech is typically unintelligible although utterances can be long. Phonological contrasts are reduced and there may be a auditory processing problem. |
| Verbal dyspraxia | Speech is dysfluent and unintelligible, confined to a few sounds or short utterances. There may also be deficits in motor planning and other motor skills. |

1.2 The functional deficits of DDSL

In this section, the functional deficits reported in populations of children with SLI are reviewed. These have been separated into linguistic and nonlinguistic deficits in an attempt to emphasise the different theoretical perspectives. The division into linguistic and nonlinguistic deficits is a difficult one to maintain, however, and the examples included under the nonlinguistic section might be considered as linguistic in essence. This is true of auditory perception of speech sounds and phonological working memory, in particular. The distinction used here is one between pure linguistic deficits and those deficits that may involve language but are not restricted to that domain or those that operate at a lower level (e.g. a perceptual level).

1.2.1 Linguistic deficits

The linguistic deficits of children with SLI have been briefly described in Section 1.1.2. They predominantly affect morphosyntax and phonology although lexical deficits are also reported, particularly during early development.

Lexical

Research has shown that children with SLI acquire their first words on average 12 months later than normally developing children (Trauner *et al.* 1995). Their use of verbs during early lexical development is abnormal even when compared to younger normally developing controls (Watkins, Rice & Molz, 1993; Watkins *et al.* 1995). As language develops to multi-word utterances, word-finding deficits may appear, which manifest as unusually long pauses in speech, frequent use of non-specific words such as “it” or “stuff”, and word substitutions (McGregor, 1994).

Morphosyntactic

Most studies of SLI have focussed on impairments in morphosyntax, which can be divided into two levels: syntactic structure and grammatical morphology. Syntactic structure is concerned with relationships between words, such as their order. Grammatical morphology concerns the morphemes of language, such as “-ed” and “-s” in inflectional morphology (e.g. *play, plays, played*) and “-er” and “-est” in derivational morphology (e.g. *strong, stronger, strongest*), as well as function words such as articles and auxiliary verbs (e.g. “*the cat*” and “*is going*”, respectively). Children with SLI show restrictions in their use and comprehension of syntax (Bishop, 1979), particularly for sentences in which the word order can be confusing,

such as reversible passives (e.g. *The cow is pushed by the boy*). The correct usage of grammatical morphemes is often delayed in children with SLI even when compared to younger normally developing children matched on other language measures (Lahey *et al.* 1992; Leonard, *et al.* 1992). Gopnik (1990b) reported an eight-year-old boy with SLI who omitted, or inappropriately produced, inflections and function words involving tense, person and number. Gopnik suggested that this child had no knowledge of the grammatical role of these morphemes. Similar findings were reported for the affected members of the KE family, also studied by Gopnik and her colleagues (Gopnik & Crago, 1991), and in school-age children with SLI studied by van der Lely (van der Lely, 1997; van der Lely & Stollwerck, 1996; van der Lely, 1994). These studies, in particular, are pertinent to the discussion of theoretical perspectives in Section 1.2.3.

Phonological

Impairments in phonology often accompany deficits in other aspects of language. Thus, a child who has been identified primarily on the basis of a phonological impairment is likely to have other language problems (Ruscello, St. Louis & Mason, 1991). Systematic sound changes that affect classes of sounds or sound sequences are known as phonological processes. Examples include: consonant cluster reduction, “no” for *snow*, “bu” for *blue*; final consonant deletion, “bo” for *boat*, “soo” for *soup*; stopping, “pood” for *food*, “tope” for *soap*; and word-initial weak syllable deletion, “nana” for *banana* (see Leonard, 1998). They occur with relatively high frequency in the speech of normally developing young children. Children with SLI persist in producing phonological processes past the age at which they disappear from the speech of normally developing children (Ingram, 1976). Phonological processes are observed in the speech of the affected members of the KE family, even in adulthood (Fee, 1995).

1.2.2 Nonlinguistic deficits

Children with SLI also show deficits on nonlinguistic tests. As mentioned in Section 1.1.3, diagnostic criteria usually select for children with at least average nonverbal intelligence. In view of this, deficits on nonlinguistic tasks are unlikely to be detected; therefore, those that are detected are significant.

Mental imagery

A number of studies indicated that children with SLI were impaired on tests of mental imagery (Kamhi *et al.* 1988; Kamhi, 1981). The results of a study by

Johnston & Weismer (1983), however, suggested that the problems of children with SLI are not related to the mental manipulation of an image but to its generation, maintenance or interpretation. This study measured the response time during a same-different mental rotation task. The pairs of objects consisted of one form in an upright position and another rotated about its centre to an increasing number of degrees. The children with SLI had slower response times than age controls, but both groups showed increases in response times with increasing degrees of rotation. Even if the deficits are not due to mental manipulation of images, they remain the best example of a purely nonlinguistic deficit in SLI.

Auditory perception

During the 1960s, a number of studies documented perceptual deficits in auditory processing in children with SLI (Lowe & Campbell, 1965; Monsees, 1968; Stark, 1967; Weiner, 1969). The studies of Tallal and her colleagues have examined these deficits extensively and will be reviewed later in this thesis (see Chapter 5). Tallal and Piercy (1973a) reported that, compared to normal controls, children with SLI required considerably greater intervals between two short tones to correctly indicate their sequence or whether they were the same or different. When the duration of the tones was increased, however, the children with SLI were able to correctly indicate the sequence of tones even if the interval between them was very short (Tallal & Piercy, 1973b). Thus, it seemed that the overall duration of tone and interval was important. Studies with verbal stimuli revealed that children with SLI performed discrimination and sequencing of vowel sounds at the same level as controls, but were impaired at discrimination or sequencing of consonant-vowel pairs (Tallal & Piercy, 1974). This deficit was attributed to the presence of very brief formant transitions in these stimuli, which provide the distinguishing information. Crucially, these studies went on to show that lengthening the brief transitions in speech sounds improved their discrimination and detection in children with SLI (Tallal & Piercy, 1975; Frumkin & Rapin, 1980; Alexander & Frost, 1982).

Phonological working memory

Children with SLI show impairments on tests of phonological working memory, such as repeating nonwords and recalling lists of real words (Gathercole & Baddeley, 1990; Montgomery, 1995; Bishop, North & Donlan, 1996; but see van der Lely & Howard, 1993). Bishop, North & Donlan (1996) replicated the study of Gathercole and Baddeley in a much larger group of twins with SLI. They found that the deficit in phonological working memory persisted in children whose language

impairment had resolved and that there was significant heritability for this deficit in SLI. Bishop's findings, however, raise the possibility that the deficit on tests of phonological working memory may in fact be due to the poor articulatory ability of children with SLI. Gathercole & Baddeley (1990) reported no difference between the children with SLI and controls on tests of articulation. However, Bishop, North & Donlan, (1996) reported that the children with SLI had significantly greater difficulty, relative to controls, with the articulatory complexity of the nonwords to be repeated, even though the sample was selected for children with no obvious articulatory difficulty.

1.2.3 Theoretical perspectives

There are two main classes of theory that have been advanced to account for the deficits in children with SLI. These have arisen from the distinction between linguistic and nonlinguistic deficits reported in SLI populations.

The linguistic account

Most of the accounts that consider the core deficit in SLI as linguistic have focussed on morphosyntactic deficits and argued that the disorder is primarily an inability to construct a normal grammar (Gopnik & Crago, 1991; van der Lely, 1997; van der Lely & Stollwerck, 1996; van der Lely, 1994). These accounts typically adopt a modular framework (Fodor, 1983) derived largely from research with adult patients with focal brain injury and selective deficits in specific cognitive processes. In such a framework, a modular deficit is a selective impairment of one area of functioning that cannot be explained in terms of a more general loss of capacity. The use of a modular framework to study developmental disorders has led to a tendency to identify modularity with innateness, which, in turn, has led to the assumption that an impairment in an autonomous language process is due to a defect in the hard-wired module for handling that process. The alternative view is that modularity is an emergent property of a developing system, rather than a pre-existing constraint on development (see Karmiloff Smith, 1992).

The linguistic account, specifically the proposal that a hard-wired grammar module is impaired in DDSL, received a great deal of attention when Gopnik and colleagues first published their findings in the KE family (Gopnik, 1990a; Gopnik & Crago, 1991). These researchers suggested that the affected members of the KE family have a modular deficit in that they exhibited "feature blindness", that is the features of number, person and tense, and, therefore, inferred that syntactic rules were absent from the grammars of these individuals. Gopnik and Crago (1991)

reported that, without access to such rules, the affected members of the KE family compensated in one of two ways: they memorised inflected forms and stored these as separate lexical items, comparable with learning irregular forms of verbs, or they learnt explicit rules of grammar, such as “add an -s” for plurals, or “add -ed” for past tense. The implication of this latter mode of compensation is that the application of an explicit rule is more taxing than that of implicit rules, such that the affected family members add endings unreliably. These reports of the KE family, however, focussed on their linguistic deficits and ignored their nonlinguistic deficits, which were described in brief by Hurst *et al.* (1990) and further detailed by Vargha-Khadem *et al.* (1995). The presence of these nonlinguistic deficits, therefore, called into question the selectivity of the grammatical impairments.

Perhaps better support for the linguistic account is offered by the findings of van der Lely and colleagues (van der Lely, 1997; van der Lely & Stollwerck, 1996; van der Lely, 1994). These report linguistic deficits in a subgroup of the SLI population referred to as “grammatical SLI”. These children do not have articulation or phonological deficits such as those reported in the KE family (Hurst *et al.* 1990; Vargha Khadem *et al.* 1995; Alcock, 1995; Fee, 1995), yet they are impaired at production and comprehension of morphological and syntactic processes.

As previously mentioned, however, the findings of nonlinguistic deficits in populations with SLI that are selected for normal nonverbal intelligence cannot be ignored. The crucial question for the linguistic hypothesis, therefore, is whether the grammatical deficits can be caused by the non-linguistic problems or whether they merely co-occur.

The nonlinguistic account

The alternative explanation to the linguistic account is that the language difficulties in SLI are a manifestation of a more general impairment. Such an impairment could affect processes upon which language development is dependent, such as auditory perception or articulation or phonological working memory. Two of the currently popular theories concerning the underlying causes of the language impairment in SLI are described below.

Auditory perceptual deficit

A commonly held view of children with SLI is that their impairments arise from a perceptual deficit in auditory processing. The suggestion is that difficulty in processing rapid stimuli produces a detrimental effect on speech perception because many of the critical cues that distinguish phonemes occur in a very brief space of

time. This hypothesis has received support from the studies of Tallal and colleagues (Tallal & Piercy, 1973a; 1973b; 1974; 1975) and, more recently, from studies by Wright *et al.* (1997). Perhaps the best evidence for a relationship between auditory processing and language development comes from training programs that have been devised for treatment of children with SLI (Merzenich *et al.* 1996; Tallal *et al.* 1996). Tallal *et al.* (1996) presented a group of children with SLI with stories and other exercises in which the duration of speech was doubled and brief transitional elements were amplified. Another group of children with SLI were presented with the same stories and exercises but without the modifications to speech. After this treatment, the children who were exposed to the modified speech made dramatic gains on standardised tests of language comprehension, whereas those made by the control group of children were considerably smaller.

This hypothesis is not without controversy (see Studdert Kennedy & Mody, 1995; Mody, Studdert Kennedy & Brady, 1997). Many researchers remain unconvinced of the causal nature of the relationship and have argued that the deficit in auditory processing is milder and less consistently evident than the speech perception difficulties shown by children with SLI; such a deficit cannot, therefore, be considered primary. In addition, many aspects of language learning do not depend on the ability to process brief or rapidly changing auditory stimuli. Children could learn to speak by mimicry of the whole word pattern. Such learning, however, would lead to a disorganised lexicon, such that word recognition would be slower as vocabulary size increased. Also, there would be difficulty in the recognition of familiar units of a novel stimulus because of a lack of generalisation.

Phonological working memory or articulation deficit

As described above, Gathercole and Baddeley (1990) proposed that the deficit in SLI is due to an underlying deficit in phonological working memory. Such a deficit would explain the finding of below age-level lexical development in children with SLI, because the acquisition of new words depends upon the availability of a stable and distinct phonological representation. Gathercole and Baddeley (1993) further suggest that deficits in phonological working memory affect the development of receptive grammar, because comprehension of complex sentences requires a temporary phonological representation of the sentence. As in the case of the auditory processing deficit, such a proposal has not been without controversy. Van der Lely and Howard (1993) have argued that the deficit in phonological working memory may be a consequence, rather than a cause of the language deficit seen in children with SLI. However, Bishop North & Donlan, (1996) replicated the initial

findings of Gathercole & Baddeley (1990) and reported that the deficit on the nonword repetition test persisted in children whose language impairment had resolved, arguing against this deficit being a consequence of other language impairments. Bishop, North & Donlan, (1996) further reported that the impairment on the nonword repetition test could be due to poor articulation of nonwords (Bishop, North & Donlan, 1996) suggesting that deficits in phonological working memory may themselves be due to articulatory deficits. Even in cases where a spoken response is not required, such as sentence comprehension, poor subvocal articulatory rehearsal could result in an impairment. Impaired performance on a test of nonword repetition in the affected members of the KE family was reported by Vargha-Khadem *et al.* (1995) in association with deficits in oral praxis. As already described, however, children with “grammatical SLI” have no articulatory deficits (van der Lely, 1997).

1.3 The genetics of DDSL

Several lines of evidence suggest that there is a genetic aetiology to DDSL. A few families have been reported with unusually high concentrations of language impairment among their members (Arnold, 1961; Samples & Lane, 1985; Borges Osorio & Salzano, 1985; Hurst *et al.* 1990). Such studies have led to a number of pedigree analyses examining the incidence of language impairment in the relatives of probands. Also, twin studies have attempted to tease apart environmental and genetic contributions to language impairment by comparing concordance rates in monozygotic and dizygotic twin pairs. The three types of study are reviewed separately in this section. It is striking that, in all of these studies, the evidence for inheritance of language skills is particularly strong for phonological and articulation disorders.

1.3.1 Family Studies

Arnold (1961) described three extended families with high concentrations of language impaired individuals, illustrating the heritability of “manual preference, musicality, and innate language ability”. Family members were considered language impaired if they had expressive language deficits, reading difficulties, stuttering or cluttering of speech. These impairments were associated with poor musical ability.

Samples & Lane (1985) describe six siblings whose parents were first cousins. All children suffered to varying degrees from expressive language impairment with features of verbal dyspraxia. Severe articulation and phonological problems were documented in all six children. In addition, morphosyntactic errors were common.

As previously mentioned, a dramatic example of DDSL with a genetic aetiology is the KE family, first described by Hurst *et al.* (1990). The KE family is a large three-generation British family, half of whose members are affected by a severe impairment of speech and language, characterised by Hurst *et al.* (1990) as a verbal dyspraxia. Of the 15 affected members, nine are female and six male, suggesting that the disorder is not sex-linked, although without evidence of male-to-male transmission this could not be ruled out. Hurst *et al.* (1990) and Pembrey (1992) reported that the pattern of inheritance is likely to be due to a single gene which is autosomal dominant. A recent genetic linkage analysis, which identified a locus for this gene on the long arm of chromosome 7, confirmed that this disorder is autosomal dominant and likely to be monogenic (Fisher *et al.* 1998).

1.3.2 Pedigree studies

Several researchers have examined the incidence of language problems in the relatives of language-impaired probands (Luchsinger, 1970; Byrne, Willerman & Ashmore, 1974; Bishop & Edmundson, 1986). They report elevated rates of language impairment in families, with 24% to 63% of probands having a positive family history. These studies were hampered by a lack of comparison with matched control families. More recent reports that included control families, however, have confirmed the earlier findings (Neils & Aram, 1986; Tallal, Ross & Curtiss, 1989; Tomblin, 1989). Specifically, higher rates of impairment were reported among the first-degree relatives of language impaired probands, ranging from 17% to 43% across different populations and for different relatives. Several methods were used to assess the language status of parents and siblings, among them parental report, examination of clinical and school records, and questionnaires. Impairments were identified not just in expressive language (Neils & Aram, 1986; Tomblin, 1989), but also in language-related skills, such as academic performance (Tallal, Ross & Curtiss, 1989). Lewis (1992) computed familial concentration in a way that permitted the separation of language impairment from reading and other learning disorders. For a group of children with phonological language disorders she found that 15% of other family members had a history of expressive language impairments, 4% had a history of reading problems, 2% had expressive language and reading difficulties, and 3% had other types of learning difficulties. In contrast, in the family members of a control group of children, the incidence of combined expressive language and reading problems was almost zero, while that of expressive language deficits alone was 2%.

These rates of inheritance of language impairment are substantially lower than expected for autosomal dominant transmission such as that seen in the KE family (see previous section). One possibility is that there is an autosomal dominant form of developmental language disorder that represents only some of the cases identified in these family studies. Tallal, Ross & Curtiss, (1989) provide data to support this view. Using questionnaire reports, they found a bimodal distribution of language impairment in family members. Thus, most families reported either no family history or a positive family history that affected greater than 32% of family members. Families with low rates of impairment affecting between one and 32%, were very rare.

1.3.3 Twin studies

Although family studies and pedigree analyses of language impaired individuals provide compelling evidence for the inheritance of language impairment, such occurrences do not necessarily mean that the disorder has a genetic aetiology, because potentially causal environmental factors (e.g. a poor linguistic environment) are also shared by families. In order to tease apart the effects of environmental and genetic factors, comparisons have been made between groups of monozygotic and dizygotic twin pairs. Twins usually share the same environment, but monozygotic and dizygotic twins differ in the number of genes they share (100% vs. 50% respectively). By comparing concordance rates for language impairment in monozygotic and dizygotic twins, genetic influences can be determined.

A few twin studies have examined concordance rates in unselected populations of twins. Dixon, Matheny & Mohr (1995) reported high concordance rates on a test of articulation in a group of monozygotic twins, compared to a group of dizygotic twins and a group of nontwin siblings. Similarly, Locke & Mather, (1987) reported greater concordance for phonological and articulation skills in monozygotic than in dizygotic twin sets.

There have been a few twin studies of SLI; all report significantly higher concordance for the impairment in monozygotic compared to dizygotic twins (Bishop, North & Donlan, 1995; Lewis & Thompson, 1992; Tomblin and Buckwalter, 1994). Bishop, North & Donlan, (1995) reported that if the exclusionary criteria for diagnosing SLI were relaxed, then there was nearly 100% concordance for language impairment in monozygotic twins, and 50% in dizygotic twins.

1.4 The neurobiology of DDSL

The neural basis of language has fascinated researchers for most of this century. Acquired pathology of specific regions of the left hemisphere is known to cause disruption of language in adults who were previously competent users of language. In DDSL, however, there is often no obvious structural lesion. The evidence for a genetic aetiology for DDSL (see Section 1.3) implies that during neurogenesis brain abnormalities may have occurred affecting brain structure and function. The brain abnormalities are likely to be the result of aberrant neuronal migration, reflected in neuronal size and number. Such abnormalities may be detectable by analysis of brain morphometry. A few brain morphometric studies have been reported in cases with DDSL. Typically, these studies have used postmortem methods or analysis of *in vivo* structural magnetic resonance imaging (MRI). In contrast, there have been only a few functional imaging studies of DDSL, mainly because of ethical considerations arising from the use of radioisotopes as markers of cerebral blood flow. With the advent of functional MRI (fMRI), it is now possible to investigate the neuropathology underlying DDSL in children and in appropriately matched normal control groups. These studies are an exciting advance in the field as they allow both structural and functional imaging studies to be conducted longitudinally and during development. In contrast to single-case postmortem studies, larger samples can be investigated *in vivo* along with suitable control groups.

Brain morphometry studies in DDSL using post mortem methods and analysis of structural MRI are reviewed in this section, followed by functional imaging studies of populations with DDSL.

1.4.1 Post-mortem studies

Brain morphometry research was stimulated by the landmark study of Geschwind & Levitsky (1968), who provided evidence of a structural asymmetry that correlates with the well-established functional asymmetry of left hemisphere dominance for language. These researchers measured the length of the planum temporale in 100 normal brains at autopsy, and found it to be longer on the left in 65%, symmetrical in 25%, and shorter on the left in only 10% of the sample. This distribution correlates well with the distribution of hemispheric specialisation for language in the normal population. On the basis of these findings, Geschwind and Levitsky proposed that a macroscopic structural feature, namely planar asymmetry, could be used as an indicator of functional specialisation for language. This pattern

of planar asymmetry was later confirmed in adults, and documented also in human fetuses and neonates (Wada, Clarke & Hamm, 1975; Chi, Dooling & Gilles, 1977; Witelson & Pallie, 1973).

Elaborating on the significance of the planar asymmetry, Galaburda, Sanides & Geschwind (1978) showed that the gross asymmetry was associated with microscopic cytoarchitectonic differences between the hemispheres. Subsequent findings by Galaburda and colleagues (Galaburda *et al.* 1985; Humphreys, Kaufmann & Galaburda, 1990) of symmetric plana in the brains of individuals with dyslexia provided much of the motivation behind morphometric studies of developmental disorders. The symmetry in individuals with dyslexia resulted from enlargement of the right planum relative to that in normal brains, rather than a reduction of the left planum. Galaburda (1988; 1993) suggested that this enlargement reflects anomalous brain development during the later stages of corticogenesis, potentially leading to improved neuronal survival, and subsequent redefinition of cortical architecture. Postmortem studies of the brains of adults with developmental dyslexia also demonstrate the presence of heterotopias predominantly in the perisylvian regions of both hemispheres (Galaburda & Kemper, 1979; Galaburda *et al.* 1985).

There have also been post-mortem studies of DDSL other than dyslexia. Cohen, Campbell & Yaghai (1989) carried out a post-mortem analysis on the brain of a girl with language impairment who had died from unrelated causes. On gross examination the brain looked normal, but further examination revealed symmetric plana temporale and a single dysplastic microgyrus in the middle of the left insular cortex. Landau, Goldstein & Kleffner (1960) reported bilateral perisylvian pathology with surrounding cortical dysplasias, and retrograde degeneration of the medial geniculate nuclei, in a young boy with "congenital aphasia", who died of a complication related to congenital heart disease. The neuropathology described in this report is remarkably similar to that revealed by MRI in cases with bilateral operculum syndrome (Kuzniecky, Andermann & Guerrini, 1993). The bilateral operculum syndrome is a disorder associated with pseudobulbar palsy, cognitive impairment, and expressive language deficits; it shares these clinical features with the Foix-Chavany-Marie (Foix, Chavany & Marie, 1926) and Worster-Drought Syndromes (Worster-Drought, 1974). MRI typically reveals abnormal cortex in the operculum bilaterally, suggestive of polymicrogyria, which is almost certainly related to a defect in neuronal migration.

1.4.2 Structural MRI studies

The use of structural MRI in the analysis of brain morphometry has many advantages over the previous method. The relative ease of data acquisition and the availability of analysis software, however, could lead to important controls being overlooked. Many of the problems with analysis of brain morphometry through structural MRI are discussed later in this thesis (see Chapter 7). This section reviews studies in DDSL (including dyslexia), and discusses some of the difficulties in the interpretation of conflicting results.

Attempts to replicate the anatomical asymmetry findings of the post-mortem studies by analysing structural MR images obtained *in vivo* have been hampered by contradictory results, which have resulted from the use of different methods of data acquisition. This is particularly well illustrated by attempts to measure the plana temporale. In a study of individuals with dyslexia, Larsen *et al.* (1990) reported an absence of the usual planar asymmetry in concordance with the postmortem results. In contrast, Hynd *et al.* (1990) found that the left planum was smaller than the right in the brains of individuals with dyslexia (i.e. the reverse asymmetry to that seen in controls at postmortem). Another investigation reported the presence of the usual planar asymmetry in individuals with dyslexia, that is left planum larger than the right, but that this difference was exaggerated in dyslexic individuals compared to controls (Leonard *et al.* 1993). Schultz *et al.* (1994) found that differences in the size of left hemisphere structures and the symmetry of the plana temporale between dyslexic and control groups were not reliable after controlling for age and overall brain size. This latter finding clearly underlines the need to consider these potential sources of variation when interpreting differences in morphological brain measures between different groups of individuals, especially in paediatric populations.

As the conflicting results of these studies demonstrate, the plana temporale are particularly difficult to visualise and measure on MRI scans. This has led some researchers to avoid this problem by measuring large *en bloc* regions of brain. This approach has been used by Filipek and colleagues in a number of studies analysing the brain scans of different groups with developmental disorders (see Filipek *et al.* 1989; 1994; for further methodological details). Plante and colleagues, and Jernigan and colleagues, have also used an *en bloc* method to analyse structural MRI scans of children with SLI.

Plante, Swisher & Vance (1989) studied a pair of four-year-old dizygotic twins, one of whom was language-impaired. They found atypical perisylvian configuration, in the form of symmetry, in the language-impaired male twin. The

female twin, who was not language-impaired, however, showed a pattern of reverse asymmetry compared to controls. Plante *et al.* (1991) also found atypical perisylvian asymmetry in six out of eight four- to nine- year-old boys with SLI. The volume of the right perisylvian region was larger than normal in these boys, whereas the volume of the left was no different from normal. There were also differences between the children with SLI and controls in extratemporal regions, but none of these regions are associated with language function. Lastly, Plante (1991) found evidence of atypical perisylvian asymmetries in the parents and siblings of four male children with SLI. These abnormalities were associated with language disorder in some of these family members.

Jernigan *et al.* (1991) selected children who were diagnosed with SLI at age four. When assessed with MRI some four to five years later, some of these children had also developed more general learning disorders. Morphometric comparisons of MRI scans were carried out between this group and a group of age-matched controls. The children with language and learning impairments had significantly smaller volumes of grey matter in the right diencephalon and a region of cortex that included the left posterior perisylvian language areas. When the analyses were limited to right-handed individuals, the volumes of the caudate nuclei and posterior perisylvian language areas were also significantly reduced bilaterally in the children with language and learning impairments relative to those in controls.

In summary, previous morphometric studies using structural MRI in children with DDSL have yielded a number of largely inconsistent results, perhaps in part because several heterogeneous groups were investigated, and a number of different methods of morphometric analysis were used. Further investigation is clearly needed, but group composition and methodology must be considered carefully.

1.4.3 Functional imaging studies

Single photon emission computed tomography

Most functional neuroimaging studies of children with DDSL have used single photon emission computed tomography (SPECT) to reveal abnormal patterns of activation during language tasks. Comparisons have been made with clinical populations rather than with normal controls, because of ethical considerations concerning the use of radioisotopes in normally developing children.

Denays *et al.* (1989) found hypoperfusion in the left temporo-parietal region and in the middle and superior regions of the right frontal lobe in children with both receptive and expressive language impairment. Children with only expressive

deficits, however, were found to have a single area of hypoperfusion in the left inferior frontal gyrus. Another SPECT study (Lou, Henriksen & Bruhn, 1990) reported hypoperfusion in the left central perisylvian region compared to the right in children with a lexical-semantic deficit. Evidence of hypoperfusion was also found in left prefrontal regions compared to the right in children with a phonological-syntactic deficit. In this same study, children with pure attention-deficit hyperactivity disorder (ADHD), or ADHD and a phonological-syntactic deficit, showed hypoperfusion of the striatum. Using SPECT, Tzourio *et al.* (1994) studied children with language impairment during a phoneme discrimination task. These children failed to show activation in the left inferior parietal regions during the task, whereas a control group of children with ADHD did show activation of these regions. In addition, children with expressive-receptive language deficits failed to show increased activation in the left hemisphere.

Positron emission tomography

Another method of investigating functional abnormalities related to developmental disorders is the study of adults with a history of such disorders. In these individuals, the use of radioisotopes is permissible with their informed consent. Even so, there are very few studies of adults with a history of DDSL and none that have examined those with SLI. Paulesu *et al.* (1996) used positron emission tomography (PET) to examine adults who had been diagnosed with developmental dyslexia in childhood, but were able to read at adult literacy levels. During phonological processing, the adults with developmental dyslexia activated only a subset of the brain regions which were activated in controls. Control participants activated Broca's area, temporo-parietal areas, and insular cortex in concert during rhyming and verbal short-term memory tasks, but those with developmental dyslexia did not show activation of the insula and the other two areas were activated only independently.

Event-related potentials

Recording event-related potentials (ERPs), a totally non-invasive functional imaging technique, has also been used to study DDSL populations. This technique benefits from hi-fidelity temporal resolution but poor spatial resolution. Neville *et al.* (1993) measured ERPs in children with SLI and age-matched controls. They recorded ERPs to auditory detection of a one kHz tone in a stream of two kHz tones, and visual detection of a small white rectangle presented in a series of large red squares. They also recorded ERPs during a semantic judgement task. In this latter

task, written sentences were presented one word at a time, with a semantically appropriate or anomalous ending, (e.g. *Giraffes have long scissors*). During the auditory detection task, the ERPs of children with SLI did not differ from those of controls. When the group was divided according to auditory processing ability, however, a subgroup with poor auditory processing showed reduced amplitude of the ERP over anterior regions of the right hemisphere and delayed latency of a negative peak at 140 ms (N140). During the visual detection task, the group of children with SLI showed reduced amplitude for some early ERPs. During the semantic judgement task, the group of children with SLI showed an abnormally large negative peak at 400 ms (N400). This latter finding was examined further. Typically the N400 is larger over the anterior regions of the left hemisphere compared to the right. For a subgroup of children with SLI who had poor grammatical skills this asymmetry was not demonstrated.

Tomblin *et al.* (1995) compared the ERPs obtained in children with SLI and age-matched controls during an auditory task and found no differences between the two groups in terms of latency and amplitude of the responses. In this study, however, recordings were made over the left hemisphere only. Furthermore, the group with SLI was not divided into subgroups on the basis of performance on measures of language. Similarly, Courchesne *et al.* (1989) found no differences between a group of children with SLI and age-matched controls. Lincoln *et al.* (1995), however, reported that children with SLI failed to show an increase in amplitude of the negative peak at 100 ms (N100) when auditory intensity was increased, whereas normal children did show an increase.

Further investigation, using ERPs in association with other noninvasive functional imaging techniques, is needed to explain the relevance of these findings for language development.

1.5 Summary

Historically, DDSL have been known by a number of different labels. In an attempt to reduce heterogeneity among research populations, diagnostic criteria for children with SLI were established. Despite this improvement, there remain a number of controversies surrounding the use of these criteria.

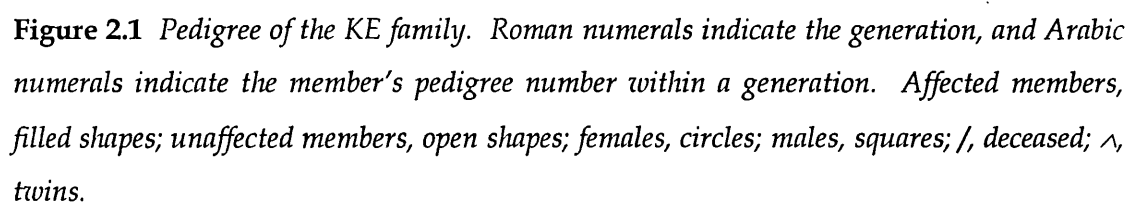
Linguistic deficits are predominantly seen in the areas of morphosyntax and phonology in SLI. The existence of nonlinguistic deficits in these populations, however, raises a problem for linguistic theories that address the nature of the impairment. The controversy lies in the question of whether linguistic and nonlinguistic deficits are causally related or co-occur.

There is strong evidence for a genetic aetiology for DDSL from family case studies, pedigree analyses and comparisons between twins. The absence of frank neurological deficits in association with DDSL suggests that genetic abnormalities result in subtle changes in brain function and structure. Neuroimaging techniques allow these changes to be detected *in vivo*, but the studies are scarce and those available often have produced conflicting results.

2. The KE family

This chapter describes the previous studies of the KE family, discussing the controversial debate surrounding the nature of the disorder in the affected family members. The impairments characterising the disorder are described in greater detail than before. Discussion of the disorder centres on the diagnostic criteria for, and subtypes of, SLI.

The pedigree of the KE family is shown in Figure 2.1. The classification for affected and unaffected status is based on the assessment of speech and language function in each member of the family. There is total agreement as to the affected versus unaffected status of the members among researchers, the family members themselves, and clinicians and teachers, who have known the family over a number of years. A genetic linkage study has mapped the disorder in the KE family to a small region on the long arm of chromosome 7 (Fisher *et al.* 1998). This analysis further corroborates the behavioural classification and can be used as an independent index of affected or unaffected status. The problems of heterogeneity that commonly affect the results of other studies of genetically based DDSL are not encountered in the study of the KE family because of the large size of the family, and the accuracy of the phenotypic classification. The KE family thus presents an opportunity to study a large number of individuals with a common genetic defect resulting in the same behavioural phenotype.



2.1 Previous studies of the KE family

2.1.1 Behavioural and cognitive studies

As mentioned in Section 1.3.1, the KE family was first reported in the scientific literature by Hurst *et al.* (1990). The affected members of the KE family were described in that report as suffering from a “severe form of developmental verbal apraxia”. Six representative case histories and a summary of the findings for four affected family members were provided. Articulation was reported to be defective; simple movements of the tongue and lips were unimpaired, but sequences of movements were impaired. The affected family members reduced consonant clusters, simplified sound structures, and reduced multisyllabic words to monosyllables or bisyllabic words. The histories of 16 family members revealed no feeding problems during infancy or any other neonatal complications. Hearing and intelligence were reported to be in the normal range, and there were no abnormal neurological signs (i.e. motor deficits) in the limbs. Hurst *et al.* (1990) summarised the main impairment of the affected family members as “organising and co-ordinating the high-speed movements necessary to produce intelligible speech”.

Subsequent reports by Gopnik and colleagues (Gopnik, 1990a; Gopnik & Crago, 1991) suggested that the affected members of the family suffered from a specific deficit in grammar. These reports focussed on the linguistic deficits of the affected family members rather than the nonlinguistic deficits, previously described by Hurst *et al.* (1990) and elaborated later by Vargha Khadem *et al.* (1995). Gopnik's more recent views (Gopnik & Goad, 1997) describe a reformulation of this theory. They suggest a deficit in implicit rule-learning forces the affected family members to learn verb forms as explicit lexical items. The suggestion that the utterances in which features were added result from the application of explicit rules was based on overt signs, namely hesitations or specific mention of the rule (such as “add an -ed”) by the affected individuals. Gopnik & Crago (1991) also observed that word endings were sometimes added that did not obey the phonological constraints of the language. For example, when producing the plural of the nonword “sas”, instead of adding -es, they lengthened the final /s/, conversely, they would erroneously add -es to words requiring -s, such as “zoop”.

Fee (1995) addressed the possibility that the affected members of the KE family fail to produce correct grammatical inflections because of a phonological deficit. She reported that affected family members had difficulties with consonants and clusters at the ends of syllables. Seven of the eight members tested showed

devoicing (e.g. /d/ pronounced as /t/) and consonant deletion, and all eight showed cluster reduction. All such errors occurred at the end of either a syllable or a word. It should also be noted that the data of two affected family members were excluded because they were unintelligible. These data could be interpreted as problematic for the linguistic account specifying a deficit in grammatical morphology, because the phonological deficits are so severe as to impede detection and analysis of morphemes, particularly when these occur at the ends of words. Fee, however, interpreted these findings as supporting the linguistic account proposed by Gopnik and colleagues. Rather than reflecting a deficit in morphosyntactic rules, she suggested an impairment in constructing learned, language-specific, phonological rules.

Vargha Khadem *et al.* (1995) reported wide-ranging deficits in the KE family, revealing the impairments of the affected members on virtually every test of language administered. In addition, they reported on nonlinguistic deficits in oral praxis and nonverbal cognition. Their report was consistent with that of Hurst *et al.* (1990) but provided a fuller description of the behavioural phenotype in this family. The claim of a specific deficit in one aspect of language, such as grammatical morphology, seemed unrealistic in view of the range of impairments seen on other tests of language, and on nonlinguistic tests. The causal nature of these deficits, however, remains to be determined.

The orofacial praxic deficits shown by affected family members were examined in detail by Alcock (1995). She found that the affected family members were impaired in the production of sets of parallel or sequential nonspeech oral movements, as were patients with aphasia acquired following left hemisphere injury. In addition, the affected family members had difficulty with *linguistic* intonation, but they were unimpaired in the production of *emotional* intonation. Production and perception of oral and manual rhythm were also impaired in the affected family members, and they had difficulty articulating words in recitations or songs.

2.1.2 Genetic studies

The initial reports by Hurst *et al.* (1990) and Pembrey (1992) state that the occurrence of the disorder in almost half of the KE family, affecting both sexes equally, suggests an autosomal dominant mode of transmission. In addition, the high concentration of a distinct disorder in one family suggests that it is unlikely that the genetic abnormality is polygenic or multifactorial.

Fisher *et al.* (1998) reported the results of a genome-wide search for linkage in the KE family, identifying a region on chromosome 7 that co-segregated with the disorder. These results confirmed autosomal dominant inheritance with full penetrance. Further analyses of microsatellites from within the region enabled fine mapping of the responsible locus to a 5.6 centimorgan interval in 7q31. This locus was designated SPCH1. Statistically, this mapping was highly significant and there were no recombinants in this region. Thus, the data for each affected family member mapped successfully to this locus. These data indicate that the disorder segregating in the KE family is likely to have resulted from the disruption of a single gene. The alternative possibility, however, that different components of the phenotype are the consequence of a contiguous microdeletion involving several genes in 7q31 cannot be ruled out.

2.2 Family history

Figure 2.1 shows three generations of the KE family. There are 37 family members, including seven spouses who married into the family, two of whom are deceased. The first generation consists of the grandmother (I-2) and her deceased husband (I-1) who is reported to have had no speech or language deficits. There are five children born to I-1 and I-2 shown in the second generation, only one of whom (II-10) is unaffected. The spouses of the three sisters and the affected brother (II-6) have no impairment in speech and language. In the third generation, five unaffected family members have children (not shown in Figure 2.1), none of whom have any difficulties with speech and language.

2.2.1 The first generation

The grandmother (I-2) is one of seven children, two of whom died in infancy. Of her four surviving siblings and her parents, none are reported to have had speech, language or learning difficulties. Similarly, all the children of her siblings are reported to be unaffected. The speech of I-2 is slow but intelligible and therefore, she is less impaired compared to her affected children and grandchildren. In her later life, she has developed a mild tremor of the hands.

2.2.2 The second and third generations

II-2 and family

A communicative woman with unusual but intelligible speech, II-2 loses clarity of speech, particularly when she is animated and speaks rapidly. Occasionally, after hesitancy, her speech is easier to comprehend for a few words, but then reverts to the unusual form. A good illustrator, II-2 has worked as an office cleaner, has run a support group for single-parent families, and has recently completed an adult-training course in business and information technology. She has nine children, four of whom are affected. All four affected children have very poor articulation and mostly unintelligible speech. They have adopted simplistic styles of speech in order to make themselves understood. The eldest of these children (III-1) had a reactive psychosis at age 21 and received in-patient psychiatric care. During this episode, he reported verbal auditory hallucinations. He has not been available for research studies since the onset of his psychosis. Only his premorbid data are reported here. Particularly unintelligible speech, which is also poorly modulated, is produced by III-5 and III-7; the latter also stutters. The youngest child in the family (III-9), is the second of dizygotic twins and is affected; her male twin is unaffected.

She has plagiocephaly and kyphoscoliosis, the latter due to fusion of the 5th to 10th thoracic vertebrae, which has been treated with surgery and a spinal brace. On entry to secondary education at age 12, III-9 was referred to a Child and Adolescent Psychiatry Service because of depression.

II-4 and family

The affected mother of this family (II-4) has refused to participate in this research programme. She has severe articulation problems and is sometimes mistakenly thought to be deaf because of her poor modulation of speech. She suffers from migraine but is otherwise well. She has five children; the three youngest are affected. Two of the affected children, both females, have severely defective speech, similar to that of their cousins (i.e. the affected children of II-2). Both achieved IQ scores in the exceptionally low range; it was thought that these scores underestimated their true ability, possibly because they both have low self-esteem and confidence. The youngest and only male child in this family (III-14), attends a school for children with autism. He has not been assessed by this research team. As a result, neither a confirmation of autism, nor a severity rating of his speech problems are available.

II-6 and family

The only affected male of the second generation (II-6) has persistent problems with speech, and his articulation is sufficiently poor for him not to be easily understood. In addition, his speech is hesitant and he stutters. As a child, he had a complex partial seizure in association with mumps, but at age 18 an electroencephalogram did not show an abnormality. At age 21, he had a psychiatric illness diagnosed as schizophrenia. In association with this illness, he had verbal auditory hallucinations and became physically aggressive. He has been on anti-psychotic medication on a long-term basis. With his first wife, II-6 had an unaffected son. Since her death, this child has been adopted by II-6's unaffected brother (II-10) and his family. From his second marriage, II-6 had three daughters, one of whom is affected. The speech of this child (III-17) is now considerably more intelligible than her similarly aged affected cousins, although she clearly has the disorder. She now attends a mainstream class with support, whereas in the past, like many of her affected cousins, she was in a special language unit.

II-9 and family

In an attempt to speak clearly, II-9 speaks slowly, although her speech is often slurred and poorly modulated. Following the birth of her third child, she suffered depression, which has recurred periodically and for which she has been treated with

anti-depressant medication. She is currently unemployed but has worked as an office cleaner. She reports her education as limited and her IQ scores are in the low range. She has four children, two unaffected daughters and two affected sons. The elder of these affected sons (III-20) is a bright young man who attempts to speak clearly, making use of strategies he has been taught through speech therapy. Even so, his articulation is poor and he is often difficult to understand. He has reasonably continuous employment as a chef and, although still living at home, he is quite independent. His younger brother (III-22) has difficulties with speech similar to those of the affected children of II-2. He can produce clear and well-articulated speech with considerable effort, but usually reverts to simplistic and deviant utterances, with poor modulation. Significant behavioural problems leading to exclusion from school have been documented in III-22. He currently attends a residential school for children with emotional and behavioural problems.

II-10 and family

The only unaffected member of the second generation (II-10) is reported to have had normal development, without any speech, language or learning difficulties. He is in good health. He has two children (one male and one female), who have no impairments of speech and language. II-10 has not participated in this research study.

2.2.3 Early development of affected family members

Developmental histories of affected family members reveal no remarkable neonatal or early developmental problems. As infants, none had significant feeding difficulties, and sucking, drinking, mastication, swallowing, coughing, and breathing are reported as normal. Emotional expression, such as smiling and crying, were also reported to be normal. Motor milestones were achieved within normal limits, but speech was markedly delayed; in some cases single words did not appear until three or four years of age. In a number of affected members, early language comprehension problems were reported, in addition to delayed speech. An extreme case is III-9, who was thought to be hearing-impaired as a young child because she showed no response to speech, but pure tone audiometry revealed normal hearing.

2.2.4 Unaffected family members

Some of the unaffected family members, particularly those in the third generation (e.g. III-2 and III-6), are also reported to have had mild delays in speech development, but their problems resolved by nursery-school age. All of the unaffected family members are in good health, and vary with respect to type and

success of employment. They continue to be very supportive of their affected siblings and parents. Family members socialise together regularly.

2.3 The KE family and SLI

The diagnostic criteria for SLI and its subtypes were described in the first chapter (see Section 1.1.2). In this section, they are discussed with reference to the affected members of the KE family.

2.3.1 Diagnostic criteria for SLI

Several affected family members do not satisfy diagnostic criteria for SLI because they have low nonverbal intelligence, or a psychiatric disorder, or a physical abnormality (see Table 2.1 for details).

Table 2.1 *Details of the affected family members*

| <i>ID</i> | <i>Age</i> | <i>PIQ</i> | <i>Psychiatric diagnosis</i> | <i>Neurological or physical abnormality</i> |
|-----------|------------|------------|---|---|
| I-2 | 75 | 95 | None | Slight hand tremor |
| II-2 | 39 | 89 | None | None |
| II-4 | n/a | n/a | n/k | n/k |
| II-6 | 41 | 83 | Schizophrenia | Seizure at age 12 |
| II-9 | 48 | 87 | Chronic depression | None |
| III-1 | 17 | 80 | Psychosis at age 21 | None |
| III-5 | 13 | 86 | None | None |
| III-7 | 10 | 81 | None | None |
| III-9 | 9 | 85 | Depression | Kyphoscoliosis; plagiocephaly |
| III-12 | 15 | 73 | None | None |
| III-13 | 13 | 71 | None | None |
| III-14 | n/a | n/a | Possibly autistic | n/k |
| III-17 | 13 | 82 | None | None |
| III-20 | 19 | 106 | None | None |
| III-22 | 15 | 64 | Emotionally and behaviourally disturbed | None |

ID, generation and pedigree number (see Figure 2.1); PIQ, performance IQ; n/a, not assessed, n/k, not known

Nonverbal intelligence

The diagnosis of SLI excludes cases with nonverbal intelligence more than one standard deviation below the mean (i.e. less than 85; see Section 1.1.3). Of the 13 affected family members assessed, seven have performance IQs (PIQs) below 85 (see Table 2.1). It is worth noting, however, that in at least three of these cases (III-12, III-13 and III-22, who had the most impaired scores), the scores did not reflect the full potential of the children, as judged by their teachers and the investigator who carried out the assessments.

Earlier, the adverse effects of language impairment on the development of nonverbal cognition were discussed. Children with SLI can show a decline in IQ over four or five years (e.g. Tallal *et al.* 1991). In the KE family, five affected family members have undergone repeated assessments of intelligence (see Table 2.2). These longitudinal data show a large drop in PIQ for three of the five children tested, consistent with the idea that a disorder of speech and language may adversely affect the development of intelligence or of the skills required to achieve 'normal' performance on intelligence tests, at later stages of development. The two cases who did not show a decline in PIQ (III-9 and -22) obtained low scores on the first test administration.

Table 2.2 *Results of longitudinal testing of PIQ*

| <i>ID</i> | <i>Age at test</i> <i>(years)</i> | <i>1st PIQ</i> | <i>Age at test</i> <i>(years)</i> | <i>2nd PIQ</i> | <i>Decline in</i> <i>PIQ (points)</i> |
|-----------|--------------------------------------|----------------|--------------------------------------|----------------|--|
| III-5 | 10.0 | 112 | 13.0 | 86 | 26 |
| III-7 | 7.3 | 91 | 10.4 | 81 | 10 |
| III-9 | 6.2 | 86 | 9.2 | 85 | 1 |
| III-17 | 5.8 | 111 | 13.0 | 82 | 29 |
| III-22 | 10.0 | 66 | 15.5 | 64 | 2 |

ID, generation and pedigree number (see Figure 2.1)

Hurst *et al.* (1990) reported average intelligence for six children based on their teachers' assessments and school records. Also, Pembrey (1992) reported that the mean PIQ for 13 family members was 95 (range 80 - 112). This latter report, however, mistakenly assumed that the 13 family members were all affected; in fact four were unaffected children from the family of II-2, but one of these four children was unclassified at the time of assessment. The recalculated mean PIQ for the nine

affected family members reported by Pembrey (1992), based on their first assessments, is actually only slightly lower at 93 (range 80 - 112). The mean PIQ for 13 affected family members reported in Table 2.1, based on either the only assessment available (eight affected members), or the most recent reassessment (five affected members, see Table 2.2), is 83 (range 64 - 106). The differences in the mean score reported by Pembrey (1992) and the current one, are due therefore, to the addition of data for four affected family members that were not previously reported, and to known age-related declines in intelligence in four of the affected family members (see Table 2.2).

The issue of excluding the affected family members from a diagnosis of SLI based on below average nonverbal intelligence is not a straightforward one, primarily because of possible developmental changes in nonverbal intelligence related to the presence of a speech and language disorder. Additionally, given that this disorder is likely to be due to a single gene, it would be inappropriate to say that those with below average nonverbal intelligence do not have SLI whereas those with average nonverbal intelligence do have it.

Psychiatric diagnoses

Diagnostic criteria for SLI also exclude individuals with a psychiatric diagnosis. Five affected family members have been diagnosed with a psychiatric disorder: two with depression; one with schizophrenia; one with a reactive psychosis; and another possibly with autism (see Table 2.1). In three of these, the onset of the disorder was in adulthood, and another was diagnosed with depression aged 12. A diagnosis of autism, which is usually made in childhood, excludes a child from a diagnosis of SLI because some of the social impairments associated with autism could explain the language impairment. Therefore, only the affected family member with the possible diagnosis of autism meets this exclusionary criterion for SLI, in the usual sense that this criterion is applied. Language impairment is commonly reported in association with schizophrenia, although a recent study suggests that at least syntactic deficits are a consequence of being in a psychotic state rather than a reflection of premorbid dysfunction (Done *et al.* 1998). Nevertheless, the co-occurrence of a high prevalence of psychiatric illness in the affected members of the KE family is intriguing.

Physical abnormalities.

Typically, criteria are employed excluding individuals with physical abnormalities from a diagnosis of SLI because such abnormalities could interfere

with production of speech, for example structural or functional oral abnormalities. Some of the affected family members have unusual oral structure. For example, their teeth are large and poorly placed, often requiring correction. This abnormality is not evident in every affected family member, however, and it is also present in a few of the unaffected family members. In the affected family members, the lower face, in particular the upper lip, is relatively immobile during speech, although occasionally extra twitches or grimaces are observed. The affected family members are able to produce simple movements of the oral apparatus (see Alcock, 1995), and therefore they would not be excluded from the diagnostic category of SLI on this basis. Complex sets of orofacial movements, however, are impaired in the affected family members (see Alcock, 1995; Vargha Khadem *et al.* 1998).

As mentioned above, II-6 had a seizure at age 12, in association with mumps. Many children have febrile seizures in association with infection. These are not usually considered as exclusionary criteria for SLI, in contrast with an ongoing convulsive disorder, which could interfere with language development. One affected family member (III-9) has a curvature of the spine (kyphoscoliosis), which is assumed to be unrelated to her speech and language difficulties.

2.3.2 Subtypes of SLI

The classifications within SLI (according to Rapin & Allen, 1989) were described in Chapter 1 (see Table 1.1). In terms of these classifications, the disorder shown by affected members of the KE family most closely resembles the phonological programming deficit subtype. This deficit is described as one of unintelligible speech with long utterances, reduction of phonological contrasts, and there may be an auditory processing problem. The family members produce unintelligible yet long utterances, but they do not have an obvious auditory processing deficit¹ and their production problems predominate. Other subtypes that resemble the disorder are verbal dyspraxia and phonological-syntactic deficit. Hurst *et al.* (1990) referred to the affected family members as suffering from a severe form of verbal dyspraxia. This diagnosis, however, was based on observations of their speech when the children were young. During development, their vocabularies have increased and their expressive language has improved beyond that typically seen in children with verbal dyspraxia, which usually is limited to a few short utterances. Despite the longer utterances in affected family members, however, the dyspraxic problems predominate throughout development, and into adulthood. Children with

a phonological-syntactic deficit speak in short utterances and commonly make errors due to omission of phonological contrasts, such that morphological suffixes are absent from their expressive language. Although the affected family members generally have longer utterances than children with a phonological-syntactic deficit, they do simplify speech such that phonological contrasts, and therefore, morphological suffixes are absent from their expressive language.

In conclusion, it appears that none of the classifications of Rapin and Allen accurately describe the disorder shown by the affected members of the KE family. At different times during development the disorder may have resembled one or the other of the subtypes described above. In adulthood, however, it has similarities with three subtypes, but cannot be accurately classed as one or the other.

¹ This was examined in further detail in the KE family and is reported later in this thesis.

2.4 Summary

Previous studies have attempted to describe the nature of the deficit in speech and language shared by the affected family members. The studies divide along the lines of the two different research groups who have independently assessed the KE family members. The studies of Gopnik and colleagues (Gopnik, 1990a; Gopnik & Crago, 1991; Fee, 1995) provide a linguistic account of the disorder. In contrast, Vargha-Khadem and colleagues (Vargha Khadem *et al.* 1995; 1998; Alcock, 1995) have described nonlinguistic deficits in addition to those seen on many tests of language.

Genetic linkage analyses have proven successful in identifying a locus segregating with the disorder seen in the KE family. They have confirmed that the disorder is due to a fully penetrant single locus with an autosomal dominant form of transmission, and suggest that this disorder is likely to result from the disruption of a single gene. Isolation of SPCH1 may offer the first insight into the molecular genetics of a developmental process that culminates in speech and language.

The ontogeny of the disorder in the affected family members is as follows. In infancy, the affected children may appear word-deaf, showing little if any interest in speech sounds. In childhood, utterances may be few and short, but with age and increasing vocabulary these become longer, although speech remains simplified with poor phonological contrasts. Abnormal phonology may be associated with apparent morphological and grammatical errors. In adulthood, speech remains deviant: mostly unintelligible and sometimes poorly modulated.

Not all the affected family members would meet strict diagnostic criteria for SLI because of low intelligence, or psychiatric illness, or physical impairments. In addition, although the disorder in the KE family shares several features of three of the subtypes of SLI described by Rapin & Allen (1989), it cannot accurately be classed as any one of them. The study of the disorder shared by the affected family members, which is of a definite genetic aetiology, may still be informative with respect to furthering understanding of the development of language. Similarly, studies of SLI populations will be relevant and informative in regards to the findings in the KE family. Hence, this literature will be drawn upon heavily throughout this thesis.

Part Two : Neuropsychological Studies

3. Behavioural and cognitive deficits in the KE family

The disorder of the affected members of the KE family was investigated using a number of linguistic and nonlinguistic tests. The aim was to establish the existence of a “core” deficit, or behavioural phenotype, that could explain the range of impairments characteristic of this disorder. The affected family members were compared with the unaffected ones and with a group of adult patients with aphasia resulting from a stroke. Discriminant function analyses revealed that one variable successfully discriminated the affected and unaffected family members. This variable was the score on a test of repetition of nonwords with complex articulation patterns. It is plausible that a deficit in articulation of speech sounds can lead to abnormal development of other verbal and, ultimately, nonverbal functions. The affected family members and the patients with aphasia had remarkably similar profiles of impairment on the tests administered, suggesting that the underlying brain pathology is similar in both groups. Premorbidly, the patients with aphasia had enjoyed a normal course of cognitive development and language experience. This benefit was reflected on a number of tests in which the patients with aphasia performed significantly better than the affected family members, and in some cases at normal levels. These findings further support the hypothesis that abnormal development of one aspect of language could lead to secondary impairments in other aspects of verbal and nonverbal development.

3.1 Introduction

The nature of the severe speech and language disorder in the affected members of the KE family has been a subject of considerable debate (see Chapter 2, Section 2.1.1). Gopnik and colleagues (Gopnik, 1990a; Gopnik & Crago, 1991; Gopnik & Goad, 1997) have focussed on the linguistic impairments of these individuals, in particular their deficit in the use of inflectional morphosyntactic rules (e.g. changing word endings to mark tense and number). This deficit is described as selective and has led some authors to the conclusion that the KE family provides evidence for the existence of grammar genes (e.g. Gazzaniga, 1992), thus lending further support to theories that postulate an innate Universal Grammar (Jackendoff, 1993). However, the first and subsequent reports of the KE family (Hurst *et al.* 1990; Vargha Khadem *et al.* 1995; Alcock, 1995) indicated that the disorder is not selective to inflectional morphosyntax but rather affects the processing and expression of phonology and syntax, as well as nonlinguistic oral praxis. In addition, affected family members have significantly lower nonverbal intelligence quotients (PIQs) compared to the unaffected family members. All of the studies agree that the affected family members are impaired on tests of morphosyntax, but the relationship between this impairment and the deficits in other language and cognitive domains is unclear. The crucial question is whether the full range of deficits merely co-occur or are causally related.

The disorder described in the KE family, whether selective or not, is developmental. It is manifested early in development in the first attempts at speech and persists throughout adulthood. Given that the disorder appears before cognition has fully developed, it is unlikely that other abilities would be unaffected, be they within the linguistic domain or extra to it. Longitudinal studies of children with SLI (Tallal *et al.* 1991) show decreases in PIQ over a period of four to five years. Also, repeated intelligence testing in a few of the affected children of the KE family revealed significant decreases in PIQ (see Chapter 2, Section 2.3.1). A low PIQ is not necessarily associated with low verbal abilities, however. For example children with William's syndrome (Bellugi *et al.* 1988) have below average PIQ in the presence of seemingly normal language abilities. Certainly, children at the lowest end of the normal distribution of intelligence do not show the type of disorder described in the KE family. This suggests that the presence of a language disorder during development might lead to subsequent restriction in the development of nonverbal cognitive skills. This issue, however, remains controversial.

A causal relationship between deficits within the linguistic domain is less controversial than that between language impairment and nonverbal cognition. It is likely that a specific linguistic deficit could result in restricted development of other linguistic skills. The question of a possible “core” deficit, which might explain the other linguistic deficits in the affected members of the KE family, needs to be addressed.

As with other developmental disorders (such as SLI, autism, Williams syndrome etc.), the disorder affecting the KE family is not associated with overt focal brain pathology. In fact, children with unilateral focal brain pathology, even when it affects the whole of the left hemisphere (Vargha Khadem *et al.* 1997; 1991; Vargha Khadem & Polkey, 1992) do not develop speech and language disorders of the type seen in SLI or in the KE family. This is presumably due to the reorganisational capacity of the immature brain, which can subserve normal development of speech and language functions providing the necessary neural substrate remains viable on one side. When speech and language functions fail to develop in the presence of a congenital or an acquired disorder, then it is strongly suspected that the responsible pathology is bilateral or diffuse. In such cases, the bilateral or diffuse pathology prevents reorganisation and compensatory processes. Support for this conclusion is provided by studies of children with bilateral pathology who do suffer severe restrictions in speech and language development (Landau, Goldstein & Kleffner, 1960; Vargha Khadem, Watters & O’Gorman, 1985). Such cases are rare, however, and because of the extensive brain pathology, they have restrictions in the development of other aspects of cognition that are not necessarily due to interactions with abnormal language development.

Patients with focal lesions of the left hemisphere acquired in adulthood suffer language disorders similar to those seen in SLI, although these are often more severe. These patients have enjoyed a normal developmental course with respect to both language and cognition and had normal use of language for many years prior to their brain insult. By comparing adult patients with aphasia and the affected members of the KE family, it is possible to examine the differential effects on cognition of a language disorder that is acquired after normal development and one that is present throughout development. It is likely that both developmental disorders and acquired disorders of language have advantages and disadvantages for cognition. The advantages of a developmental disorder over an acquired one are that there is maximal brain plasticity and capacity for reorganisation and compensation. However, if the developmental disorder language arises from

bilateral pathology, then the reorganisational capacity will be considerably reduced compared to cases with at least one intact hemisphere. In contrast, an acquired disorder could have advantages over a developmental one because of the premorbid period of normal development and normal use of language and other cognitive functions. It is likely that behaviours and strategies learnt during a period of normal development influence the recovery process after an acquired lesion.

In this chapter, the performance of the affected members of the KE family on a number of tests of language is compared to that of the unaffected family members and to a group of adult patients with aphasia resulting from left hemisphere stroke. The aim of the analyses is to establish whether the profiles of the affected family members and the aphasic patients differ significantly, thus specifically addressing the question of the differential effects of developmental versus acquired pathology of the speech and language system. In addition, the question is raised as to whether any of these impairments are of useful predictive value in establishing a behavioural phenotype and characterising a “core” deficit. If such a core deficit can be identified, its relationship to the other deficits needs to be explored and hopefully defined.

Some of the data on the KE family members have been previously reported (Vargha Khadem *et al.* 1995), but the data presented in this chapter are more complete both with respect to the comparison with the group of adult patients with aphasia and the type and extent of statistical analyses performed.

3.2 Methods

3.2.1 Participants

Thirteen affected and 12 unaffected members of the KE family were assessed (see Figure 2.1). The affected group consisted of the only surviving member of the first generation (I-2), three members of the second generation (II-2, II-5, and II-9) and nine members of the third generation (III-1, III-5, III-7, III-9, III-12, III-13, III-17, III-20, and III-22). The age range of the affected group was from nine to 75 years, with a mean of 25.3 years and a median of 15.5 years. The unaffected group consisted of 12 members of the third generation (III-2, III-3, III-4, III-6, III-8, III-10, III-11, III-16, III-18, III-19, III-21, III-23). The age range of this group was from nine to 27 years, with a mean of 17.1 years and a median of 16.5 years. Three unaffected family members (III-10, III-18, and III-23) had incomplete data sets; consequently their data are not included in some of the analyses described.

Eleven patients with aphasia resulting from left hemisphere stroke were also investigated in collaboration with Dr. Nina Dronkers and colleagues at the Veterans Administration Hospital, Martinez, California. Details of these patients are given in Table 3.1. Their ages ranged from 52 to 79 years, with a mean of 69.0 years and a median of 72.8 years. The time elapsed from stroke to test ranged from two to 13 years.

Table 3.1 *Details of the group of patients with acquired aphasia*

| <i>Patient ID</i> | <i>Sex</i> | <i>Age at test (years)</i> | <i>Previous occupation</i> | <i>Time since stroke (years)</i> | <i>Type of aphasia</i> | <i>Size of lesion (cm³)</i> | <i>Description of lesion</i> |
|-------------------|------------|----------------------------|-----------------------------|----------------------------------|-------------------------------------|--|---|
| APH1 | F | 52 | Employed in a travel agency | 10 | Conduction | 157.2 | DLPFC, sensorimotor and TL cortex, and subcortical g/m |
| APH2 | M | 62 | Sanitation engineer | 11 | Anomic; dysarthric | 85.2 | DLPFC, Ins. and some PL cortex, and subcortical g/m |
| APH3 | M | 72 | Insurer | 11 | Dysarthric; AOS | 102.6 | DLPFC, Ins., TL and PL cortex and subcortical g/m |
| APH4 | M | 79 | Professor of Chemistry | 13 | Anomic, dysarthric, AOS | 56.1 | DLPFC, Ins., some TL and PL cortex |
| APH5 | M | 54 | Maitre d' in large hotel | 9 | Broca's; dysarthric; AOS | 91.6 | Inferior FL, DLPFC, Ins. and TL cortex. |
| APH6 | M | 69 | Geologist | 11 | Anomic | 37.1 | Medial FL, anterior cingulate, inferior FL, DLPFC, and posterior PL cortex, capsular w/m and possibly putamen |
| APH7 | M | 68 | Flight attendant | 2 | Anomic; dysarthric; AOS | 25.3 | DLPFC and anterior Ins. |
| APH8 | M | 73 | Surveyor | 2 | Conduction; anomic; dysarthric; AOS | 39.8 | Ins., posterior TL and PL cortex |
| APH9 | M | 76 | Self-employed plumber | 9 | Anomic; dysarthric | 12.2 | Ins. cortex, underlying w/m extending to periventricular w/m and possibly subcortical g/m |
| APH10 | F | 75 | Computer specialist | 11 | Anomic; dysarthric; AOS | 26.2 | Ins. cortex and underlying w/m extending to periventricular w/m and possibly caudate nucleus |
| APH11 | M | 74 | Electronics technician | 3 | Conduction | 25.2 | Posterior TL and PL cortex and posterior periventricular w/m |

M, male; F, female; AOS, apraxia of speech; DLPFC, dorsolateral prefrontal cortex; TL, temporal (lobe); PL, parietal (lobe); FL, frontal (lobe); Ins., insular; g/m, grey matter; w/m, white matter.

3.2.2 Tests and Procedures

Intelligence tests

The Performance Scale of the age-appropriate Wechsler intelligence scale (WISC-III, Wechsler, Golombok & Rust, 1992; WAIS-R, Wechsler, 1986) was administered. This included the following subtests: Picture Completion, Picture Arrangement, Block Design, Object Assembly and Coding (Digit Symbol). Performance intelligence quotients (PIQ) and scaled scores for each subtest were calculated according to instructions in the test manuals.

Receptive language tests

Receptive vocabulary (Lexical decision)

Thirty words and 30 nonwords (selected from those used in the Word and Nonword Repetition test; Gathercole & Baddeley, 1989) were read to each participant in a fixed random order. Participants were asked to indicate whether each word was a real word or a nonsense word. Responses were recorded and scored as number correct out of 60.

Receptive grammar

The Test for Reception of Grammar (TROG; Bishop, 1982) was administered. Participants heard a sentence and were required to indicate which one of four pictures matched the sentence. The test consists of 80 sentences, presented in blocks of four, each block testing a different syntactic contrast. This test is used clinically to assess receptive grammar in children between four and 12 years. Blocks are failed if one of the four sentences in a block is incorrectly matched with a picture. Standard scores are obtained based on the number of blocks passed. In this study, the participants were older than the oldest age group for which normative data are available (i.e. 12 years). Therefore scores were calculated as number of correct sentences out of a total of 80. In addition, the scores for 16 sentences from blocks L, N, R and T, which specifically examine embedded relative clauses (see Table 3.2), were calculated.

Table 3.2 *Examples from the TROG assessing embedded relative clauses*

| <i>Block</i> | <i>Syntactic contrast assessed</i> | <i>Example of test sentence</i> |
|--------------|------------------------------------|--|
| L | reversible passive | the elephant is pushed by the boy |
| N | postmodified subject | the circle in the star is yellow |
| R | relative clause | the pencil is on the book that is yellow |
| T | embedded sentence | the cat the cow chases is black |

Expressive language tests

Word and nonword repetition

A list of 40 words and one of 40 nonwords (Gathercole & Baddeley, 1989) were read to each participant who was required to repeat each item. The words ranged from two to five syllables in length and the nonwords from one to four syllables. There were ten words and nonwords at each syllable length. Half of the words and nonwords contained only single consonants (e.g. *killer*, *rubid*), thus requiring simple articulatory output; the other half contained consonant clusters (e.g. *thimble*, *hampent*) requiring more complex articulation. During testing, each response was scored as either correct or incorrect and the scoring was later verified by reviewing the recorded audio- or videotape. Total scores out of 40 were obtained separately for the word and nonword versions of the test, along with scores out of five for either simple or complex articulation at each syllable length.

Naming

The Wingfield-Oldfield Object Naming test was administered (Oldfield & Wingfield, 1965). This test consists of 36 pictures that the participant has to name upon confrontation. The first clear response spoken was scored; response latencies were recorded using a stop watch. Each item was recorded as correct or incorrect out of a maximum score of 36. An average response latency was calculated for the items correctly named.

Verbal Fluency

Verbal oral fluency was assessed by asking each participant to generate words that either began with a specific letter (phonemic category) or belonged to a semantic category. The two letters were F and M and the two semantic categories

were fruit and animals. The number of words generated in two minutes was recorded, and separate average scores were calculated for phonemic and semantic fluency.

Written fluency was assessed by asking participants to write words beginning with the letter S. Participants were told not to be concerned about spelling, although this was checked after completion of the timed test. The number of words beginning with the letter S generated in five minutes was recorded. Different forms of the same word (e.g. swim, swims, swimming, swimmer) were only counted as one instance of the word.

Inflectional and derivational morphological production

Word and nonword versions of a test of morphological production were administered (Vargha Khadem *et al.* 1991). The participants were shown a picture while listening to a pair of sentences read by the examiner. Twenty pairs of sentences were used in each version. In the word version, the first sentence contained a word that could be modified to complete the second sentence, (e.g. "Look at how *small* these elephants are. This one over here must be the *smallest*"). In the nonword version, novel creatures were used in the pictures and nonwords were presented in the first sentence to be modified in completion of the second sentence, (e.g. "This creature is *snozzing*. We call him a *snozzzer*"). Modifications required the change or addition of a final morpheme, (e.g. *-est*, or *-er*, in the examples above). In each of the versions, ten words required a derivational morpheme (i.e. a morpheme that alters the meaning of the word, sometimes changing its grammatical class; e.g. "This boy has lots of *spots* [noun]. He is very *spotty* [adjective]") and ten required an inflectional morpheme (i.e. a morpheme that indicates change in tense or number; e.g. "This boy loves to *ski*. He says nothing is as much fun as *skiing*"). Scores out of 20 for each test were obtained along with scores out of ten for the derivational and inflectional changes separately.

Past tense production

A specific type of inflectional morphology was examined, namely, past tense production. Twenty sentence pairs (K. Patterson, personal communication) were read to each participant. The participant heard the first sentence of each pair, which was in the present (habitual) tense, and the start of the second sentence, which began "Yesterday ...". The participant was required to complete this sentence in the past tense using the verb that was presented in the first sentence. If necessary they were given an example before the test ("Every day I wash my hands. Yesterday I *washed*

my hands"). Ten of the sentences required construction of regular past tense (e.g. walk - walked) and ten required an irregular past tense form (e.g. teach - taught). Each response was scored as correct or incorrect to obtain a maximum score of 20 for the whole test and two scores out of ten for the regular and irregular verbs.

Nonword Reading and Spelling

Thirty monosyllabic pronounceable nonwords were presented one at a time, on cards for reading. Correct responses were scored out of 30.

Thirty monosyllabic nonwords were presented by the examiner one at a time for written spelling. These were scored as correct if the written form corresponded to the written form of the nonword that was used in the test or to a possible homophone, (e.g. reat or reet, are acceptable spellings of the same nonword).

Praxis

Limb

Limb praxis was assessed using a rating scale for fifteen simple movements of the arms. Movements were meaningful (e.g. combing hair), meaningless (e.g. making a circle in the air) or demonstrated the use of an object (e.g. a key). Each movement was rated on a scale from zero to three points: zero for no movement or an incorrect movement, one point for an attempt at the correct movement but poor execution, two points for a correct movement with minor problems in execution, and three points for a correct execution of the movement required. Therefore a maximum score of 45 was possible for this test.

Orofacial

Orofacial praxis was assessed using a rating scale for movements of the oral and facial musculature. Twenty-nine single movements and three sequences of movements were assessed. Items required meaningful noise production (e.g. the noise a dog makes; six items), meaningless noise production (e.g. clicking the tongue; five items), singing (e.g. sing *Happy Birthday*; four items), nonvocal movements (e.g. biting the bottom lip; ten items), eye movements (e.g. closing the left eye; four items) and sequences of three movements (e.g. blowing up the cheeks, then licking the lips, then smacking the lips). If the movement was not executed perfectly following the verbal command, then it was demonstrated by the examiner and the imitation of the movement was scored according to the rating scale from zero to three as described above. The maximum score possible for this test was 96.

3.2.3 Statistical analysis

Separate one-way analyses of variance (ANOVAs) were run for each test, comparing the scores of the three groups: affected family members, unaffected family members, and aphasic controls. Post-hoc comparisons were made using Tukey's honestly-significant-difference ranges test with a significance level of $p < 0.05$. Tests for homogeneity of variance were carried out and if there was a significant difference in the variance of the groups then nonparametric analyses were carried out. Some of the expressive language subtests were examined further using mixed between-within design multivariate ANOVA with within-subject factors, for example comparison of word and nonword versions of the same test. These analyses are described in further detail as appropriate. If an ANOVA included a factor with more than two conditions (e.g. number of syllables in Word Repetition had four possible conditions) these were examined separately using ANOVA and a correction made to the F-ratios. This correction involved calculation of the mean of the mean squares error term for the four conditions. The mean was then used as the new mean squares error term to calculate a new F-ratio and the significance for this new ratio was reported. Similarly, t-tests were corrected for multiple comparisons using the Bonferroni method.

Discriminant function analyses (DFA) were run to determine which variables, or combination of variables, best discriminated the affected family members from the unaffected family members and from the aphasic controls. Variables were selected for the DFA based on the results of the ANOVAs. Only those variables which showed significant group differences between the two groups being analysed were entered into the DFA. Stepwise DFA was used allowing statistical criteria alone to determine the order of entry of variables into the analysis.

3.3 Results

3.3.1 Analyses of variance

Intelligence tests

There was a significant difference in the PIQs of the three groups ($F(2,33)=6.95$, $p=0.003$). Post-hoc ranges tests revealed that the affected group had significantly lower PIQ (mean = 83.2, SD = 10.6, range = 64 - 106) than the unaffected (mean = 98.3, SD = 14.6, range = 73 - 119) and aphasic (mean = 105.7, SD = 19.7, range = 75 - 139) groups, which did not differ from each other. Thus, the affected group, who differ from the aphasic group in that their language disorder is developmental, have significantly reduced nonverbal intelligence. The aphasic group, who have a language disorder acquired after normal cognitive development, are not significantly different from the unaffected group, who have normal language and also had normal cognitive development.

There were significant differences among the three groups for three of the subtests of the performance scale: Picture Completion ($F(2,33)=5.19$, $p=0.011$); Picture Arrangement ($F(2,22)=7.14$, $p=0.004$); and Coding ($F(2,29)=13.63$, $p<0.001$). Post-hoc ranges tests revealed that, for the Picture Completion subtest, the aphasic group had significantly higher scores than the affected group; for the Picture Arrangement subtest, the aphasic group had significantly higher scores than both the affected and the unaffected groups; and for the Coding subtest, the unaffected group had significantly higher scores than both the affected and the aphasic groups (see Figure 3.1). In sum, the affected group have lower scores than the other two groups for all five subtests, but the only significant impairment relative to the unaffected group was on the Coding subtest. This may be due to a grapho-motor deficit or poor visual memory. The aphasic group were also significantly impaired relative to the unaffected group on the Coding subtest. This might have been expected because some patients have little or no use of the dominant hand as a result of their stroke.

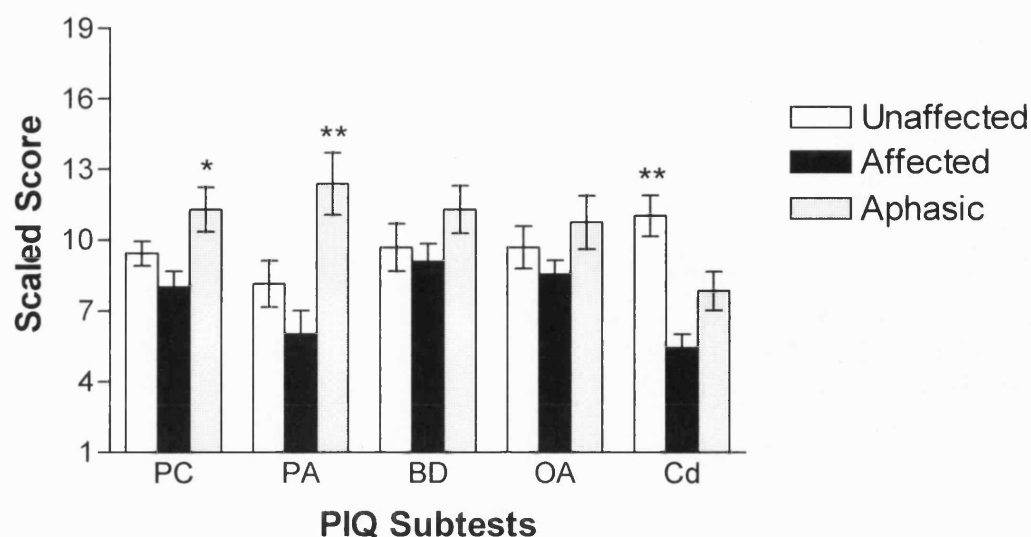


Figure 3.1 Performance subtests of the Wechsler scales. Bars, group means; error bars, standard error of the mean; PC, Picture Completion; PA, Picture Arrangement; BD, Block Design; OA, Object Assembly; Cd, Coding; * significant difference compared to the affected group; ** significant difference compared to the other two groups.

Receptive language tests

Receptive vocabulary (lexical decision)

One-way ANOVA revealed a significant difference among the three groups for the scores on the Lexical Decision test ($F(2,31)=10.64$, $p<0.001$). Post-hoc tests showed that this was due to significantly lower scores for the group of affected family members compared to the other two groups, which did not differ from each other (see Table 3.3 for the group means). Thus, the affected group have restricted lexical knowledge as a result of their developmental disorder, whereas the aphasic group, who had acquired their lexical knowledge prior to their stroke, are unimpaired on this test.

Receptive grammar

A test for homogeneity of variance revealed significant differences among the three groups for their scores on the TROG. Nonparametric tests were therefore carried out. The unaffected group had significantly higher scores than the affected group ($Z=2.26$, $p=0.024$) and the aphasic group ($Z=3.18$, $p=0.002$). A significant difference was revealed among the scores of the items of the TROG that assess embedded relative clauses (i.e. blocks L, N, R and T; $F(2,29)=6.59$, $p=0.004$). Post-hoc

ranges tests revealed that the unaffected group had significantly higher scores than the other two groups, which did not differ from each other (see Table 3.3 for the group means). Thus, both the affected and aphasic groups are impaired at receptive grammar despite the fact that their disorders are predominantly due to expressive language impairment. The receptive impairment is not just related to morphosyntax but to syntax at the word order level also.

Table 3.3 *Receptive language tests: group means and standard deviations*

| Test [/max.] | Mean (SD) | | |
|------------------------|---------------|---------------|--------------|
| | Unaffected | Affected | Aphasic |
| Lexical decision [/60] | 55.27 (4.13) | *46.75 (6.65) | 54.64 (3.29) |
| TROG [/80] | +75.90 (3.57) | 71.09 (4.57) | 64.72 (9.02) |
| TROG blocks LNRT [/16] | +13.00 (2.49) | 9.36 (2.69) | 9.82 (2.23) |

*Significantly lower score than the other two groups; +significantly higher score than the other two groups.

Expressive language tests

Word and nonword repetition

One of the patients with acquired aphasia (APH8 in Table 3.1) was unable to repeat words of more than one syllable and found this test distressing. Therefore he did not participate in these tests and no data were analysed for this participant. Also, one of the unaffected family members (III-3 in Figure 2.1) did not complete the Word Repetition test. Hence, only the Nonword Repetition data are reported in his case. The data from the Word and Nonword Repetition tests were analysed separately and then compared directly using mixed between-within design ANOVAs.

(i) Word Repetition

For the analyses of the Word Repetition test there were two within-subject factors, the number of syllables (four levels: two to five) and articulation difficulty (two levels: simple and complex), and the between-subject factor of group (three groups: affected, unaffected and aphasic). There were significant main effects of group ($F(2,30)=25.82$, $p<0.001$), number of syllables ($F(3,90)=29.85$, $p<0.001$) and articulation difficulty ($F(1,30)=24.55$, $p<0.001$). There was also a significant interaction between group and number of syllables ($F(6,90)=4.90$, $p<0.001$), but not

between group and articulation difficulty, nor between number of syllables and articulation difficulty. The three-way interaction was not significant.

The main effects were examined using simple planned contrasts. The main effect of group was due to significantly higher scores of the unaffected group compared to both the affected group ($t=7.18$, $p<0.001$) and the aphasic group ($t=3.64$, $p=0.001$). The aphasic group, in turn, had significantly higher scores than the affected group ($t=3.31$, $p=0.002$). The other main effects were as expected, namely scores decreased as syllable length increased and words containing simple articulation patterns were repeated more accurately than those with complex articulation patterns.

The significant interaction between group and syllable length was examined by separate ANOVAs at each syllable length. In these analyses the main effect of group was significant at all syllable lengths. Simple planned contrasts showed that the unaffected group had significantly higher scores than the affected group at all syllable lengths. Compared to the aphasic group, the unaffected group had significantly higher scores at syllable lengths of three and four and the affected group had significantly lower scores at syllable lengths of three and five (see Figure 3.2 a. and b.).

In summary, the affected family members were impaired at repetition of words of both simple and complex articulation relative to the unaffected and the aphasic groups. Also, the effect of increased syllable length was significantly more pronounced in the affected group relative to the other two groups. The aphasic group were also impaired at word repetition compared to the unaffected group and the effect of increased syllable length was more significant in the aphasic group compared to the unaffected group.

(ii) Nonword Repetition.

The analyses of the Nonword Repetition test were the same as those for word repetition except that the four levels of the within-subject factor of number of syllables were from one to four syllables rather than from two to five as in the previous analysis. There were significant main effects of group ($F(2,31)=35.08$, $p<0.001$), number of syllables ($F(3,93)=67.52$, $p<0.001$) and articulation difficulty ($F(1,31)=57.20$, $p<0.001$). There were also significant interactions between group and number of syllables ($F(6,93)=4.46$, $p=0.001$), between group and articulation difficulty ($F(2,31)=8.97$, $p=0.001$), and between number of syllables and articulation difficulty ($F(3,93)=8.04$, $p<0.001$). The three-way interaction was not significant.

The main effects were examined using simple planned contrasts. These revealed that the significant main effect of group was due to higher scores for the unaffected group compared to the affected ($t=7.62$, $p<0.001$) and aphasic ($t=6.87$, $p<0.001$) groups, whose scores were not significantly different. The significant main effects of number of syllables and articulation difficulty were the same as those for the analysis of word repetition.

The significant interaction between group and syllable length and that between articulation difficulty and syllable length were examined by separate ANOVAs at each syllable length. In these analyses, the main effect of group was significant at all syllable lengths. Simple planned contrasts revealed that the unaffected group had significantly higher scores than the affected and aphasic groups at all syllable lengths, but that the affected and aphasic groups were not significantly different from each other. The main effect of articulation difficulty was also significant at each syllable length, but the difference between the scores for simple and complex articulation was considerably less significant at one-syllable length compared to all other syllable lengths.

The significant interaction between group and articulation was examined by separate ANOVAs for nonwords of simple and complex articulation. In these analyses, the main effects of group were significant for both simple and complex articulation. Simple planned contrasts showed that the unaffected group had significantly higher scores than the other two groups for nonwords with simple and with complex articulation, but these group differences were less significant for simple articulation than for complex articulation. The affected and aphasic groups were not significantly different from each other (see Figure 3.2 c. and d.).

In summary, the affected and aphasic groups were significantly and equally impaired in repetition of nonwords relative to the unaffected group. These effects were significantly more pronounced for nonwords requiring complex articulation compared to those requiring simple articulation. Similarly, these group effects increased in significance with increasing syllable length.

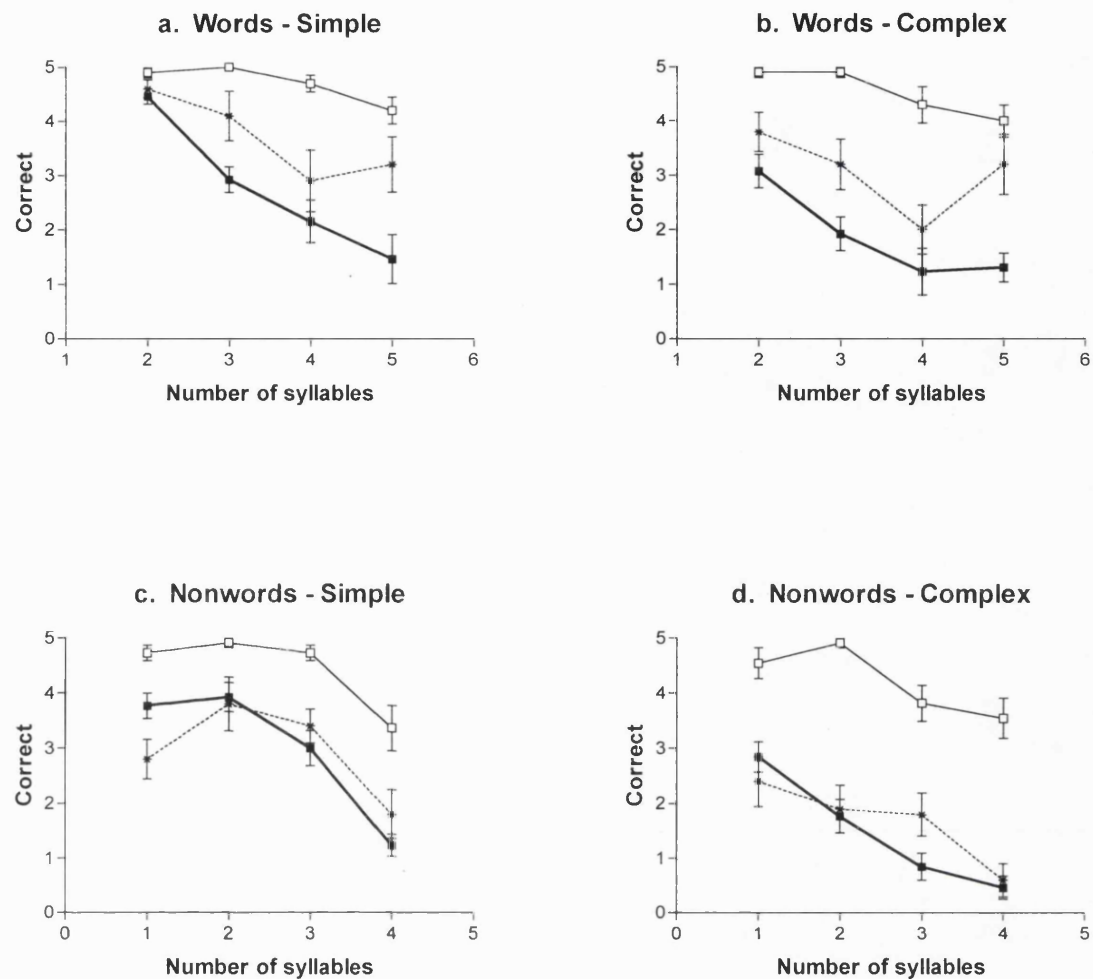


Figure 3.2 Word (a. and b.) and Nonword (c. and d.) Repetition tests for items with simple (a. and c.) and complex (b. and d.) articulation patterns by syllable length. Filled squares and thick lines, affected group; unfilled squares and thin lines, unaffected group; stars and dotted lines, aphasic group; error bars, standard error of the mean.

(iii) Comparing Word and Nonword Repetition.

In order to directly compare the Word and Nonword Repetition tests, another ANOVA was performed. This analysis had two within-subject factors of lexicality (two levels: words and nonwords) and articulation difficulty (two levels: simple and complex), and one between-subject factor of group (three groups: affected, unaffected and aphasic). There was a significant main effect of group ($F(2,30)=33.44$, $p<0.001$). The main effect of lexicality was also significant ($F(2,30)=18.99$, $p<0.001$) and was involved in a significant interaction with group ($F(2,30)=6.97$, $p=0.003$). Similarly, the main effect of articulation was significant ($F(1,30)=52.95$, $p<0.001$) and interacted with group ($F(1,30)=10.66$, $p=0.003$). The three-way interaction was not significant.

The main effect of group was examined using simple planned contrasts. These revealed significantly higher scores for the unaffected group compared to the affected and aphasic groups. The aphasic group also had significantly higher scores than the affected group. The other two main effects were due to significantly higher scores for words compared to nonwords and for both words and nonwords with simple articulation compared to those with complex articulation.

The significant interaction between group and lexicality was examined by separate ANOVAs for words and nonwords. There was a significant effect of group for both words and nonwords and planned comparisons revealed that the unaffected group had significantly higher scores than the affected group and the aphasic controls. The aphasic controls also had significantly higher scores for words than the affected family members, but for nonwords the two groups were not significantly different (see Figure 3.3 and Figure 3.4).

The significant interaction between articulation and group was examined using separate ANOVAs for simple and complex articulation in words and nonwords together. There was a significant effect of group for both simple and complex articulation. Simple planned contrasts revealed that the unaffected group had significantly higher scores than the affected group and the aphasic controls for both simple and complex articulation, but the effect was more pronounced for complex articulation.

In summary, direct comparison of word and nonword repetition revealed that the affected group were significantly impaired relative to the unaffected group and aphasic group, and that the aphasic group was impaired, in turn, relative to the unaffected group. The significance of the impairment of the affected and aphasic groups relative to the unaffected group was more pronounced for repetition of words and nonwords with complex articulation than for those with simple articulation. Also, the aphasic group showed significantly better repetition of words than nonwords, whereas the affected group was equally impaired at both. Thus, the complexity of articulation was significantly more problematic for the affected and aphasic groups relative to the unaffected group. The aphasic group, however, were able to benefit from familiarity with the articulation patterns of words, and repeated words significantly more accurately than the unfamiliar articulation patterns of the nonwords. This is presumably because, premorbidly, the aphasic patients had learnt and used the articulation patterns of the words in the word repetition test.

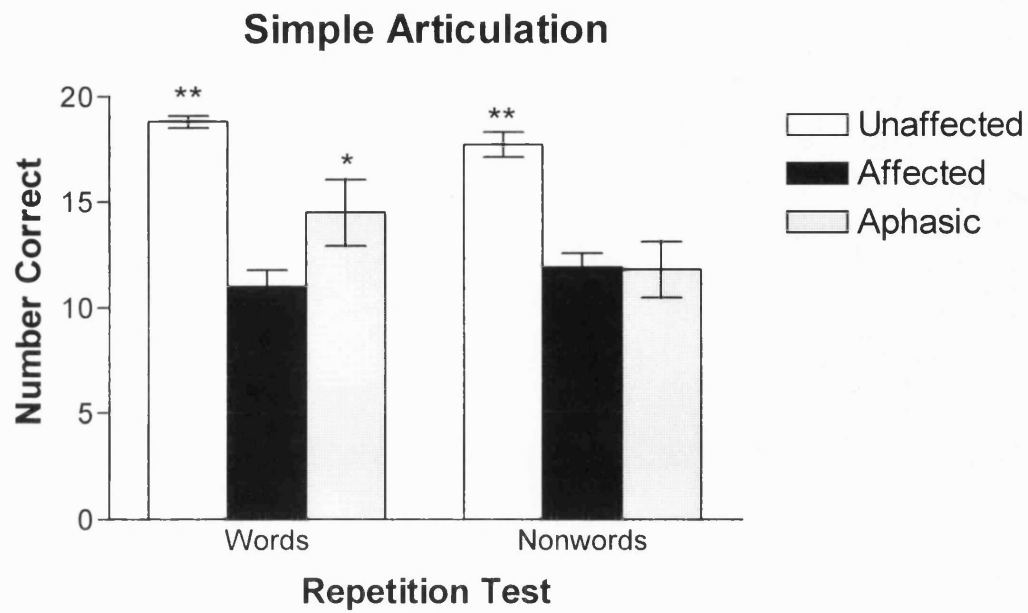


Figure 3.3 Simple Word and Nonword Repetition. Bars, group means; error bars, standard error of the mean; ** significantly greater than both affected and aphasic groups; * significantly greater than affected group only.

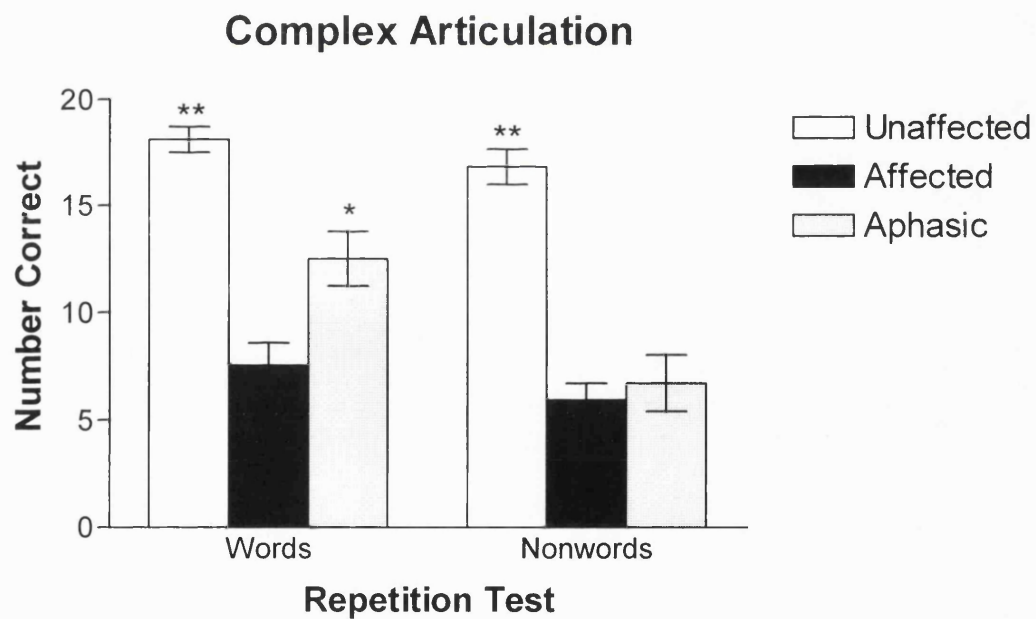


Figure 3.4 Complex Word and Nonword Repetition. Bars, group means; error bars, standard error of the mean; ** significantly greater than both affected and aphasic groups; * significantly greater than affected group only.

Naming

The test for homogeneity of variance revealed significant differences among the three groups for the number of items correctly named on the Wingfield-Oldfield Object Naming test and for the response latencies; therefore nonparametric tests were carried out. The unaffected group had significantly higher accuracy scores on the naming test than the affected group ($Z=2.26$, $p=0.024$) and the aphasic group ($Z=2.41$, $p=0.016$), whose scores did not significantly differ from each other. The unaffected group had significantly shorter response latencies than the aphasic group ($Z=2.39$, $p=0.017$), but the affected group did not differ significantly from either of the other two groups (see Table 3.4 for the group means). In summary, the affected and aphasic groups were both impaired at naming to confrontation, but were not significantly different from each other. However, the aphasic group alone was impaired at the time taken to produce a response.

Table 3.4 Object Naming test: group means and standard deviations.

| | | | Mean (SD) | | |
|-----------------------|---------|--------------|---------------|--------------|--------------|
| Test [/max.] | | | Unaffected | Affected | Aphasic |
| Naming Accuracy (/36) | | | *30.50 (2.07) | 26.23 (4.21) | 24.18 (6.35) |
| Response | Latency | (in seconds) | +1.14 (0.25) | 1.49 (0.42) | 1.86 (0.74) |

*significantly higher score than the other two groups; +significantly less than the aphasic group only.

Verbal fluency

The verbal oral fluency data were analysed using a mixed between-within design ANOVA with the within-subject factor of fluency type (two types: phonemic and semantic category) and a between-subject factor of group (three groups: affected and unaffected family members and aphasic controls). There was a significant main effect of group ($F(2,29)=32.86$, $p<0.001$) but the effect of fluency type was not significant nor was the interaction between group and fluency type. Simple planned contrasts revealed that the aphasic group had significantly lower scores compared to both the affected ($t=4.53$, $p<0.001$) and the unaffected ($t=8.08$, $p<0.001$) groups; the affected group also had significantly lower scores compared to the unaffected group ($t=3.94$, $p<0.001$; see Figure 3.5).

Since five of the aphasic participants were unable to write, the test of written fluency was not administered to them. A one-way ANOVA revealed a significant group difference ($F(2,25)=19.81$, $p<0.001$), which post-hoc tests showed to be due to significantly lower scores of the aphasic group compared to the affected and unaffected groups and of the affected compared to the unaffected group (see Figure 3.5). Thus, the affected group were impaired at generating lexical items under semantic and phonemic (both oral and written) conditions, but the aphasic group was even further impaired on the same tests.

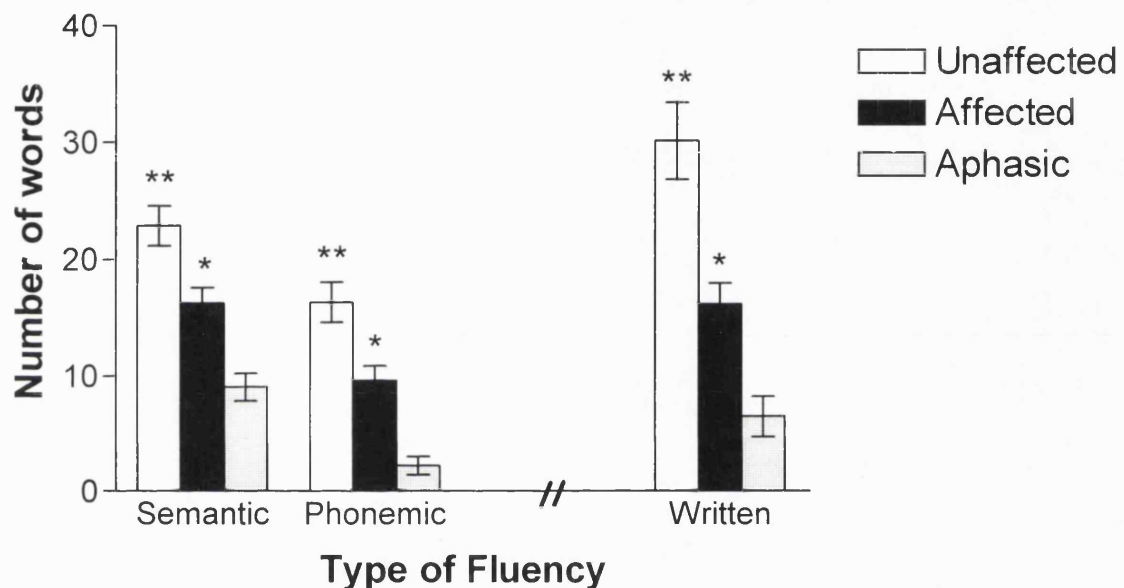


Figure 3.5 Verbal fluency tests. Bars, group means; error bars, standard error of the mean; *significantly greater than aphasic group; **significantly greater than both affected and aphasic groups. Note: The time limit was two minutes for the semantic and phonemic fluency conditions and five minutes for written fluency.

Inflectional and derivational morphology

Two aphasic patients (APH2 and APH6 in Table 3.1) were unable to attempt the nonword version of this test. Therefore their data were not included in the analysis below. The data for the word and nonword versions of morphological production were analysed using a mixed between-within design ANOVA, with two within-subject factors, lexicality (two levels: words and nonwords), and type of morphology (two types: inflectional and derivational) and one between-subject factor of group (three groups: affected and unaffected family members and aphasic controls). There were significant main effects of group ($F(2,30)=36.68$, $p<0.001$),

lexicality ($F(1,30)=231.20$, $p<0.001$) and type of morphology ($F(1,30)=7.63$, $p=0.010$). There was also a significant interaction between group and lexicality ($F(2,30)=9.15$, $p=0.001$).

Simple planned contrasts revealed that the main effect of group was due to significantly higher scores for the unaffected group compared to both the affected ($t=8.10$, $p<0.001$) and aphasic ($t=6.42$, $p<0.001$), who did not differ significantly from each other. The main effect of type of morphology was due to higher scores for inflectional morphology than for derivational. Similarly the word version of the test was significantly easier than the nonword version, which reflects the main effect of lexicality.

The interaction between group and lexicality was examined by separate analyses for the word and nonword versions of the test. For both versions, the main effect of group was significant (words: $F(2,30)=16.30$, $p<0.001$; nonwords: $F(2,30)=38.63$, $p<0.001$), but a stronger effect of group was seen for the nonwords. Simple planned contrasts demonstrated the same significant group differences as in the main analyses, that is the unaffected group had significantly higher scores than either the affected or the aphasic group, who did not differ significantly.

Thus, the affected and aphasic groups were significantly and equally impaired, relative to the unaffected group, in producing inflectional and derivational morphology for both words and nonwords. The effects were significantly more pronounced for the nonword version of the test.

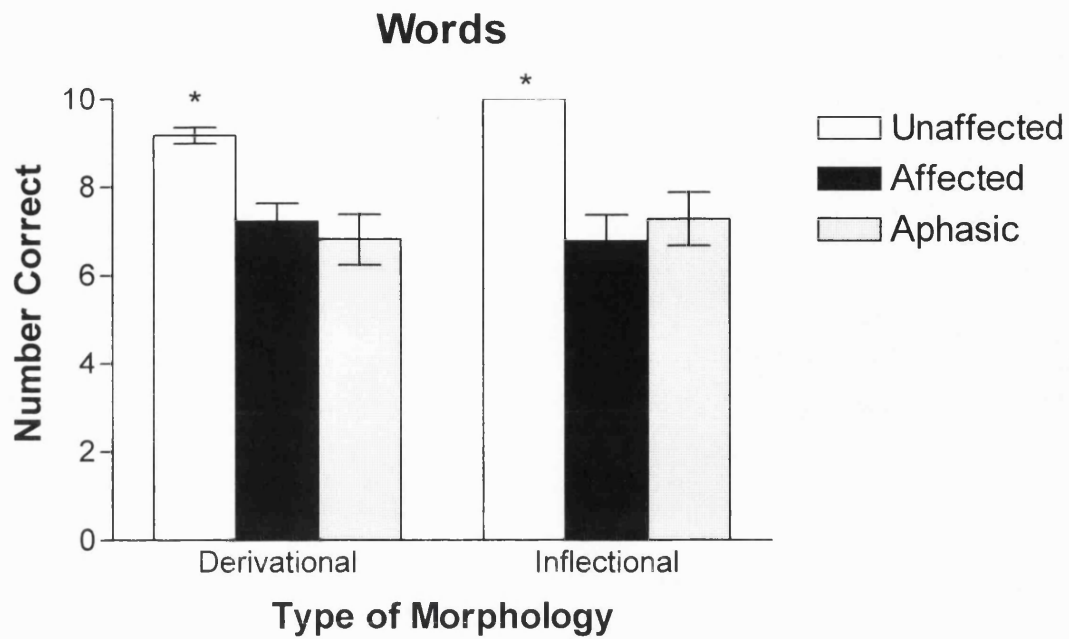


Figure 3.6 Production of derivational and inflectional morphology for words. Bars, group means; error bars, standard error of the mean; * significantly greater than affected and aphasic groups.

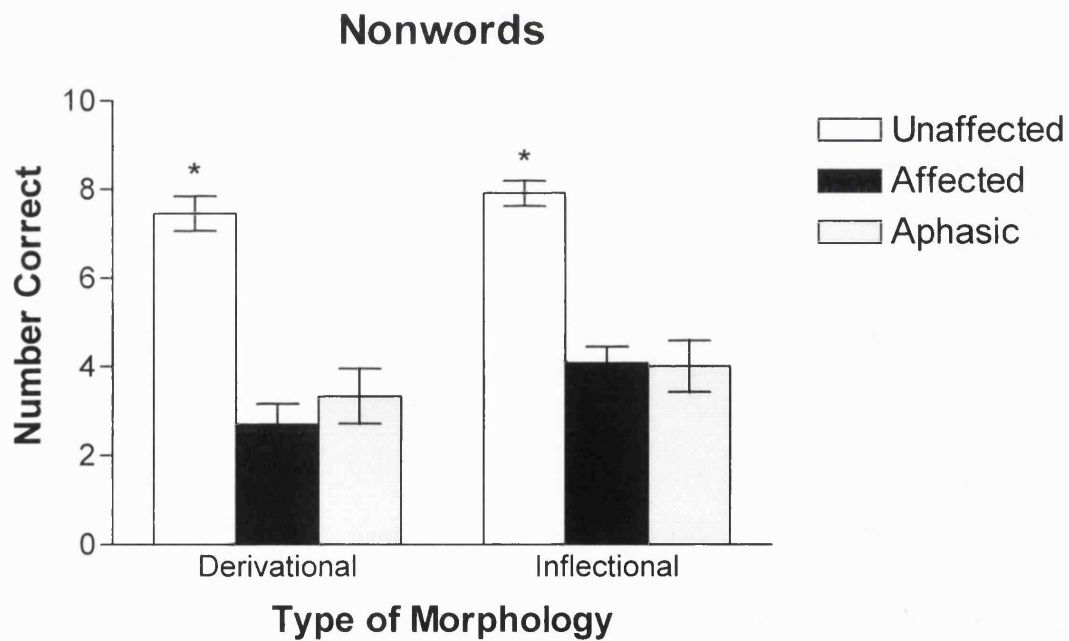


Figure 3.7 Production of derivational and inflectional morphology for nonwords. See legend to Figure 3.6.

Past Tense Production

The data for the Past Tense Production test were analysed using a mixed between-within design ANOVA with a within-subject factors of verb type (two types: regular and irregular) and a between-subject factor of group (three groups: affected, unaffected and aphasic). There was a significant main effect of group ($F(2,31)=8.75$, $p=0.001$), but not of verb type, and the interaction was not significant. Simple planned contrasts revealed significantly higher scores for the unaffected group compared to both the affected ($t=3.62$, $p=0.001$) and the aphasic ($t=3.64$, $p<0.001$) groups. The scores for the affected and aphasic groups were not significantly different. Thus, the affected and aphasic groups were significantly impaired at past tense production for both regular and irregular verbs relative to the unaffected group

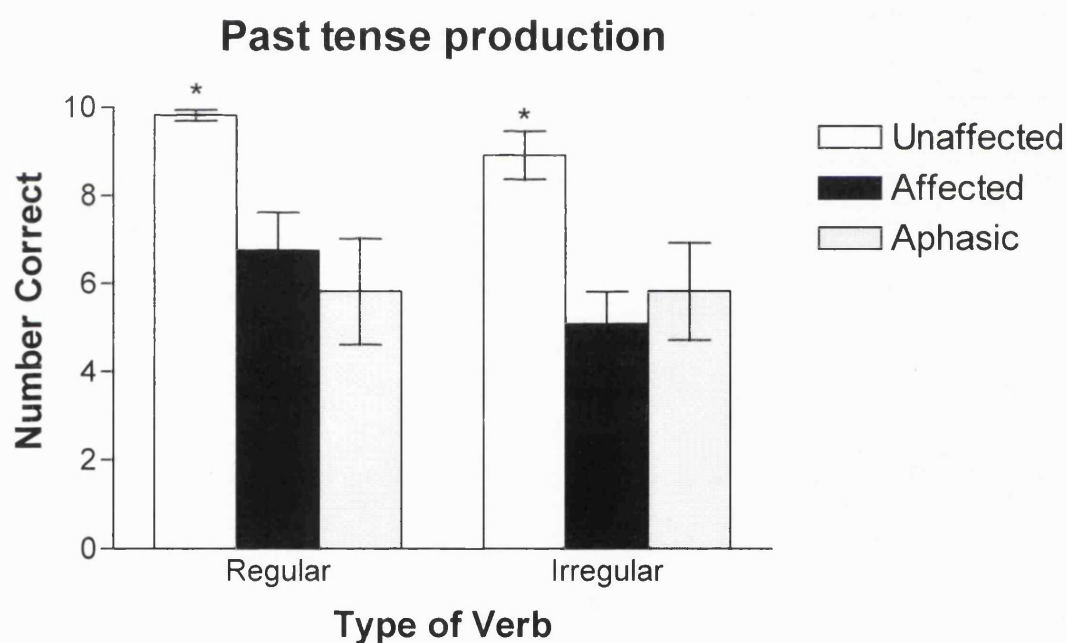


Figure 3.8 Past Tense Production. Bars, group mean; error bars, standard error of the mean; * significantly greater than affected and aphasic groups.

Nonword Reading and Spelling

Five aphasic participants were unable to write. Therefore they did not complete the nonword spelling test and their data were not included in these analyses. The test for homogeneity of variance revealed that the variance of the group scores for the nonword reading test was significantly different; therefore

nonparametric tests were performed. The unaffected group had significantly higher scores on this test compared to the affected group ($Z=3.56$, $p<0.001$) and the aphasic group ($Z=3.07$, $p=0.002$). The affected and aphasic groups did not differ significantly. Similarly, for the nonword spelling test, there was a significant difference among the three groups ($F(2,22)=11.55$, $p<0.001$). Post-hoc ranges tests revealed that this was due to significant group differences between the unaffected group and the other two groups, which did not significantly differ from each other (see Table 3.5 for group means). The difference in the group means shows that reading and spelling nonwords is a severe impairment in both the affected and the aphasic groups.

Table 3.5 *Nonword Reading and Spelling tests: group means and standard deviations*

| <i>Test [/max.]</i> | <i>Mean (SD)</i> | | |
|------------------------|-------------------|-----------------|----------------|
| | <i>Unaffected</i> | <i>Affected</i> | <i>Aphasic</i> |
| Nonword Reading [/30] | +26.57 (3.10) | 9.08 (5.11) | 12.38 (7.29) |
| Nonword Spelling [/30] | +20.63 (7.67) | 7.83 (7.30) | 4.40 (2.70) |

*significantly higher scores than affected and aphasic groups.

Praxis

The data for the tests of Limb and Orofacial Praxis were ratings. Therefore nonparametric analyses were performed.

Limb

Nonparametric tests for the scores for limb praxis revealed no significant group differences (see Table 3.6 for the group means).

Orofacial

For orofacial praxis, the unaffected group had significantly higher scores than the affected group ($Z=3.64$, $p<0.001$) and the aphasic group ($Z=3.76$, $p<0.001$). The affected and the aphasic groups were not significantly different from each other (see Table 3.6 for the group means).

Table 3.6 *Praxis tests: group means and standard deviations*

| <i>Test [/max.]</i> | <i>Mean (SD)</i> | | |
|------------------------|-------------------|-----------------|----------------|
| | <i>Unaffected</i> | <i>Affected</i> | <i>Aphasic</i> |
| Limb praxis [/45] | 44.89 (0.33) | 44.08 (1.55) | 43.82 (2.36) |
| Orofacial praxis [/96] | *92.67 (2.65) | 80.70 (5.85) | 75.18 (11.87) |

*significantly higher score than the other two groups.

3.3.2 Discriminant function analysis

Affected versus unaffected family members

ANOVA revealed that, compared with the unaffected group, the affected group was significantly impaired on the following tests: PIQ, Coding subtest, Lexical Decision, TROG and TROG Blocks LNRT, Word and Nonword Repetition (both Simple and Complex articulation), Object Naming, Phonemic, Semantic and Written Fluency, Word and Nonword Morphological Production, Past Tense Production, Nonword Reading and Spelling, and Orofacial Praxis. A discriminant function analysis (DFA) was performed, with the purpose of finding a linear function (DF) of several independent variables such that when an ANOVA is carried out to compare the affected and unaffected groups with respect to the linear function, the ratio of the between groups variance to the total variance is as large as possible.

As a result of the analyses in Section 3.3.1, the following variables were selected for the DFA: PIQ, Lexical Decision, TROG (score out of 80), Complex and Simple Nonword repetition (separately), Naming accuracy, Verbal Fluency (combined score for phonemic and semantic categories), Word and Nonword Morphological Production (combined inflectional and derivational scores), Past Tense Production, and Orofacial Praxis. There were missing data for the Coding subtest, Word Repetition, Written Fluency, Nonword Reading and Nonword Spelling tests; therefore those variables were not entered into the DFA. Similarly, because there had been no significant group interactions with the type of morphology in the Morphological Production test, and type of fluency in the Verbal Fluency tests, the scores for these conditions within the tests were combined, thereby reducing the number of variables entered into the analysis. Data for eleven affected and nine unaffected family members were entered into the DFA.

The variable of Complex Nonword Repetition was entered on the first step of the analysis. It accounted for 100 percent of the variance and was statistically significant (Chi-square = 30.81, $p < 0.001$). The analysis was terminated, as none of the other variables survived a statistical test for entry into the analysis. The resulting DF is as follows:

$$DF = 2.3 (\text{Complex Nonword Repetition score}) - 1.88$$

The weighting of 2.3 on the Complex Nonword Repetition score ensures a maximal difference between the DF variable for the affected and unaffected groups. Each affected family member was successfully classified according to this function with scores for the DF ranging from -3.36 to -0.41. Each unaffected family member was successfully classified also, with scores for the DF ranging from +0.33 to +3.29.

Table 3.7 shows the F-ratios calculated for each variable before entering the model, followed by those calculated after the Complex Nonword Repetition score was entered. The highest F-ratio prior to the analysis is that for Complex Nonword Repetition. When this variable entered into the DFA, the F-ratios for the remaining variables were dramatically reduced, suggesting that nearly all of the between group variance in the scores for these tests can be attributed to that in the scores for Complex Nonword Repetition.

Table 3.7 *Steps of the DFA between affected and unaffected family members*

| <i>Variable</i> | <i>F-ratio at</i> | <i>F-ratio at</i> |
|-------------------------------------|-------------------|-------------------|
| | <i>Step 0</i> | <i>Step 1</i> |
| PIQ | 7.93 | 0.18 |
| Lexical decision | 8.66 | 0.15 |
| TROG | 7.98 | 1.79 |
| Simple Nonword Repetition | 35.49 | 1.16 |
| Complex Nonword Repetition | 86.70 | entered |
| Naming Accuracy | 7.61 | 0.01 |
| Verbal Fluency | 11.08 | 0.04 |
| Morphological Production - words | 24.29 | 0.81 |
| Morphological Production - nonwords | 63.92 | 3.58 |
| Past Tense Production | 20.18 | 0.30 |
| Oral Praxis | 18.84 | 1.03 |

Thus, the affected family members can be best discriminated from the unaffected ones by their performance on a test of repetition of nonwords with complex articulation patterns.

Affected family members versus patients with aphasia

ANOVA revealed that the aphasic group was significantly impaired relative to the affected group on the three fluency tests only, namely, Phonemic, Semantic and Written Fluency. In contrast, the affected group was significantly impaired relative to the aphasic group on the following tests: PIQ, Picture Completion subtest, Picture Arrangement subtest, Lexical Decision, and Word Repetition. The DFA was performed for the affected and aphasic groups as described above for the affected and the unaffected groups.

As a result of the analyses in Section 3.3.1, the following variables were selected for the DFA: PIQ, Picture Completion subtest, Lexical Decision, Word Repetition and Verbal Fluency score (combined score for phonemic and semantic categories). The data for the Picture Arrangement subtest were not included because of missing data. The scores for phonemic and semantic categories were combined because there was no significant group interaction with the type of fluency on the Verbal Fluency tests. Data for 12 affected family members and ten aphasic controls were entered into the DFA.

The variable of Verbal Fluency was entered on the first step of the analysis, followed by Lexical Decision on step two. The analysis terminated with no further steps, accounting for 100 percent of the variance and was statistically significant (Chi-square = 28.99, $p < 0.001$). The resulting DF is as follows:

$$DF = 0.16 (\text{Verbal Fluency}) - 0.18 (\text{Lexical Decision}) + 6.28$$

Each affected family member was successfully classified according to this model with scores for the DF ranging from -0.08 to 3.62. Each aphasic control was successfully classified also, with scores for the DF ranging from -0.82 to -3.41.

Table 3.8 shows the F-ratios calculated for each variable before entering the analysis, after step one and after step two. Prior to the analyses the highest F-ratio was for Verbal Fluency. On this test the aphasic controls were significantly impaired relative to the affected family members, whereas for all the other variables in the

model the affected family members were significantly impaired relative to the aphasics. Unsurprisingly, therefore, the F-ratios did not change very significantly following the entry of the variable Verbal Fluency into the model; in fact, the F-ratios for two variables increased considerably. Lexical Decision was entered on the second step and the significance of the remaining variables decreased suggesting that these variables shared a significant amount of variance with the scores of the Lexical Decision test.

Table 3.8 *Steps of the DFA between the affected family members and the aphasic controls*

| <i>Variable</i> | <i>F-ratio at Step 0</i> | <i>F-ratio at Step 1</i> | <i>F-ratio at Step 2</i> |
|--------------------|------------------------------|------------------------------|------------------------------|
| PIQ | 9.41 | 8.73 | 0.79 |
| Picture Completion | 6.43 | 6.74 | 0.40 |
| Lexical Decision | 11.05 | 23.07 | entered |
| Word Repetition | 6.93 | 12.11 | 3.26 |
| Verbal Fluency | 21.53 | entered | - |

Thus, the affected family members can be best discriminated from the aphasic patients by their performance on two tests, namely, verbal fluency and lexical decision.

3.4 Discussion

3.4.1 Test considerations

Before discussing the results, a number of issues concerning testing need to be raised. Selection of the tests appropriate for the affected family members was difficult because of the wide age range of the participants and the variability in the severity of the disorder. Some of the tests administered to the affected family members were too easy for the unaffected family members, resulting in ceiling effects on those tests. Similarly, for those tests on which the unaffected family members were not at ceiling, some of the affected family members performed almost at floor levels.

Another general problem in the administration of language tests to language-impaired individuals arises from their difficulty in understanding or remembering test instructions. This difficulty was evident particularly in affected family members and aphasic patients on the nonword version of morphological production and the past tense production tests.

It was not possible for the investigator to be blind to the group membership of the participants. The speech problems were so obvious in both affected and aphasic individuals that their classification was clear to the investigator. For most of the test results, however, the investigator's awareness of group classification was not a major concern, but the rating of limb and oral praxis could have been influenced by different expectations of performance of the unaffected family members compared to the affected family members and the aphasic patients.

The unaffected family members seemed the most appropriate controls for the affected family members, because they have shared the same environment, have the same dialect and have attended mostly the same schools. For future studies, however, it would be informative to assess another control group matched for other variables, such as receptive language or articulation.

3.4.2 Statistical considerations

Parametric statistical methods were used to compare group scores on most of the tests analysed. This allowed within-test comparisons to be made. In cases where the variances of scores on a particular test were significantly different among the three groups, nonparametric analyses were used.

It would have been preferable, in addition to the analyses used, to have taken into account variations in test age and intelligence using analyses of covariance.

Even though the mean ages of the affected and unaffected family members were not significantly different, the aphasic controls were considerably older than most of the members of the other two groups. In addition, the PIQs of the aphasic patients were higher than those of the affected and unaffected family members. It was not possible to covary for age and PIQ, however, because the relationship between age and PIQ and other test scores was often significantly different among the groups. Also, it was not possible to subdivide the groups into high and low PIQ groups for separate comparison, because of small group sizes, and because there was little overlap in the ages at testing and PIQs among the three groups.

A further problem concerns the use of DFA with small numbers of subjects relative to the number of variables. To overcome this problem, additional individuals with the same disorder must be identified and their scores entered into a new DFA. At present, there are no prospects of testing further subjects, however, and new families with the same disorder have not yet been identified. The results of the DFA should, therefore, be interpreted cautiously. Despite this caveat, the results provide a plausible explanation of the language disorder in the KE family.

3.4.3 Discussion of the results

Identifying a "core" deficit in the affected family members

The results reported in this study confirm those reported by Vargha Khadem *et al.* (1995). The affected family members as a group are impaired on almost every test administered. The analyses reported here were performed to examine more specific impairments in each domain and to identify a "core" deficit that may underlie the range of impairments seen on tests of speech and language. The results of the DFA, comparing affected and unaffected family members, demonstrated that performance on a test of repetition for nonwords containing complex articulation patterns could alone successfully discriminate the two groups from each other. It is therefore a good candidate for a behavioural phenotype for the disorder.

Word and nonword repetition deficits in affected family members

The analyses of the Word and Nonword Repetition test revealed an interesting and complex set of results. On the Word Repetition test the affected family members were impaired at all syllable lengths relative to the unaffected ones, but both affected and unaffected groups showed similar effects for simple and complex articulation (i.e. there was no interaction between group and articulation difficulty). For the nonwords, however, in addition to the affected family members

being impaired relative to the unaffected ones at all syllable lengths, the interaction of group with articulation was significant. This effect was more pronounced in the affected family members, although both groups found the nonwords with complex articulation more difficult to repeat than the nonwords with simple articulation. Also, a direct comparison of Word and Nonword Repetition revealed that neither the unaffected nor the affected family members showed a lexicality effect, although this was close to significance in the unaffected group, and the latter were unimpaired at both Word and Nonword Repetition, performing almost at ceiling levels. The absence of a lexicality effect in the affected family members suggests that they fail to benefit from familiarity with the word to be repeated and presumably from familiarity with the articulation pattern required.

What is the deficit in nonword repetition?

Repetition of nonwords requires the formulation of novel combinations of sequences of phonological units; the individual units are based on English phonology and are therefore familiar. The units must be held in working memory, presumably in the articulatory loop, until repetition takes place. In normal development, the ability to repeat nonwords is influenced by the extent to which the nonwords resemble words, such that nonwords that more closely resemble the phonological structure of real words are more easily repeated than those that do not, because the patterns are familiar. It is assumed, therefore, that normal individuals with large vocabularies and skill in phonological analysis are more likely to draw analogies between nonwords and real words and rely on familiar patterns of articulation, thus gaining high scores on this test. The affected family members, however, do not have good phonological analysis skills, nor large vocabularies; also their articulation of words is impaired. They are therefore less likely to draw analogies with familiar word patterns.

Several studies have shown that children with SLI have difficulty in repeating nonwords (Kamhi & Catts, 1986; Kamhi *et al.* 1988). For example, Kamhi *et al.* (1988) found that children with SLI were impaired at repeating monosyllabic nonwords, strings of three monosyllabic nonwords, and polysyllabic nonwords. Gathercole and Baddeley, who devised the test used in this study, suggest that impairment is related to a specific deficit in the storage of phonological information in working memory. In their study (Gathercole & Baddeley, 1990), a group of children with SLI were impaired at recalling lists of words and at nonword repetition. This deficit was thought to be unrelated to articulation, however, because the children with SLI did

not show a differential effect of complex versus simple articulation on nonword repetition, nor were they impaired at a test of articulation rate. Bishop and colleagues, however, reported a nonword repetition impairment in a much larger group of children with SLI (Bishop, North & Donlan, 1996) and found that even after those with poor or atypical articulation were excluded, the children with SLI showed significantly greater impairment at repetition of nonwords with complex articulation compared to nonwords with simple articulation. Further, Bishop reported that performance on this test was a good phenotypic marker for SLI even in adolescents whose apparent language deficits had resolved. These results are remarkably consistent with those of the KE family. The problem with the test used in this study is that the effects of articulation and memory for increasing strings of phonemes are confounded at the longer syllable lengths. However, impairments in the affected family members were seen at all syllable lengths, even for single syllables when working memory is least taxed, suggesting that the articulation deficit is primary. It is worth considering, therefore, that the deficits seen in these individuals and other populations with SLI on tests such as those devised by Gathercole and Baddeley may not be due to phonological working memory deficits *per se*, but possibly related to sequential articulation of phonological units, which may be unrelated to memory capacity.

Impaired morphosyntax in the affected family members

As mentioned in the introduction to this chapter, there are two separate accounts of the nature of the disorder in the affected members of the KE family. One states that the disorder is selective to morphosyntax (Gopnik, 1990a; Gopnik & Crago, 1991; Gopnik & Goad, 1997). The other argues against the selectivity of the disorder, describing a range of impairments (Vargha Khadem *et al.* 1995). Critical to this debate is the claim that the morphosyntactic deficits in this family are specific and unrelated to the other deficits.

The results of the analyses reported in this study confirm that the affected family members have a deficit in the use of morphosyntactic rules. They were significantly impaired relative to the unaffected family members on a test of inflectional and derivational morphological production. Even more specifically, this deficit was demonstrated on a test of past tense production. Contrary to the previous report by Gopnik and colleagues (Gopnik, 1990a; Gopnik & Crago, 1991), however, the affected family members were impaired at production of both regular and irregular past tense. Since, irregular past tense production is not rule-based and it

relies upon lexical knowledge, there is at least one deficit that is unrelated to morphosyntactic rule use in this family. The analyses reported here also demonstrate deficits in the affected family members on many other linguistic tests. The claim for a specific deficit in morphosyntactic rule use is therefore untenable. Even so, the relationship between the articulation deficit, the deficit in morphosyntax and the other deficits require explanation.

Relating the articulation impairment to other language deficits

The articulation problem in the affected members of the KE family is the most obvious feature of the behavioural phenotype. How might an impairment in articulation of speech explain the deficits seen in morphosyntax and other aspects of language?

One explanation is that the deviant articulation results in poor phonology, rendering morphological production difficult. This explanation is supported by the findings of Fee (1995) who reported phonological abnormalities in the speech of affected family members (also see Vargha Khadem *et al.* 1995). It is worth noting that in her study, Fee excluded the data for two affected family members because they were unintelligible. In the Fee study, final word consonants were either devoiced (e.g./d/ pronounced as /t/), or deleted, and consonant clusters were reduced. Such productions are crucial for accurate morphological production, particularly in past tense productions where the distinguishing morpheme occurs at the end of the word.

Another possibility is that a deficit in articulation could lead to not only impaired phonological representation, but also impoverished language representation more generally. Impaired phonological analysis, resulting from poor subvocal rehearsal of incoming speech, could possibly interfere with the ability to draw analogies between words and to recognise (even implicitly) the rules of syntax. Lexical development could also be impaired as might the ability to understand complex grammatical constructions, such as embedded relative clauses. The latter, of course, is also dependent upon working memory (Gathercole & Baddeley, 1993) and this is also significantly impaired in the affected family members (see scores for Digit Span, Vargha Khadem *et al.* 1995). According to the Baddeley and Hitch model of working memory (Baddeley & Hitch, 1974), the articulatory loop is critical for rehearsal of verbal material, keeping it active in working memory until it is acted upon. An impairment in the articulatory loop, therefore, might restrict development of working memory and thereby language learning. Evidence for this view comes from a study of a woman with severe and selective limitations in working memory

following acquired brain damage^{who} had no difficulties processing language learnt prior to her brain damage, but she was severely impaired at learning new vocabulary (Baddeley, Papagno & Vallar, 1988).

If poor articulation does affect the development of other aspects of language then children with articulation disorders, particularly if due to central nervous system damage, should demonstrate similar restrictions in language ability. Studies of such children are rare and produce conflicting results (see Bishop, Brown & Robson, 1990, and Bishop & Robson, 1989). In support of this claim, Bishop, Brown & Robson (1990), report that in children with cerebral palsy and speech difficulties (anarthria and dysarthria) receptive vocabulary is restricted and same/different judgements of nonwords are impaired.

Examining the nonverbal intelligence impairment

Ultimately, the combination of impairments in components of the language system can influence the development of the nonverbal domain. The detrimental effects of a developmental language disorder on nonverbal cognition were described earlier (see Chapter 2) with reference to SLI populations in general, and the KE family in particular. Nonverbal cognitive development may appear normal at younger ages until it plateaus in early adolescence (or even earlier), when an apparent decline is witnessed. As previously reported, the affected family members had significantly lower PIQs than the unaffected family members.

In view of this finding, and the impairment in verbal intelligence previously reported (Vargha Khadem *et al.* 1995), the possibility cannot be ruled out that the genetic abnormality in the KE family produces a general, but mild developmental delay affecting both verbal and nonverbal abilities, as well as a more specific verbal impairment that arises from the articulation deficit.

The difference between the nonverbal abilities of the affected and unaffected family members was examined in further detail by analysis of the subtest scores. This revealed generally, but not significantly, lower mean scores for four of the subtests and a significantly lower mean score for the Coding subtest in the affected family members (see Figure 3.1). The Coding subtest requires the association of a series of symbols with a set of digits ranging from one to nine. The symbols must be copied beneath the digits, which are presented in a random order. This is a timed test, which is aided by rapid learning of the associations between the symbols and the digits. This test, therefore, requires good eye-hand coordination and short-term visual memory. The patients with aphasia might have been expected to be impaired

on this subtest because some of them have a hemiplegia affecting their right hand and were forced, therefore, to use their nondominant hand. Even so, they achieved a higher mean score than the affected family members who do not have any neurological impairment of the limbs.

Similarities between the affected family members and patients with aphasia

In comparison with the unaffected family members in whom speech and language abilities are unimpaired, the affected family members and the patients with aphasia demonstrated a range of impairments on nearly all of the tests administered. The pattern of impairment in the affected family members and the patients with aphasia was remarkably similar. They were equally impaired in receptive grammar, nonword repetition, particularly for nonwords requiring complex articulation, object naming, production of inflectional and derivational morphology, both regular and irregular past tense production, nonword reading and spelling, and orofacial praxis. These results suggest that the impairments of the affected family members and the patients with aphasia arise from a common neurobiological basis. More specifically, the brain regions on the left side known to be damaged in the aphasic group are likely regions of abnormal structure and function in the affected family members, except that in their case, because of the developmental origins of their disorder, the abnormality is likely to be bilateral.

Differences between the affected family members and the aphasic patients

Despite the similarities, the comparison of the affected and aphasic groups also revealed the differential effects of a developmental versus an acquired speech and language impairment. For example, the affected group had significantly higher scores than the aphasic group on the tests of verbal fluency. The principal locus for a deficit in verbal fluency in brain damaged adults appears to be left orbito-frontal cortex (Milner, 1964). Patients with lesions to the face area of the motor strip (posterior to Broca's area), however, are often even more impaired in verbal fluency than those with orbito-frontal lesions (Milner, 1964; Kolb & Wishaw, 1990). Many of the aphasic patients had lesions to insular cortex and dorsolateral prefrontal cortex and it is likely that these lesions encroach upon the motor face area. The reduced fluency on the written form of this test seems to suggest that the impairment is not related simply to impaired speech production, but that subvocal articulation, or phonological assembly could play a role in verbal generation or lexical retrieval, even in the written form.

The aphasic group was found to have significantly higher scores than the affected group on PIQ, Picture Completion and Picture Arrangement subtests, Lexical Decision and Word Repetition. With the exception of the scores for the Word Repetition test, these results were not significantly lower than those for the unaffected group, whose performance is normal. Thus, it appears that a developmental disorder has detrimental effects on different components of nonverbal intelligence, lexical development and familiarity with the articulation patterns of common words.

The results of the DFA supported these conclusions. The verbal fluency score best discriminated between the performance of these two groups, followed by the lexical decision score. The latter appeared to share a significant amount of the variance with the other variables, namely PIQ, Picture Completion, and Word Repetition, suggesting that these variables are related to a common underlying factor. It is suggested that the common factor is previous normal development and use. Thus, there is further evidence that a developmental speech and language disorder can have detrimental effects on both linguistic and nonlinguistic function.

Praxic impairments in the affected family members and the patients with aphasia

Finally, impairments were found in the affected and aphasic groups on a test of orofacial praxis but not on a test of limb praxis. The lack of an impairment in the patients with aphasia on limb praxis, despite the presence of a hemiplegic right arm in some of them, is explained by the fact that the movements only required one limb rather than both. A genetic abnormality that affects brain mechanisms responsible for articulation of speech sounds via the orofacial apparatus or frank neurological damage of the same system is unlikely to be so selective as to leave other components of the orofacial system unaffected (Kimura & Watson, 1989; Mateer & Kimura, 1977). Speech is probably the most sophisticated and complex product of the orofacial system, requiring highly organised coordination of movements. Even so, impairments in less sophisticated orofacial movements, which do not involve speech, but require either simultaneous or sequential movements, have been documented in the affected family members by Alcock (1995). These findings led Vargha Khadem *et al.* (1995) to suggest that the articulatory impairment in the affected family members was due to an underlying oral dyspraxia. This is a reasonable suggestion, but on the basis of the tests used, it was not possible to distinguish between the linguistic and nonlinguistic components of orofacial praxis. As a result, the relationship between these components and the effects that they

exert, either independently or interactively, on the efficient operation of the orofacial musculature remains unclear.

3.5 Summary

The comparison of results of affected members with those of unaffected members revealed impairments on tests of oral praxis, expressive language (including repetition, fluency, inflectional and derivational morphosyntax), receptive language and nonverbal cognition. The “core” deficit in the affected family members appears to be a restriction in production of complex articulation patterns. This deficit is most obvious in the deviant speech produced by the affected family members. It renders production of morphological suffixes difficult, which could account for the deficit in morphosyntax, previously described by Gopnik and colleagues. Furthermore, in a developmental context, such a deficit could also give rise to impoverished language representation, which would in turn be reflected in impairment on many other tests of language function. It is possible that such seemingly low-level impairment could lead to higher order deficits in cognitive domains, such as nonverbal intelligence, which appear to be unrelated to language ability. The possibility, however, that a more general mild developmental delay is a result of the genetic abnormality, cannot be ruled out.

The comparison of affected family members with aphasic controls revealed differences in behavioural and cognitive performance that could be attributed to the effects of a developmental disorder of speech and language versus an adult onset aphasia. The aphasic group had enjoyed a normal course of language and cognitive development and prolonged use of language over many years prior to the onset of left hemisphere pathology in adulthood. To some extent the premorbidly normal levels of function of this group were reflected on tests of nonverbal cognition, receptive vocabulary, and word repetition. Similar to the affected group, however, the aphasic group was impaired relative to normal levels in oral praxis, repetition of unfamiliar articulation patterns (i.e. nonwords) and production of morphosyntax. The areas of brain damage in the aphasic controls usually included the cortex posterior to Broca’s area, the motor face area, which might explain their considerable deficit on tests of verbal fluency. The patients with aphasia were even more impaired than the affected family members on the tests of verbal fluency, suggesting that there are also benefits to a developmental disorder of speech and language over an acquired one.

4. Morphological and syntactic processing in the KE family

The mental representation of regular and irregular past tense morphology and the processing of three types of syntax were examined in four affected members of the KE family. A test of auditory lexical decision compared priming in regular versus irregular past tense, semantic, and phonological conditions. The affected family members did not show priming for regular past tense. Significant priming effects were found, however, for irregular past tense and semantic conditions. The morphological complexity of the primes used in the regular past tense condition may have resulted in the failure to show a priming effect in the affected family members. This was not a problem for irregular past tense and semantic conditions because the primes were monomorphemic. The members' difficulty in producing morphologically complex words is likely to be associated with a disordered internal representation.

Syntactic processing at the sentence level was examined using a word monitoring paradigm. This revealed an impairment in the affected family members. This impairment was demonstrated only for sentences that examined auxiliary verb syntax. Whether or not a sentence contained a correct or incorrect auxiliary verb, the affected family members were significantly slower to process it, compared to sentences testing phrase structure and subcategory constraints. It is concluded that abnormal language development has resulted in an abnormal representation of different aspects of syntax.

4.1 Introduction

The proposal made by Gopnik and colleagues (Gopnik, 1990a; Gopnik & Crago, 1991) that the deficit shown by the affected members of the KE family was specific to inflectional morphosyntax was based on findings of impaired past tense marking for regular past tense in pilot studies. Production of irregular past tense was reported to be unimpaired. A subsequent report by Vargha Khadem *et al.* (1995) of impairments on a number of tests of language in the KE family, and those described in Chapter 3, bring into question the “specificity” of the impairment in inflectional morphology shown by affected family members. The deficits described were not selective to regular past tense but extended to irregular past tense, as well as to other aspects of syntax and language. In Chapter 3 (Section 3.4.3) it was suggested that the deficit in regular past tense production could arise from a primary deficit in articulation, which in itself could explain the phonological deficits in the affected family members. These phonological deficits make production of word endings, such as the morphemes necessary to mark tense and number, difficult.

In addition to impairments in regular and irregular past tense production, Chapter 3 described an impairment in receptive grammar in the affected family members. Thus, they are impaired at the morpheme level of grammar, as well as at the sentence level. Comprehension of sentences with embedded relative clauses was significantly impaired in the affected family members relative to the unaffected members. Comprehension of these sentences does not require interpretation of morphology; rather it depends upon knowledge and understanding of word order. The possibility has been raised (see Chapter 3) that the impairment in receptive grammar was related to an impoverished language representation in the affected family members that could have resulted from an interaction of their defective articulatory abilities and working memory. Gathercole & Baddeley (1993) have proposed that deficits in phonological working memory could result in receptive language impairments. If there is a limit on the size of the phonological store, then comprehension of sentence structures where the word order precludes sequential analysis on-line (such as embedded clauses) would be difficult to process and understand, because they require a temporary phonological representation of the sentence (also see Montgomery, 1995).

Two experiments are described in this chapter, which undertook further investigation of the affected family members’ deficits in inflectional morphology and receptive syntax. These studies were carried out in collaboration with Professor L.K.

Tyler. They are preliminary; only four affected family members were assessed. Each experiment is described and discussed separately below before a more general discussion.

4.2 Experiment one: inflectional morphology

The vast majority of English verbs are inflected to form the past tense by adding the ending -ed. Depending upon the stem of the verb, this ending is pronounced as /d/ as in *played*, /t/ as in *jumped* or /ed/ as in *posted*. New verbs entering the language are often produced in a regular past tense form (e.g. *fax* - *faxed* and *email* - *emailed*) and, similarly, the past tense forms of nonwords are usually of the regular verb form (e.g. *goop* - *gooped*) (see Kim *et al.* 1994 and Pinker, 1991). In addition, young children often produce regular forms of irregular verbs (over-regularisations, e.g. “goed” for *went* and “brokeed” for *broke*; see Marchman & Bates, 1994; Stemberger, P. 1993), despite never having heard these forms spoken. Such findings have led to the idea that a linguistic rule of the form “add an -ed” is mentally represented in and implemented by the human brain (see Pinker, 1991).

The exception to this rule is the relatively small number (less than 200) of irregular English verbs. These verbs are among those most frequently used in English and their past tense forms are often unpredictable (e.g. *go* - *went*, *be* - *was*). These forms, therefore, require learning as single lexical items. There are subgroups of irregular verbs, however, that share phonological changes when forming the past tense, for example, vowel changes such as from “i” to “a” in *sing*, *ring*, *drink* and *shrink*. Pinker (1991) proposes a dual-mechanism account of English past tense construction, which suggests that regular verbs are stored as bare stems and that the past tense forms are constructed by the addition of the “-ed” ending according to a mentally represented rule, whereas the past tense forms of irregular verbs are stored as lexical items and retrieved from memory just like many other words.

A problem for the dual-mechanism account, however, is provided by connectionists who have developed artificial neural networks that successfully mimic the language development of children. The original model (Rumelhart & McClelland, 1987) learnt hundreds of verbs and was able to generate regular past tense forms for new verbs, but it also produced over-regularisations similar to those seen in normal child development (e.g. *brokeed* for *broke*). The network learnt by giving weightings to correlations between the sounds of verb stems and their past tense forms; whilst it did not use rules *per se*, it exhibited rule-governed behaviour.

Gopnik (1990a; Gopnik & Crago, 1991) used her preliminary data on the KE family to support the view that regular and irregular verbs have different mental representations. Subsequent findings (Vargha Khadem *et al.* 1995; see Chapter 3 also) failed to support the dissociation between regular and irregular past tense

production in the KE family, documenting equal impairments in both. Further, the affected family members were reported to produce over-regularisations, similar to those produced by young children, and demonstrated explicit knowledge of the -ed rule. On the basis of these findings, it is difficult to suggest that the KE family provide evidence for a dissociation in the mental representation of regular and irregular past tense verb forms.

Recent neuropsychological studies of brain damaged adults (Ullman *et al.* 1997; Marslen-Wilson & Tyler, 1997) and functional imaging studies in normal adults (Jaeger *et al.* 1998), however, provide support for the dual-mechanism theory (rules for regulars and lexical retrieval for irregulars). The approach used by Marslen-Wilson and Tyler is of particular interest for further studies of morphology in the KE family because it does not require speech production. Therefore a preliminary investigation of the mental representation of regular and irregular verbs was carried out in four affected members of the KE family using an auditory lexical decision test, similar to that described in their study (Marslen-Wilson & Tyler, 1997).

4.2.1 Methods

Participants

Four affected family members, two females from the second generation and two males from the third generation, (II-2, II-9, III-5 and III-20; see Figure 2.1) participated in these experiments. The ages of the participants at time of testing were 48, 50, 18, and 24 years, respectively.

Materials and procedure

During the auditory lexical decision test, participants heard pairs of words over headphones, and indicated, using a response key, whether the second word of each pair (the target word) was a real word or a nonword. Response latencies to target words that were preceded (i.e. primed) by a related word (test prime) were compared with the response latencies to the same target word preceded by an unrelated word (control prime). Conditions where the priming relationship was regular past tense and irregular past tense were compared with two other conditions where the relationship between the target word and the test prime was either phonological (e.g. winter - win) or semantic (e.g. table - chair). An advantage of this particular paradigm over more explicit tasks is that the subjects perform a lexical

decision task and their attention is not explicitly drawn to the priming effect, which is being measured.

Stimuli consisted of word pairs (see the examples in Table 4.1). For regular and irregular past tense conditions, 42 related word-pairs per condition were selected, the first word being the past tense form of the target word. For phonological and semantic conditions, 24 related word-pairs per condition were selected. In the phonological condition, the first word phonologically overlapped with the target word but was not related to it either semantically or morphologically. In the semantic condition, the first word semantically related to the target word. Two versions of the task were designed, such that the target words were only presented once in each version, preceded by either the test or the control prime. Half of the target words were preceded by the test prime in version A and half in version B. Within these versions there were a number of filler items, which were pairs of words with either word or nonword targets. The two versions were run at least three weeks apart for each participant.

Word-pairs were recorded and digitised and timing pulses were placed at the onset of each target word, triggering a timing device which was stopped by pressing a button. The interval between the onset of the target word and the button press was defined as the reaction time (RT) and recorded for each response. There was a 250 ms interval between prime and target and a three second interval between pairs of words.

Table 4.1 *Examples of targets and primes for the four conditions.*

| | <i>Regular</i> | <i>Irregular</i> | <i>Phonological</i> | <i>Semantic</i> |
|---------------|----------------|------------------|---------------------|-----------------|
| target | pull | swing | beak | tree |
| test prime | pulled | swung | beacon | bush |
| control prime | lungs | curls | chisel | crane |

Statistical Analyses

The RT data of each participant were entered onto a spreadsheet and prepared for analysis in the following way. Lexical decision errors, and both anticipated or missed responses, were removed from the data, as were all outliers (responses that were either 100 ms greater or less than the main distribution of RT's). Items that corresponded to these data on the alternative version of the test were also removed. Data that exceeded two standard deviations (SD) from the mean, within

each version, were replaced with the appropriate cut-off values (either mean+2SD or mean-2SD). The data were normalised by dividing each RT by the mean RT for that version and multiplying by 100. Analyses of variance (ANOVAs) of the normalised data with repeated measures were run first for all the participants as a group and then separately for each individual. A large ANOVA was run initially with all conditions (e.g. four conditions for lexical decision). Subsequently, separate ANOVAs were run for each condition. The mean squares error term in each of these separate ANOVAs was corrected by taking the mean of all the mean squares error terms and using the mean value as the new mean squares error term. New F ratios were then calculated and their significance reported.

4.2.2 Results

The normalised RT data for the group of four subjects were analysed as follows. ANOVA was run with the repeated measure of priming (2 levels; test vs. control prime) and factors of participant (4 subjects), condition (4 types; regular past tense, irregular past tense, phonological and semantic) and version (2 versions; primed in version A vs. primed in version B). Priming was significant for the whole group ($F(1,395)=9.04$, $p=0.003$), but there was no significant interaction of priming with condition ($F(3,395)=2.02$, $p=0.11$). There were no significant main effects of participant, condition or version. The only significant interaction was between condition and version ($F(3,395)=3.74$, $p=0.011$).

Separate ANOVAs were run for each condition with the repeated measure of priming (test vs. control prime) and factors of version (primed in version A vs. primed in version B) and participant (4 subjects). There were significant effects of priming for irregular past tense ($F(1,136)=8.42$, $p=0.002$) and semantic ($F(1,78)=6.90$, $p=0.023$) conditions, but not for regular past tense and phonological conditions. There was a significant effect of version for the phonological condition ($F(1,59)=6.82$, $p=0.009$) only. Examination of the mean RTs revealed that, for the phonological condition, the mean RT was quicker for items in version A. There were no significant interactions between priming and version in any of the conditions. These separate analyses explain the interaction between version and condition that was significant in the main analysis. The effect of version was significant for only one condition, namely phonological priming. The interaction that was close to significance ($p=0.11$) in the main analysis, namely that between condition and priming, is also explained; there were significant priming effects for two conditions only, namely irregular past tense and semantic conditions.

Table 4.2 *Lexical decision test results. Mean normalised RT for each condition*

| Condition | Related Prime | Unrelated prime | Difference | Significance |
|----------------------|---------------|-----------------|------------|--------------|
| Regular past tense | 100.27 | 99.59 | -0.68 | n.s. |
| Irregular past tense | 95.87 | 101.95 | 6.08 | 0.002 |
| Phonological overlap | 97.50 | 99.89 | 2.39 | n.s. |
| Semantic | 96.09 | 103.59 | 7.50 | 0.023 |

n.s., not significant ($p > 0.05$)

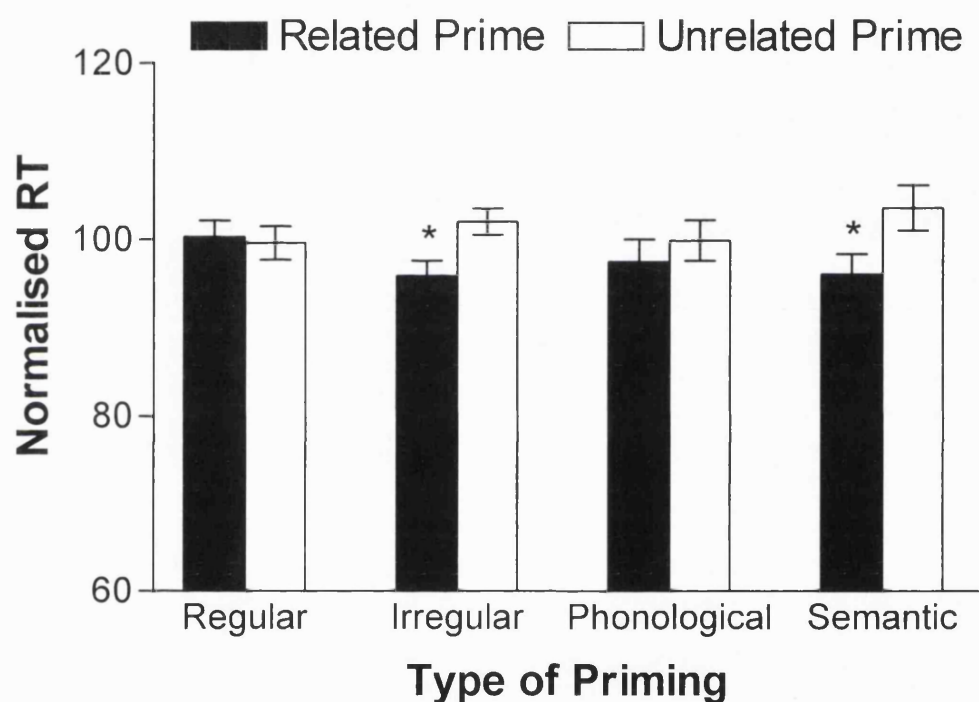


Figure 4.1 *Priming effects by condition. Bars, group mean; error bars, standard error of the mean; * $p < 0.05$. Note: Y-axis starts at 60.*

4.2.3 Discussion

Priming in the affected members of the KE family

The auditory lexical decision test examined two types of morphology, namely inflectional morphology for regular past tense and irregular past tense. The effects of priming in these conditions were compared with a semantic condition and a phonological condition. Under these test conditions, normal controls show positive priming (i.e. a facilitation of the response latency in related word pairs) for regular

and irregular past tense, and semantic conditions. Normal controls, however, do not show positive priming in the phonological condition (for further details of the performance of controls see Marslen-Wilson & Tyler, 1997; 1998).

In this study the group of four affected family members showed significant priming for all conditions but no interaction between priming and condition. When the four conditions were analysed separately, however, the group showed significant priming effects for semantic and irregular past tense conditions. The effects for regular past tense and phonological conditions were very small and not significant (see Figure 4.1).

The difference between this pattern of results and that for normal controls, therefore, is that the affected family members failed to show priming in the regular past tense condition. These results are consistent with the initial findings of Gopnik and colleagues (Gopnik, 1990a; Gopnik & Crago, 1991) that the affected family members have a selective impairment in regular past tense. They are also consistent with the theoretical conclusion that the affected family members were unaware of the implicit rule for generating regular past tense, namely addition of the morpheme “-ed”. Gopnik described explicit mention of the “add an -ed” rule by affected family members. The findings of over-regularisation of irregular verbs (Vargha Khadem *et al.* 1995) are also consistent with explicit awareness of this rule. The auditory lexical decision tests, however, examined implicit processes. Also, the performance of affected family members on tests of past tense production (see Chapter 3) was significantly impaired for both regular and irregular verbs. According to Tyler (1992) language-impaired patients typically show preserved implicit and impaired explicit processing, with explicit tasks tending to overestimate the severity of a patient’s deficit. An alternative view, however, is that irregular verbs have a normal mental representation in the affected family members, but explicit awareness of a required rule in past tense production results in over-regularisation of irregular verbs in production.

Previous studies of priming in agrammatic aphasic patients

The pattern of results observed in the affected family members is remarkably similar to that seen in two out of three patients with agrammatic aphasia resulting from large lesions of the left hemisphere (Marslen-Wilson & Tyler, 1997; 1998). These two patients (DE and JG) were assessed using a similar test of auditory lexical decision. They showed positive priming effects for irregular past tense and semantic

conditions only, and strongly negative priming (i.e. an inhibitory effect of the prime) for the regular past tense condition.

Regular and irregular past tense priming effects

One explanation of the differences in regular and irregular past tense priming effects reported in their patients is offered by (Marslen-Wilson & Tyler, 1998). Regular past tense verb forms, which were used as primes in this study, are morphologically complex; they are constructed phonologically from the verb stem and the inflectional morpheme “-ed”. Irregular past tense verbs forms, however, are monomorphemic. The aphasic patients DE and JG were both severely impaired at production of morphologically complex words, rarely producing inflections in their speech and it is likely, therefore, that they had similar difficulties in comprehension of morphologically complex words. Such difficulties would lead to impaired processing of regular inflections (such as regular past tense). In contrast, these patients would have less difficulty with monomorphemic words, such as irregular past tense verb forms or the nouns used in semantic priming conditions.

This explanation is pertinent to the pattern of results documented in the affected family members. These individuals also have difficulty producing morphologically complex words. In Chapter 3, this difficulty was related to the problems the affected family members have with articulation of words and nonwords, particularly those with complex patterns of articulation. In spontaneous speech, the affected family members often omit or reduce final word consonants and consonant clusters (Fee, 1995). It is likely, therefore, that as for the patients DE and JG, the affected family members would have difficulty in phonologically processing the regular past tense primes leading to a deficit in the priming effect normally seen under such conditions. The irregular past tense verbs and the semantic primes were simple monomorphemes that did not require phonological disassembly and therefore normal priming effects were observed under these conditions.

This interpretation of the results is consistent with the suggestion that individuals who have difficulty in speech production, manifested in poor phonology, may economise their grammatical production to maximise meaning and thereby, the comprehension of the listener (Leonard, 1989). In doing so, they may omit morphemes in their productions because these do not contribute substantially to the meaning of the production. Bates, Wulfeck & MacWhinney (1991) have argued that in such cases, the whole language system can be seen to be under stress, with the possible consequence being a marked simplification and reduction of linguistic

output. It is feasible that this impairment extends to the receptive domain as well, such that features added to convey tense or number are not considered relevant for meaning and are ignored, or possibly not perceived at some level.

4.3 Experiment two: syntactic processing

On-line language comprehension tests have proved successful in assessing syntax implicitly in developmentally language-impaired populations (Tyler *et al.* 1997a; Karmiloff Smith *et al.* 1998). Therefore the affected family members' ability to use syntactic information in the process of interpreting a sentence was examined in further detail using this method.

4.3.1 Methods

Participants

The participants for the word monitoring test were the same as those for the auditory lexical decision test, described in Section 4.2.1.

Materials and procedures

A word monitoring paradigm was used and sensitivity to three types of syntactic violation was measured. Participants listened to spoken sentence pairs, played over headphones, and pressed a response key when they heard a prespecified target word in the second sentence. The target word was printed on a card placed in front of the participant and read by the examiner before each sentence pair was heard. The latency to target words occurring in particular syntactic constructions was compared with the latency to the same target word spoken in a sentence where the same syntactic construction was violated to determine whether the subject's sensitivity to the violation had increased the latency as demonstrated by normal controls. As a control for this test, the affected family members' ability to use semantic information in the process of interpreting a sentence was examined in the same way by measuring their sensitivity to two types of semantic violation.

Three types of syntactic information were examined: phrase structure rules within local constituents, subcategory constraints on verbs, and the constraints imposed by auxiliaries on the form of the subsequent verb. Stimuli consisted of pairs of sentences. The first sentence was a context sentence and the second contained the target word that participants were required to detect. Good (grammatical) and bad (ungrammatical) sentences were constructed as described below and subjected to several pre-tests with normal people (see Karmiloff Smith *et al.* 1998, for further details). Two types of semantic information were also examined: pragmatics and semantic anomalies. Good (in a semantic sense) and bad (in a semantic sense) sentences were constructed as described below and were also subjected to several

pre-tests with normal people. As a result of analysis of the pre-testing, 100 sentences were selected (20 testing each of the three syntactic violations and two semantic conditions described above). The 100 test sentences were interleaved with a large number of filler sentences consisting of a variety of different syntactic and semantic structures. The number of good and bad sentences across test and filler items was the same. Two versions of the test and filler sentences were constructed, so that only one of the sentences was included in each version. Half of the good sentences appeared in version A and half in version B. The two versions of the test were administered separately at least three weeks apart.

Sentences were recorded and digitised onto a computer. Timing pulses were placed at the onset of each target word, triggering a timing device which was stopped by a button press.

(i) Sentences testing syntactic processing

Good sentences testing phrase structure rules were constructed of the form (noun phrase (NP) + verb + object NP) and then violated according to these rules to create a new set of “bad” sentences (see Table 4.3). In the grammatically correct (good) sentences the target word occurred in the object NP following the verb and the object NP was in the correct configuration with respect to the verb. In the violated (bad) sentences, the target word followed a sequence of words in the object NP that violated the legal configuration of grammatical categories. This violation was brought about by a change in the word order (e.g. *blue the* and *unusual some*, in the examples below).

Sentences testing subcategory constraints were constructed containing selected verbs and then violated according to the subcategory constraints on the main verb, as in Table 4.3. The sentences were all of the structure: (NP + verb + object NP) plus a few additional words. The object NP (e.g. MEN and NIGHT in the examples below) was always the target word. In the grammatical condition, the object NP was syntactically appropriate in that it was consistent with subcategory restrictions on the verb. In the ungrammatical condition, the verb could not take a direct object and thus the presence of the target noun, not preceded by a preposition, constituted a grammatical violation. All the verbs used for the sentences testing subcategory violations were intransitive; therefore all of the grammatically correct sentences contained a preposition (e.g. *at* and *for*, in the examples above) which was omitted in order to violate the subcategory constraints on the verb and produce an ungrammatical sentence.

Sentences testing auxiliary constraints on the verb were constructed of the form: (NP + auxiliary + verb + target noun) followed by additional material (see Table 4.3). In these grammatically correct sentences the auxiliary is syntactically appropriate for the inflected form of the following verb. Sentences were violated by changing the auxiliary so that the combination of the auxiliary and the verb was ungrammatical (e.g. *had making* and *should using*, in the examples below).

Table 4.3 *Examples of items used in the Syntactic conditions of the Word Monitoring test*

| Context Sentence | "Good" Sentence | "Bad" Sentence |
|--|---|--|
| Phrase structure rules | | |
| Pat was searching all over the house | She couldn't find the blue GLASSES anywhere | She couldn't find blue the GLASSES anywhere |
| It had been a busy day | They had made some unusual PICTURES for Halloween | They had made unusual some PICTURES for Halloween |
| Subcategory constraints | | |
| Dorothy was an awkward girl | To begin with, she laughed at MEN who asked her out | To begin with, she laughed MEN who asked her out |
| We tried to keep everyone calm | They had to wait for NIGHT to fall | They had to wait NIGHT to fall |
| Auxiliary constraints on the verb | | |
| The visit had been relaxing | Before we left, we were making PATTERNS in the sand | Before we left, we had making PATTERNS in the sand |
| He was not the only one | John was using COLLEGE as an excuse to waste time | John should using COLLEGE as an excuse to waste time |

Note: The target word is printed in upper case in all the example sentences shown

(ii) *Sentences testing semantic processing*

Sentences testing pragmatics were constructed (see Table 4.4) and then violated according to pragmatic rules to create a new set of sentences. In the semantically correct sentences the target word was semantically appropriate, in a pragmatic sense, to the noun phrase preceding the verb. Sentences were violated by changing the noun phrase preceding the verb in a way that made the relationship with the subsequent target noun physically implausible, but not entirely anomalous (e.g. *fly lifted the pebble* and *scissors cut the gate*, in the examples below).

Sentences testing semantic anomalies were constructed (see Table 4.4). In the semantically correct sentences the target word was semantically appropriate with relation to the preceding adjective. Sentences were violated by changing the

adjective preceding the target word in such a way that the relationship between the target word and the adjective was semantically anomalous (e.g. *sad road* and *dry rain*, in the examples below).

Table 4.4 *Examples of items used in the Semantic conditions of the Word Monitoring test*

| <i>Context Sentence</i> | <i>"Good" Sentence</i> | <i>"Bad" Sentence</i> |
|--|--|--|
| Pragmatics | | |
| There was a strange scratching noise | Very slowly the boy lifted the PEBBLE to see what was underneath | Very slowly the fly lifted the PEBBLE to see what was underneath |
| No-one need have worried about the equipment | The saw cut the GATE in half quite easily | The scissors cut the GATE in half quite easily |
| Semantic anomalies | | |
| Anabel arrived at nine o'clock | The new ROAD had allowed her to do the journey in half the time | The sad ROAD had allowed her to do the journey in half the time |
| Anne stood silently | She felt the cool RAIN trickle down her neck | She felt the dry RAIN trickle down her neck |

Note: The target word is printed in upper case in all the example sentences shown

Statistical analyses

Statistical analyses of the word monitoring data were carried out as for the auditory lexical decision data described in Section 4.2.1.

4.3.2 Results

For the three conditions testing syntactic processing, the normalised RT data for the group of four subjects were analysed as follows. An ANOVA was run with the repeated measure of grammaticality (2 levels; correct vs. violated syntax) and factors of participant (4 subjects), condition (3 types; phrase structure, subcategory and wrong auxiliary) and version (2 versions; sentence was correct in version A vs. sentence was correct in version B). The repeated measure of grammaticality was significant ($F(1,219)=19.82$, $p<0.0005$) for the whole group, as was the interaction of condition and grammaticality ($F(2,219)=3.82$, $p=0.040$). There was no significant main effect of participant or version but there was a significant interaction between version and condition ($F(2,219)=5.44$, $p=0.005$).

Three separate ANOVAs were run for each condition with grammaticality as a repeated measure, and participant and version as factors. There were significant

effects of grammaticality for phrase structure violations ($F(1,73)=17.15$, $p<0.0005$) and subcategory violations ($F(1,79)=9.56$, $p=0.004$) but not for auxiliary violations (see Table 4.5 and Figure 4.2). There was also a significant effect of version for phrase structure violations ($F(1,73)=10.78$, $p=0.001$) but not for the other two conditions. For good and bad sentences testing phrase structure, the mean RT in version A was significantly shorter than in version B. The interaction between participant and grammaticality was close to significance for subcategory violations ($p=0.095$) only. There were no other significant interactions among grammaticality, participant and version in any of the conditions. Thus, the interactions in the first, large ANOVA are explained. The interaction between grammaticality and condition was due to grammaticality being significant for phrase structure and subcategory items but not for wrong auxiliary items. The interaction between version and condition is explained by the main effect of version for phrase structure items only and not for the other two.

Examination of the mean RT's in Table 4.5 (Figure 4.2 also) shows that the lack of sensitivity to auxiliary violations in the affected family members is due to longer processing of the grammatical sentences testing this type of syntax, suggesting that they are slow to integrate this type of syntactical information rather than insensitive to violations of this type of syntax. In summary, the affected family members as a group have shown that they are sensitive to syntactic violations of phrase structure and subcategorisation but not to the wrong auxiliary.

Table 4.5 *Word Monitoring test. Mean normalised RT for the three conditions examined.*

| <i>Condition</i> | <i>Good</i> | <i>Bad</i> | <i>Difference</i> | <i>Significance</i> |
|------------------|-------------|------------|-------------------|---------------------|
| Phrase Structure | 88.55 | 103.71 | 15.16 | <0.0005 |
| Subcategory | 95.77 | 106.57 | 10.80 | 0.004 |
| Wrong auxiliary | 100.89 | 102.97 | 2.08 | n.s. |

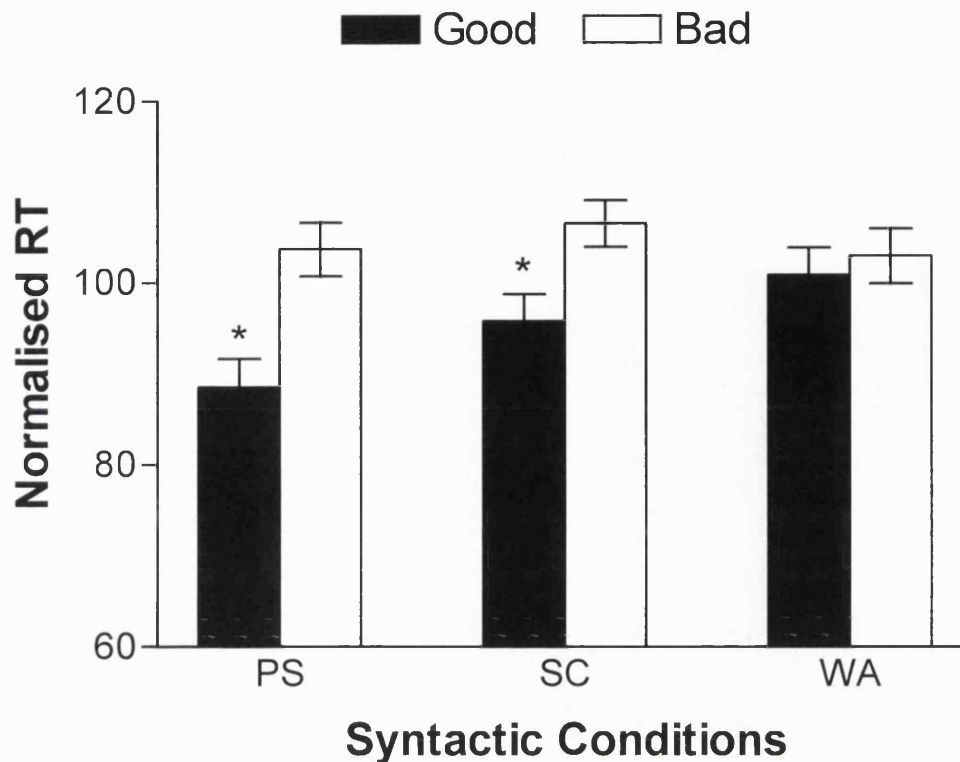


Figure 4.2 Effects of good and bad syntax on RT. PS, phrase structure; SC, subcategory constraints; WA, wrong auxiliary; * $p < 0.05$. Note: Y-axis starts at 60.

The RT data for the group of four subjects for the two conditions testing semantic conditions were analysed as follows. An ANOVA was run with semantic appropriateness as a repeated measure (2 levels: semantically correct vs. incorrect), and factors of participant (4 subjects), condition (2 types: pragmatic vs. anomalous), and version (2 versions; sentence was correct in version A vs. sentence was correct in version B). There was a significant effect of semantic appropriateness ($F(1,136)=12.48$, $p=0.001$) and a significant effect of condition ($F(1,136)=4.52$, $p=0.035$), but no effect of participant ($p=0.999$), or version ($p=0.217$) and no significant interactions.

Separate ANOVAs were run for each condition, with semantic appropriateness as a repeated measure, and participant and version as factors. There was a significant effect of semantic appropriateness for sentences testing pragmatics ($F(1,69)=3.78$, $p=0.047$) and for sentences testing semantic anomalies ($F(1,67)=9.25$, $p=0.005$), but no significant effect of participant or version and no significant interactions in either condition.

Table 4.6 *Word Monitoring test. Mean normalised RT for the conditions examined.*

| Type of violation | Good | Bad | Difference | Significance |
|--------------------|-------|--------|------------|--------------|
| Pragmatics | 91.29 | 99.65 | 8.36 | 0.047 |
| Semantic anomalies | 97.39 | 110.63 | 13.24 | 0.005 |

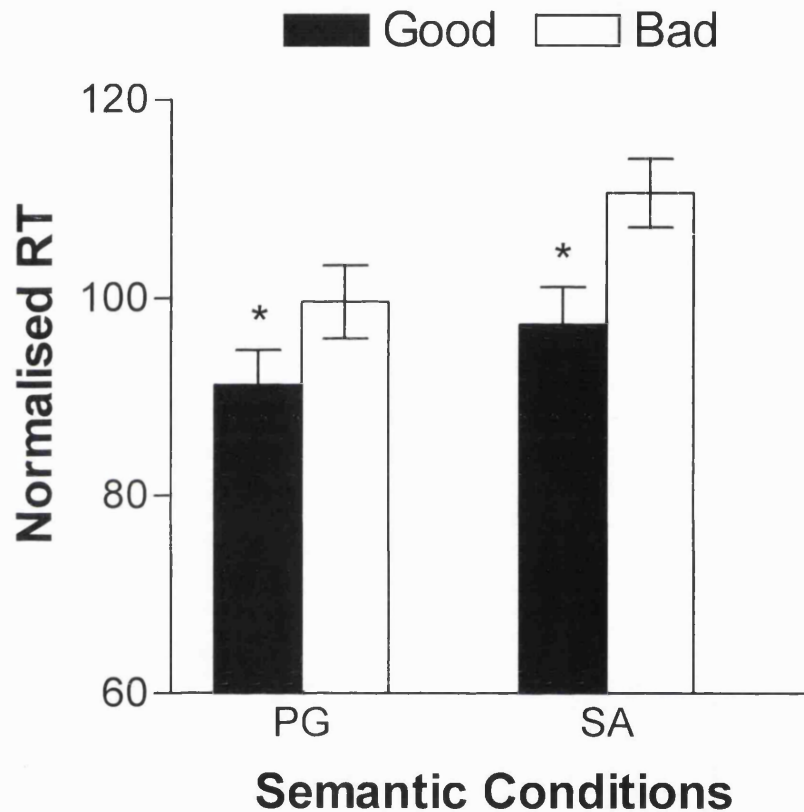


Figure 4.3 *Effects of good and bad semantics on RT. PG, pragmatics; SA, semantic anomalies; * $p < 0.05$. Note: Y-axis starts at 60.*

4.3.3 Discussion

Processing of syntax in the affected family members

Three types of syntax processing were examined in the affected family members, namely phrase structure rules, subcategory constraints and auxiliary constraints on the verb. Normal controls show sensitivity to all three types of syntax, in that their word monitoring latencies are increased when the syntax is violated compared to conditions when it is not.

The group analysis for the four affected family members showed sensitivity to syntactical violations for the sentences testing phrase structure rules and subcategory constraints, but not for sentences testing auxiliary constraints on the verb (see Figure 4.2). The affected family members, as a group, showed increased monitoring latencies for sentences with good syntax that were designed to test auxiliary constraints, relative to the good sentences in the other two conditions. This suggests that they have difficulty processing this type of sentence structure, in addition to being insensitive to violations of auxiliary constraints. It is also worth noting that the size of the difference between good and bad sentences testing subcategory constraints was somewhat reduced compared to that for sentences testing phrase structure and this difference was less significant (see Table 4.5).

These results are consistent with those in Chapter 3 for performance on a test for reception of grammar (TROG; Bishop, 1982). The affected family members were impaired on this test across all items. Further, they were impaired on the items of this test that require sentential processing and comprehension of syntax at the word order level. In Chapter 3 and in the introduction to this chapter, it was suggested that the impairment in receptive grammar could be due to restriction of verbal working memory arising out of a phonological or articulatory deficit. The memory requirements of the word monitoring test are not high, as target words immediately followed the syntactic construction being tested; even so, an impairment in verbal working memory cannot be ruled out as a possible influence on performance of this test.

As discussed for the results of the auditory lexical decision test, individuals with impaired speech and phonological production may omit morphemes that do not substantially add to the meaning of their productions (Leonard, 1989; Bates, Wulfeck & MacWhinney, 1991). Auxiliary verbs and prepositions are often omitted from the speech of the affected family members, presumably because they simplify their output in order to maximise understanding. In contrast, they do not produce confused word order e.g. "blue the glasses" instead of "the blue glasses". It is likely, therefore, that the affected family members also have difficulty in perceiving the meaning of auxiliary verbs and prepositions, which would explain why they showed increased monitoring latencies even in conditions where the auxiliary verb was correct with respect to the following verb. It also explains why the effect in sentences testing subcategory constraints was less significant than in sentences testing phrase structure.

Syntactic processing in Williams syndrome

The pattern of results observed in the affected family members is similar to that seen in a group of patients with Williams syndrome, who were examined using an almost identical test (Karmiloff Smith *et al.* 1998). The patients with Williams syndrome showed no sensitivity to the syntactic violation of sentences testing subcategory constraints on the verb. They also showed increased word monitoring latencies for the sentences with good subcategory syntax, suggesting they were slow to integrate this kind of information. Unlike the affected members of the KE family, the patients with Williams syndrome were sensitive to violations in sentences testing the auxiliary constraints on the verb.

The affected family members, however, showed sensitivity to violations in syntax in sentences testing subcategory constraints, although this was less significant than those testing phrase structure. The test used with the affected family members was slightly different from that used with the patients with Williams syndrome. In this study, all the sentences constructed to test subcategory constraints contained an intransitive verb that required a preposition immediately following in the sentence. In order to violate the sentence, the preposition was omitted. In the study of patients with Williams syndrome, however, transitive verbs were also included and sentences were violated by addition of a preposition immediately following the verb and not required (e.g. Maria always needed *for* partners vs. Maria always needed partners). It would be interesting to know if the patients with Williams syndrome were equally impaired on these two sets of sentences and if the affected family members showed sensitivity to both.

Adults who have acquired language normally, and then suffered a stroke or developed a neurodegenerative disease, do not show selective impairments in syntactical processing; they are either impaired at all three types of structure or none at all (Tyler *et al.* 1997b). The finding of a selective impairment in Williams syndrome and in the affected members of the KE family suggests that in developmental disorders of a genetic origin language may be acquired via a somewhat different route from normal. In these populations, therefore, different types of syntactic structure may be differentially represented.

Processing semantics in the affected members of the KE family

Two types of semantic processing were examined in the affected family members, namely pragmatics and semantic anomalies. Normal controls show sensitivity to both types of semantic processing, in that word monitoring latencies

are increased during conditions where the semantics are violated compared to conditions where it is not.

The group analysis for the four affected family members showed sensitivity to both types of semantic violation (see Figure 4.3). There was a significant difference between the two types of semantic violation. The affected family members were significantly quicker at processing the sentences testing pragmatics than those testing semantic anomalies, irrespective of whether the semantics were violated or not. It is unclear why this difference should occur in conditions where semantics were not violated.

4.4 General Discussion

Four affected family members were administered auditory lexical decision and word monitoring tasks, which examined their sensitivity to grammatical morphology and syntax, respectively. The results of analysis of these tests have been discussed. However, before drawing firm conclusions from these results a number of points need consideration.

4.4.1 Test and data analysis considerations

The data reported in this chapter are preliminary data. Only four affected family members were assessed and the pattern of their results was compared with that previously described in normal controls for the same test. Direct, statistical comparisons between the affected family members and normal controls have not been made. Further data collection will include not just affected family members but the unaffected ones also, in order to compare the two groups.

The analyses presented here were group analyses, similar to those carried out for control subjects. In contrast, the previous reports of patients DE and JG on the auditory lexical decision test described data analyses for each individual separately. The different methods of analysis are likely to produce different results. Group analyses allow increased statistical power relative to analyses of the results for individual participants. In this study, a factor of participant was used to check for significant individual differences. This factor did not achieve statistical significance as a main effect or in interaction with other main effects in any of the analyses. It is valid, therefore, to treat the results of the group analyses as representative of the four individuals. However, the results of analyses for individual participants revealed interesting differences that were not obvious from the group analyses. These are presented for interest in the Appendix to this chapter. The differences between the results of the group analyses presented here and those of the individual analyses described in the Appendix suggest that interpretation of data presented for individuals should be cautious, particularly if the comparison is with group data.

A further point to consider concerns the statistical analyses of the auditory lexical decision test. Although the separate analyses per condition revealed significant results for irregular past tense and semantic conditions only, the large ANOVA revealed a priming effect for all conditions and no interaction. This apparent conflict in the results is due to the difference in variance across the four conditions. Again a cautious interpretation of these results is suggested.

Finally, the differences in RTs for test versus control primed words, or word monitoring in syntactic and semantically appropriate versus inappropriate sentences, that were demonstrated in the affected family members were small. In particular, the significant priming effects were about six or seven percent of the mean RT in those conditions. These effects are therefore not very robust and are easily susceptible to failures in attention or changes in motivation of the participant. The affected family members assessed were chosen for this preliminary study because it was felt that they would be able to cope with the demands of these tests in terms of understanding the task requirements and maintenance of attention. However, data collection is time consuming and relatively undemanding of the participant, which may result in attentional lapses. It remains to be seen if the results reported in this chapter are maintained in a larger group analysis, including some of the less able affected family members.

4.4.2 Summary of results

In summary, four affected family members showed differential effects of priming for regular and irregular past tense. On a test of auditory lexical decision, they did not show a facilitation of response latencies for conditions in which a verb stem was primed by a regular past tense form of the verb. In contrast, they did show decreased response latencies for the condition in which a verb stem was primed by an irregular past tense form and for the condition in which a word was primed by another semantically related word. An explanation for the different effects under regular and irregular past tense priming conditions in the affected family members is that they have difficulty in breaking down the morphologically complex words used as primes in the regular past tense condition. The words used as primes in the irregular past tense and the semantic conditions were monomorphemic and therefore cannot be disassembled into morpheme and stem. It is suggested that, in the affected family members, difficulties in producing complex morphological words in spontaneous speech, which are most likely related to their articulation deficits, may result in similar difficulties in receptive processing of such words. Such a difficulty might result in a failure of facilitation of the response latency to a morphologically related word.

On a word monitoring test examining three types of syntactic processing, the four affected family members were found to be insensitive to a specific type of syntax, namely auxiliary constraints on the verb. They showed increased word monitoring latencies for sentences containing auxiliary syntax compared to sentences

testing phrase structure rules and subcategory constraints on the verb. When the auxiliary syntax was violated by substituting a wrong auxiliary verb, word monitoring latencies did not significantly increase relative to the unviolated conditions. This pattern of results might be explained by the lack of auxiliary verbs in spontaneous language production of the affected family members. In contrast to the syntactic impairments observed using word monitoring, the affected family members were found to show sensitivity to two types of semantic processing. Thus, semantic processing in these affected family members is unimpaired.

Before drawing firm conclusions from these studies, further testing of additional family members is required. Different methods of statistical analyses of these data can result in different patterns of results. Effect sizes are weak; results, therefore, should be interpreted cautiously.

5. Auditory Processing in the KE Family

The affected and unaffected members of the KE family were compared on tests of auditory processing and dichotic listening. The auditory processing test involved sequences of nonverbal stimuli presented either with long or with short interstimulus intervals. The affected and unaffected family members demonstrated greater difficulty on this test at the shorter intervals and on the longer sequences, but there were no significant differences between the two groups. Similarly, the two groups did not differ on the dichotic listening test. Neither group showed the typical pattern of a right ear advantage in reporting dichotically presented digits. However, the affected group reported significantly fewer digits correctly compared to the unaffected group. This impairment, and a trend towards an impairment on the longer sequences of the auditory processing test, suggests a deficit in auditory working memory rather than a discrimination or sequencing deficit due to rapid changes in or presentation of auditory stimuli. The possibility that a working memory deficit may be a consequence rather than a cause of a developmental speech and language disorder is discussed.

5.1 Introduction

A significant number of investigations have demonstrated an auditory processing deficit in children with SLI (see Section 1.4.2 and references therein). These studies report that children with SLI have an impairment in discriminating auditory stimuli if the critical distinguishing information is brief, or if stimuli occur in rapid succession. The impairment is not evident if the same stimuli are either lengthened in duration or presented at longer stimulus intervals. Much of the information important for discriminating verbal stimuli relies on cues of relatively brief duration rapidly followed by further stimulation. The explanation that a deficit in language development could arise because of a failure to process such verbal stimuli is, therefore, a parsimonious one.

It has also been proposed that processing of brief or rapidly occurring stimuli is a specialisation of the left cerebral hemisphere and underlies the dominance of this hemisphere for language processing. Evidence for this proposal comes from investigations of patients with lesions and from functional imaging and dichotic listening studies. For example, Tallal & Newcombe (1978) showed that patients with left hemisphere lesions and aphasia were impaired at discrimination of consonant-vowel pairs but unimpaired at vowel discrimination. This pattern of impairment is the same as that seen in children with SLI (Tallal & Piercy, 1974). Functional imaging studies using positron emission tomography (PET; Johnsrude et al, 1997; Fiez *et al.* 1995) have shown increased left hemisphere activation during conditions in which stimulus transitions were short.

In dichotic listening tasks, competing information is presented simultaneously to both ears and discrimination or recall is assessed separately for each ear (Kimura, 1967). Since auditory pathways are primarily crossed, this method allows a relative comparison of performance mediated by each ear separately and, by inference, the hemisphere contralateral to the ear. This method has consistently shown a right ear advantage (REA), implying left hemisphere dominance, for processing of speech sounds (see Bryden, 1982, for a review). It appears that this dominance for processing speech sounds is due to the temporal nature of speech. Halperin, Nachshon & Carmon (1973) demonstrated a REA for nonverbal stimuli, such as tone sequences, that have a temporal pattern similar to speech, but a left ear advantage for nonverbal stimuli with no temporal pattern. Shankweiler & Studdert Kennedy (1967) reported that normal subjects showed a right ear advantage (REA) for consonant-vowel sounds, but no ear advantage for steady-state vowel sounds.

Further to this finding, Schwartz & Tallal (1980) reported that changing the duration of the formant transitions in consonant-vowel sounds altered the magnitude of the REA.

In order to establish whether the affected members of the KE family show auditory processing deficits similar to those seen in children with SLI, performance on the Tallal Auditory Repetition Test was measured. Further, if such a deficit exists, it is predicted that the hemispheric organisation of speech processing in the affected family members would be abnormal. Hemispheric organisation of speech processing was therefore assessed, using a dichotic listening test.

5.2 Methods

5.2.1 Participants

Seventeen family members, ten affected and seven unaffected, completed the Tallal Auditory Repetition Test. The age ranges were 11 to 78.75 years for the affected group (median = 17.9, mean = 30.1, SD = 23.0), and 11 to 23.67 years for the unaffected (median = 17.4, mean = 17.6, SD = 4.7). Of these, eight affected and six unaffected family members also completed the dichotic listening test. The age ranges were 12.7 to 49.3 years for these affected family members (median = 20.5, mean = 28.1, SD = 16.4), and 12.7 to 23.8 years for these unaffected family members (median = 21.9, mean = 20.1, SD = 4.3).

5.2.2 Materials and procedure

Auditory Repetition Test (ART)

The version of the repetition test designed by Tallal (Tallal & Piercy, 1974) and used in this study is the same as the one used by (Bishop *et al.* 1999) and referred to in that study as the Auditory Repetition Test (ART). In order to avoid confusion with other repetition tests reported earlier in this thesis, and for consistency across studies, the test will be referred to here in the same way.

The ART consists of a series of subtests that assess auditory discrimination and memory for sequences of stimuli presented with either long (500 ms) or short (10 or 70 ms) interstimulus intervals (ISIs), and at increasing sequence lengths. Only two stimuli are used throughout the test; these are two 75 ms tones, one with a fundamental frequency of 100 Hz (stimulus 1) and the other with a fundamental frequency of 300 Hz (stimulus 2). The sequences of tones were played via a tape-recorder at an amplitude that was comfortable for the participant and clearly audible. The ART consists of a training section, followed by the subtests of Association (one tone per trial), Sequencing (a sequence of two tones presented with a long ISI), Rate (a sequence of two tones with a short ISI), and subtests of Serial Memory for sequences increasing in length from three to seven tones presented with either long or short ISIs (see Table 5.1 for details).

In the training section the participant first had to learn the association between two tones and two buttons arranged vertically. The participant first heard stimulus 1 and was instructed to press the bottom button whenever this stimulus was presented. Stimulus 2 was then presented and the participant was instructed to

press the top button. Each stimulus was then repeated until the participant produced five consecutive correct button presses to each.

The Association subtest of the ART consists of 24 trials in which the two stimuli are presented in a fixed random order, one stimulus per trial. The participant was required to press the bottom button when stimulus 1 was presented and the top button when stimulus 2 was presented. Errors were corrected immediately. This subtest was scored as the number of correct trials out of 24.

The Sequencing subtest consists of four demonstration trials and 12 test trials, each presenting a two-tone sequence of stimuli 1 and 2 with a long ISI. The four possible sequences, namely 1-1, 1-2, 2-2, 2-1, were presented in a fixed random order. The participant was required to press the response buttons in the order corresponding to the presentation of the two-tone sequence. This subtest was scored as the number of correct trials out of 12, on the first administration of this subtest. If more than five errors were made then the participant was retrained and the Association and Sequencing subtests were repeated before going on to the Rate subtest.

The Rate subtest also consists of 12 test trials presented just like those in the Sequencing subtest, but with short ISIs. The participant was required to respond after hearing each sequence by pressing the response buttons as described above.

The Serial Memory subtests consists of sequences of stimuli 1 and 2 that gradually increase in length until a length of seven is reached or testing is discontinued. At each sequence length the participant is first tested on a subtest with long ISIs and then on a subtest with short ISIs. At sequence lengths of three, subtests consist of one demonstration trial and ten test trials; these were scored as the number of correct trials out of ten. At sequence lengths of four to seven, the subtests consist of one demonstration trial and five test trials; these were scored as the number of correct trials out of five. If more than 40% errors were made at either the slow or the fast rate on a given sequence length, then the participant was not given sequences of longer lengths at that presentation rate.

Table 5.1 *Details of subtests of the ART*

| <i>Subtest</i> | <i>Sequence length</i> | <i>ISI</i> | <i>Demonstration</i> | <i>Test Trials</i> |
|----------------|------------------------|------------|----------------------|--------------------|
| Association | Single tone | None | Training section | 24 |
| Sequencing | 2 tones | Long | 4 trials | 12 |
| Rate | 2 tones | Short | None | 12 |
| SM 3 Slow | 3 tones | Long | 1 trial | 10 |
| SM 3 Fast | 3 tones | Short | 1 trial | 10 |
| SM 4 Slow | 4 tones | Long | 1 trial | 5 |
| SM 4 Fast | 4 tones | Short | 1 trial | 5 |
| SM 5 Slow | 5 tones | Long | 1 trial | 5 |
| SM 5 Fast | 5 tones | Short | 1 trial | 5 |
| SM 6 Slow | 6 tones | Long | 1 trial | 5 |
| SM 6 Fast | 6 tones | Short | 1 trial | 5 |
| SM 7 Slow | 7 tones | Long | 1 trial | 5 |
| SM 7 Fast | 7 tones | Short | 1 trial | 5 |

SM, Serial Memory; Long, ISI of 500 ms; Short, ISI of 10 or 70 ms

On all subtests involving sequences (Sequencing, Rate and Serial Memory), scores were calculated as proportions of the sequence identified correctly. If a participant was not given a sequence length because of making more than 40% errors at a shorter sequence length, then the participant received a score of zero for that sequence. The highest sequence length achieved with less than 40% errors, for long and short ISIs separately, was determined. Also, standard scores were calculated for each participant's overall performance on this test (S. Miller and P. Tallal, personal communication). Finally, two additional scores were calculated as suggested by Bishop *et al.* (1999): ART-G (a general performance measure) and ART-R (a rate-specific measure). ART-G was calculated by summing the raw scores for each subtest with sequences from two to seven, at both presentation rates. ART-R was calculated by summing the scores for the two subtests of sequence length two and three with short ISIs and dividing that score by the sum of the scores for the same two subtests with long ISIs.

Dichotic listening test

Participants listened to sequences of digits recorded on tape by a female speaker and presented at a rate of about two per second (Kimura, 1961). These were

played back through digital monitor stereophonic headphones (Gamma LH 735). There were three conditions of presentation: monaural, alternating, and dichotic. In the monaural condition, three series of six digits each were presented separately to each ear, for a total of 18 digits per ear. In the alternating condition, digits in each series were presented alternately to the two ears, with no stimulus overlap. There were eight series of six digits, three digits to each ear, for a total of 24 digits per ear. Half of the series began with left ear presentation and half with right. In the dichotic condition, each series was divided into paired digits presented simultaneously to the two ears, one digit to each, synchronised for voice onset. There were twelve series of six digits, three digits presented to each ear, for a total of 36 digits per ear. The participants were told they would hear digits in both ears and that they were to report orally as many digits as they could recall, in any order. The number of digits correctly reported per ear was scored for each condition separately. In addition, the raw data for the dichotic condition were converted to laterality coefficients so that the distribution of responses between ears could be analysed independently of accuracy. This coefficient was defined as the number of digits correctly reported from the right ear minus the number correctly reported from the left ear, divided by the total number of errors from both ears.

5.2.3 Analysis

For the ART, the affected and unaffected groups were compared using an ANOVA with two repeated measures: sequence length (two, three, four and five tone sequences²) and ISI (long vs. short). In addition, the group means for individual subtest scores, the highest level achieved at long and short ISIs, the standard scores, and the ART-G and ART-R scores were compared using independent t-tests.

For the dichotic listening test, the two groups (affected vs. unaffected) were compared using an ANOVA with a within-subject factor of ear (left vs. right) for each condition separately. An independent t-test was used to compare the mean laterality coefficients of the two groups.

² There was no variance in the scores obtained for sequence lengths greater than five with short ISIs.

5.3 Results

5.3.1 Auditory Repetition Test (ART)

The groups of affected and unaffected family members did not differ significantly in mean age at testing, although the age range of the affected group was considerably wider than that of the unaffected group as it included four affected adults from the first and second generations. Also, three family members (two affected and one unaffected) achieved fewer than ten out of 12 correct responses on the Sequencing subtest (i.e. sequences of two tones presented with long ISIs), indicating that they did not fully understand the requirements of the test. Therefore, the analyses were run three times, once with all participants included, once without the four adults of first and second generations, and once without the three participants who had performed poorly on the Sequencing subtest. These analyses did not yield appreciably different results. Those reported below are from the analysis which excluded the three participants who did not achieve ten out of 12 correct responses on the Sequencing subtest. The scores derived from the ART did not correlate significantly with age at testing, nor with any of the IQ scores (VIQ, PIQ or FSIQ). There were highly significant main effects of sequence length ($F(3,36)=111.68$, $p<0.001$) and ISI ($F(1,12)=155.73$, $p<0.001$). However, the main effect of group fell short of significance ($F(1,12)=3.92$, $p=0.071$), and there was no interaction between this factor and either of the two repeated measures. Further, independent t-tests did not reveal significant differences between the two groups on any of the subtest scores derived from the ART. Finally, nonparametric statistics likewise failed to reveal any significant differences between the two groups. The results are shown below in Table 5.2, Figure 5.1 and Figure 5.2. Despite these negative findings, it may be noted that, on both long and short ISIs (Figure 5.1 and Figure 5.2, respectively), the mean of the affected group fell more than two standard errors below that of the unaffected group on one or more sequence lengths.

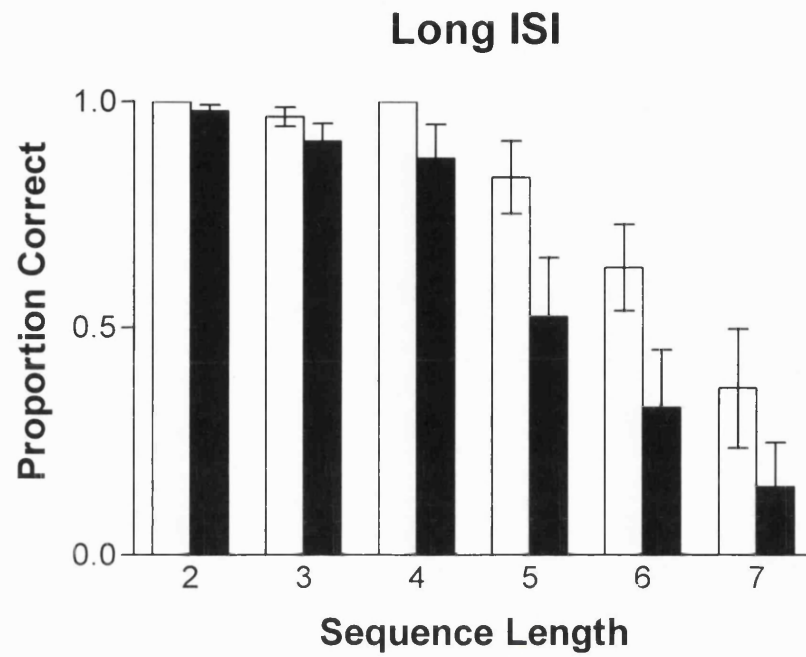


Figure 5.1 ART subtest with long ISIs. Filled bars, affected group; unfilled bars, unaffected group; error bars, standard error of the mean.

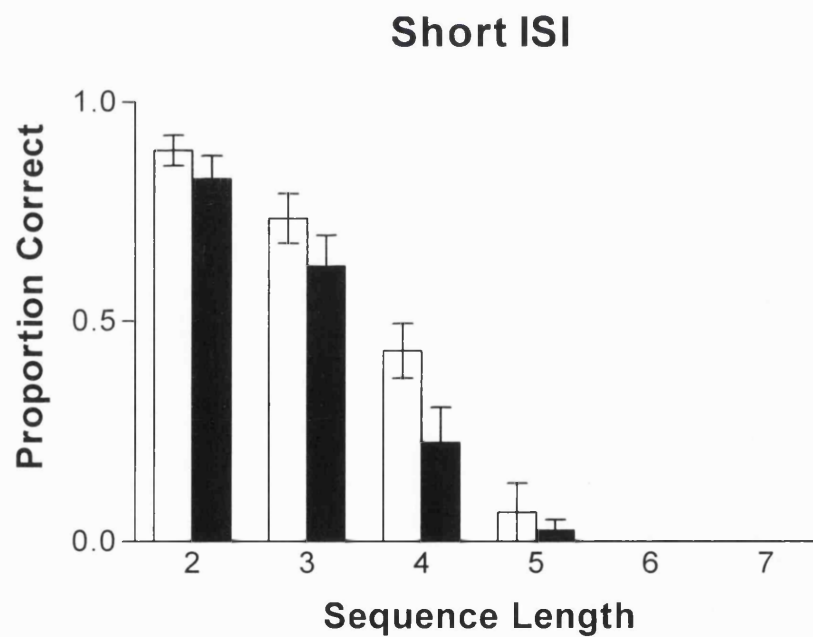


Figure 5.2 ART for subtests with short ISIs. Filled bars, affected group; unfilled bars, unaffected group; error bars, standard error of the mean.

Table 5.2 Means \pm SD for scores derived from the ART.

| <i>Variable</i> | <i>Affected (N=8)</i> | <i>Unaffected (N=6)</i> |
|---------------------------------|-----------------------|-------------------------|
| ART-G | 47.63 \pm 9.55 | 56.33 \pm 4.41 |
| ART-R | 0.77 \pm 0.14 | 0.83 \pm 0.08 |
| Association trials (max. = 24) | 24 \pm 0 | 24 \pm 0 |
| Longest sequence with long ISI | 5.25 \pm 1.49 | 6.00 \pm 0.89 |
| Longest sequence with short ISI | 2.62 \pm 0.74 | 3.17 \pm 0.75 |
| Standard score (100 \pm 15) | 99.02 \pm 15.22 | 101.51 \pm 9.76 |

Max., maximum score

5.3.2 Dichotic Listening Test

The affected group reported significantly fewer digits than the unaffected group in all conditions (monaural: $F(1,12)=7.04$, $p=0.021$; alternating: $F(1,12)=12.51$, $p=0.004$; dichotic: $F(1,12)=19.55$, $p=0.001$; see Table 5.3 and Figure 5.3). The difference in the number of digits reported for left and right ears, and the interaction between ear and group were not significant in any of the conditions. An independent t-test comparing the mean laterality coefficients of the two groups also revealed no significant difference (see Table 5.3 for the means, and Figure 5.4). Four of the eight affected family members and one of the six unaffected family members showed negative laterality coefficients, that is they reported more digits from the left ear than from the right, which is the reverse of the typical pattern for right-handers. Chi-squared tests of significance for these frequencies were not carried out because of the small group numbers.

Table 5.3 Means and Standard Deviations for the dichotic listening test

| Condition [/max. score] | Ear | Affected (n=8) Mean \pm SD | Unaffected (n=6) Mean \pm SD |
|----------------------------------|-----|---------------------------------|-----------------------------------|
| Monaural [/18] | L | 15.0 \pm 2.8 | 17.7 \pm 0.8 |
| | R | 15.8 \pm 2.0 | 17.7 \pm 0.5 |
| Alternating [/24] | L | 18.9 \pm 2.2 | 22.5 \pm 1.4 |
| | R | 18.4 \pm 3.1 | 22.8 \pm 1.3 |
| Dichotic [/36] | L | 22.8 \pm 4.8 | 30.0 \pm 1.4 |
| | R | 23.3 \pm 6.9 | 31.5 \pm 3.4 |
| Laterality coefficient [-1 to 1] | | 0.031 \pm 0.3 | 0.234 \pm 0.44 |

L, left ear; R, right ear

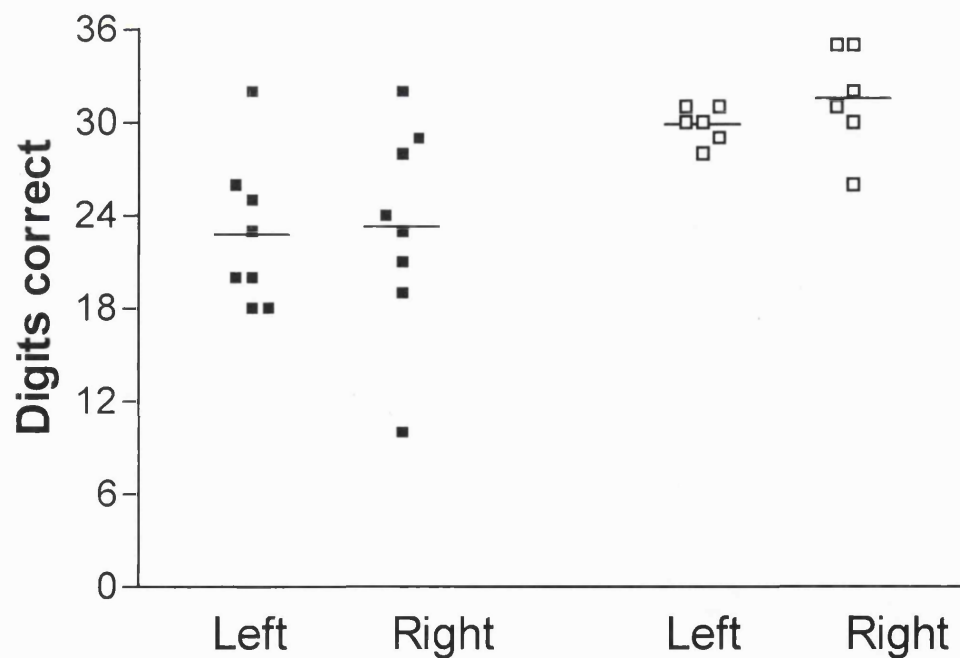


Figure 5.3 Dichotic Listening test. Individual scores per ear (Left and Right) under dichotic conditions. Filled squares, affected family members; unfilled squares, unaffected family members; horizontal bar, group mean.

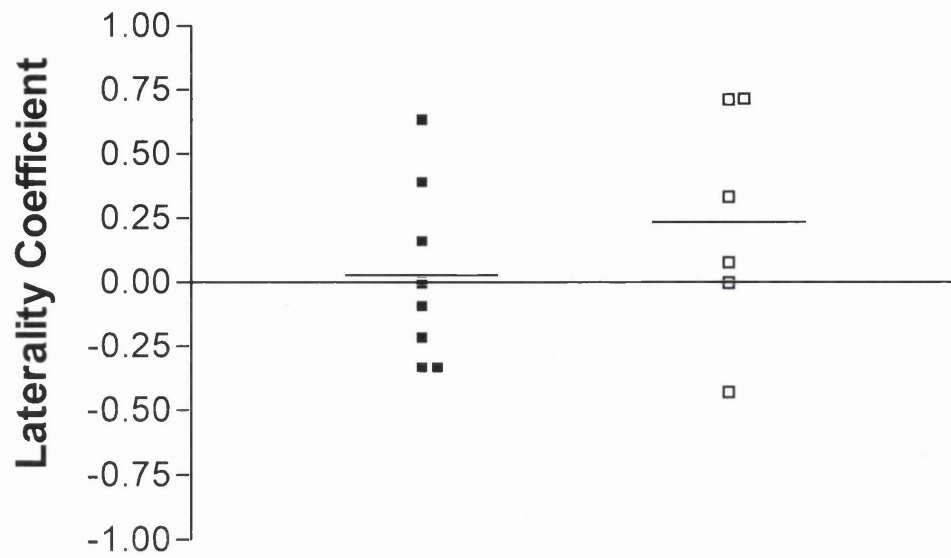


Figure 5.4 *Dichotic listening test. Individual laterality coefficients. Filled squares, affected family members; unfilled squares, unaffected family members; horizontal bar, group mean.*

5.4 Discussion

5.4.1 Auditory Repetition Test (ART)

The affected family members did not differ from the unaffected family members in performance on the ART. Both groups found the longer sequences of tones more difficult than the shorter sequences, and the sequences with short ISIs more difficult than those with long ISIs. If the affected group had a deficit in the auditory processing of rapidly presented material then they would be expected to show significantly greater difficulty than the unaffected group at sequences with short ISIs. In short, the crucial interaction was that between the length of ISI and group, and this was not significant.

One explanation for the lack of an auditory processing deficit in the affected members of the KE family is that they are considerably older than the children with SLI in whom such a deficit has been demonstrated. It has been reported that by early adolescence, children with SLI can achieve near normal performance on tests of auditory discrimination. Tallal *et al.* (1981) tested a group of children aged six and found that 19 out of 29 children with SLI failed to discriminate reliably between two synthetic speech sounds. Four years later the same children were retested by Bernstein, & Stark, (1985), who reported that only five children remained impaired on this task and that the SLI group did not differ in performance from controls. In addition, Lincoln *et al.* (1992) tested a group of adolescents and young adults with SLI using a version of the auditory repetition test similar to the one used in the present study. They reported that these individuals were at ceiling in their performance of the two-tone sequences whether these were presented with long or short ISIs, but that at longer sequences (six or seven tones) their performance was impaired, independent of the duration of the ISI.

Only eight of the family members tested (four affected, four unaffected) passed sequence lengths greater than five tones presented with long ISIs, and none passed sequence lengths greater than four tones presented with short ISIs. This may seem a rather low level of performance for both groups in view of Lincoln *et al.*'s (1992) report that the auditory deficits observed in their study of language-impaired subjects were apparent only on sequence lengths of six or seven tones; this means, presumably, that controls, at least, and some individuals with language impairment were able to perform these long sequence subtests to some degree. However, standard scores obtained for the KE family members ranged from 84 to 120 for the affected group and from 90 to 113 for the unaffected group (not including the three

participants who failed the Sequencing subtest), suggesting that the performances of individuals within both groups were unimpaired relative to normal control data.

5.4.2 Disorders of genetic aetiology and auditory processing deficits

A recent study by Bishop *et al.* (1999) suggests that the auditory processing deficits of children with SLI may not have a genetic aetiology. These researchers reported that in their investigation of a number of twin pairs, there was no significant heritability for performance on the ART. However, Tallal *et al.* (1991) showed that auditory processing problems were more evident in children with SLI who had a family history of language impairment than in those without such a history. In addition, using a conditioned head turning paradigm to estimate auditory thresholds in infants, Benasich & Tallal, (1996) found significantly elevated thresholds in those who were at high risk for SLI because of a positive family history of speech and language impairment. Clearly, further studies are needed to resolve the conflicting results of these studies. Whatever the outcome, however, it appears that the inherited speech and language disorder in the KE family is not accompanied by a frank auditory processing deficit.

5.4.3 Deficit in verbal working memory?

Bishop *et al.* (1999) found that whereas children with SLI were impaired on the ART relative to controls, this impairment was not related to the length of the ISIs; rather, they performed poorly at the longer sequence lengths. The same pattern of performances was observed in the language-impaired adolescents and young adults studied by Lincoln *et al.* (1992) as well as in the affected members of the KE family in the present study (although the difference between the affected and unaffected family members fell short of significance). These findings suggest that the ART deficit may be due to an impairment in verbal working memory rather than in processing rapidly changing auditory material. In Chapter 3, the possibility was raised that a deficit in articulation, particularly of the severe form present in the affected family members, could impair the development of verbal working memory because of poor verbal rehearsal through "inner speech" or subvocal articulation.

Even though a causal relationship between subtle deficits in auditory perception and in language comprehension is highly plausible (see Tallal, Stark & Mellits, 1985), a causal relationship between such deficits and severely impaired articulation is less plausible. Instead, poor auditory perception could well be a consequence of poor speech production. Locke (1988) suggested that the child's own speech production may make the task of analysing and organising speech sounds

more explicit. As speech movements are strongly related to the categories of phonemic sounds, recognition of the articulations related to auditory patterns might aid awareness of their phonological structure. Repetition of a word entails recoding auditory input in articulatory form and this facilitates a phonological analysis of the input. Repeated imitation of speech allows the child to become more accurate, gradually extracting the common patterns of articulatory production. By this argument, an auditory processing deficit in the KE family could have been expected due to the effect their impaired articulatory abilities might have on their perception and analysis of auditory material.

5.4.4 Dichotic Listening

The affected family members reported significantly fewer digits than the unaffected family members under all conditions of listening in the dichotic listening test. This is consistent with their impairment in digit span³ (see Vargha Khadem *et al.* 1995) and the suggestion that the trend towards an impairment on the longer sequence lengths in the ART may be due to a deficit in auditory verbal working memory. It is worth noting that, according to Thapar, Petrill & Thompson (1994), verbal short-term memory, as tested by digit span, is one area of cognition where genetic factors play little or no role. This is in line with the suggestion made above that the auditory working memory deficit in the affected family members is a consequence rather than a cause of a developmental speech and language disorder.

There were no significant laterality differences between the affected and unaffected groups on any of the conditions of the dichotic listening test. It was expected that the affected group might show an atypical pattern of hemispheric dominance for language but, as it turned out, the unaffected family members were also atypical as determined by this test. The finding of no significant REA in the affected members of the KE family is in accord with previous dichotic listening studies of children with developmental speech and language disorders (Witelson & Rabinovich, 1972; Sommers & Taylor, 1972; and Pettit & Helms, 1979). The finding of no significant REA in the unaffected family members, however, was surprising. One possible explanation is that this test is insufficiently sensitive for the study of small groups for which a more robust test may be required.

³ The scaled score for Digit Span was entered as a covariate in the above analyses even though it did not correlate significantly with the measures analysed, and, in fact, did not affect the results of those analyses.

5.4.5 Language lateralisation

The finding that children with SLI have problems processing brief, rapidly changing acoustic stimuli, a type of stimulus processing for which the left hemisphere is specialised, suggests left hemisphere dysfunction in these children. Isaacs *et al.* (1996) reported hemispheric reorganisation in some children with early left hemisphere brain damage based on the finding from dichotic listening tests of a left ear advantage (LEA) for speech stimuli in these particular children. The implication, however, is that the right hemisphere is also able to process rapidly changing auditory stimuli if the left hemisphere is injured and the injury occurs sufficiently early in development for reorganisation to take place. Why such reorganisation appears not to occur in children with SLI is unclear. One possible explanation is that the dysfunction of the left hemisphere in these children is not sufficiently severe to force hemispheric reorganisation. Another, suggested by studies of the neurological status of such children (Johnston *et al.* 1981), is that they have bilateral dysfunction.

Given that there was no clear-cut auditory processing deficit in the affected family members, the explanation for their abnormal pattern of hemispheric organisation for speech perception likewise is unclear. Perhaps the genetic anomaly in this family interfered directly with the normal development of language representation. Alternatively, the speech abnormality itself may have affected the way their language is represented in the brain.

5.5 Summary

The affected members of the KE family tested on the ART did not show a deficit in auditory processing. However, before concluding that their auditory perception is unaffected by their genetic abnormality, at least two possibilities must be considered. First, the deficit in processing rapidly changing auditory material is not a permanent one even in typical SLI populations. In this study, the period during development when such a deficit was present may have been missed. If so, it may be possible to detect it in the next generation by testing at earlier ages. Second, the ART may not be sensitive enough to detect a deficit in the affected family members. To reveal it may require the use of more items at the intermediate sequence lengths or of backward masking paradigms such as those suggested by Wright *et al.* (1997).

On the dichotic listening test, the affected and unaffected family members showed no clear pattern of hemispheric specialisation for language. The lack of a clear pattern in the affected family members could be a direct result of their genetic abnormality or a consequence of their abnormal speech. However, the lack of a clear pattern in the unaffected group as well favours an interpretation in terms of either the small numbers of family members tested or, once again, the inadequacy of the test employed in this study.

Part Three : Neuroimaging Studies

6. Abnormal brain function in the KE family: a positron emission tomography study

Positron emission tomography (PET) was used to investigate functional abnormalities in the brains of two affected members of the KE family. The paradigm used compared repetition of heard words with repetition of a single word whilst listening to reversed speech. Patterns of activation were compared between two affected family members and a group of four normal controls. The affected family members had regions of both underactivity and overactivity compared to the controls. These regions included a number of components of the motor system. It is suggested that this pattern of functional abnormality provides a plausible explanation for the impaired performance of the affected family members on tests of expressive language and oral praxis.

6.1 Introduction

Several PET studies have investigated the brain regions involved in language processing in normal volunteers (see Price *et al.* 1996, for a review). Activation in Broca's area (i.e., posterior inferior frontal gyrus) has been observed on a variety of tasks requiring auditory-verbal working memory, such as holding words in memory whilst either phonological or semantic decisions are made, related words are retrieved, or nonwords are repeated. Broca's area has been less consistently activated during word repetition tasks and auditory perception tasks. Wernicke's area has been observed to be activated during word repetition and phonological judgement tasks. Price *et al.* (1996) suggest that Broca's area is involved in both auditory word perception and repetition but that the detection of activation is dependent on task (more evident during repetition than hearing) and stimulus presentation variables (more evident when hearing words at a slow rate).

In collaboration with Dr. Cathy Price and colleagues at the Wellcome Department of Cognitive Neurology, PET was used to investigate patterns of activation during word repetition in two of the affected members of the KE family. Use of this paradigm in normal right-handed control volunteers (Price *et al.* 1996) reveals the major speech and language areas of the left hemisphere. The results presented here are also described by Vargha Khadem *et al.* (1998).

6.2 Methods

6.2.1 Participants

Two second-generation affected females, II-9 and II-20 in Figure 2.1, aged 43 and 49 respectively, underwent PET scanning. Both are of low average intelligence (full-scale IQ 80 - 89) and right-handed. At the time of this study, none of the other 13 affected family members could be scanned either due to poor health (I-2, II-6 and III-1), unavailability (III-20), or ineligibility for exposure to radiation⁴. Four right-handed, English speaking, male, normal control subjects, aged between 28 and 62 years, were also scanned.

6.2.2 Procedure

PET imaging was performed using H₂¹⁵O and a dedicated head scanner (Siemens 935B, CTI, Knoxville, USA). The two affected family members had the procedure explained to them by a researcher with whom they were familiar. They also practised the paradigm several weeks prior to the study to ensure that they would be able to perform the procedure. During the scan, the participants listened via headphones to either a pre-recorded tape of a male voice speaking real words at a rate of 40 stimuli per minute or a reversed recording of this tape. They were instructed to repeat the real words aloud and to say one pre-specified word ("crime") repeatedly when presented with the words played in reverse. Both conditions require acoustic processing and motor output, but repeating heard words also requires phonological analysis and reformulation of speech sounds into articulation plans. Each participant received six scans under each of the two conditions, presented in alternating order, for a total of 12 scans per participant and 72 scans across the six participants.

6.2.3 Image and Statistical Analyses

Image and statistical analyses were performed using statistical parametric mapping software (SPM; Wellcome Department of Cognitive Neurology). The images were reconstructed, resulting in a transaxial resolution of 8.5 mm full width at half maximum (FWHM) displayed in a 128 x 128 pixel format. In the axial dimension the resolution was 6 mm. The data were motion corrected, spatially normalised and resampled so that the size of each voxel in the transformed image

⁴ Children and women who could possibly be child-bearing are not scanned for research studies in the UK.

was 2.05 mm in the x and y dimensions and 4 mm in the z dimension (see below for discussion of coordinate system). These images were smoothed using an isotropic 16 mm kernel to account for variation in gyral anatomy and individual variability in structure-function relationships, and to improve the signal-to-noise ratio. The main effects of conditions and the interactions of pathology by condition were assessed using analysis of covariance (ANCOVA) and linear contrasts implemented in SPM. The coordinates of significant foci are given in standard stereotaxic space using a template image which conforms to the three-dimensional (3-D) coordinate system of Talairach & Tournoux (1988). Reported values are distances, in millimetres, from an anatomical origin, which is defined as the intersection of three orthogonal planes: a sagittal (vertical) plane through the longitudinal fissure; a coronal (vertical) plane through the anterior commissure; and a transverse (horizontal) plane through the anterior and posterior commissures (AC-PC line). In the x-dimension (parasagittal), values increase to the right of the origin and decrease to the left. In the y-dimension (coronal), values increase anteriorly and decrease posteriorly. In the z-dimension (transverse), values increase superiorly and decrease inferiorly. Thus the coordinates -10, 12, 48 denote the voxel in stereotaxic space that is 10 mm to the left of the longitudinal fissure, 12 mm anterior to the vertical (coronal) plane through the anterior commissure (VAC) and 48 mm above the horizontal plane through the AC-PC line.

6.3 Results

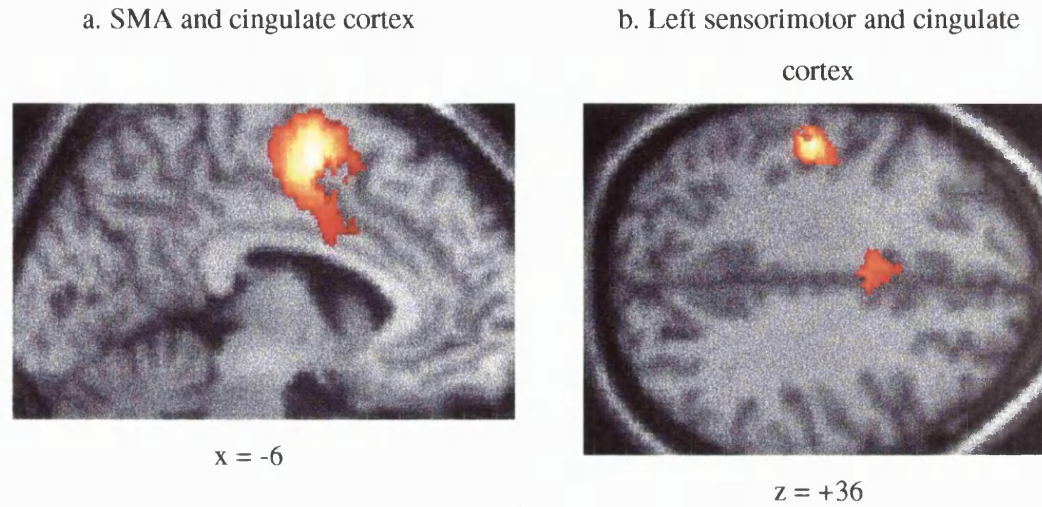
The results are shown in Table 6.1. Comparison of activation patterns in the two affected family members and the four controls (i.e. the interaction of pathology by condition) revealed differences in activation between these two groups in several brain regions. The supplementary motor area (SMA), underlying cingulate cortex, and preSMA/cingulate cortex (see Figure 6.1a) were not found to be activated during word repetition in either of the affected family members, whereas all of these areas were activated in the controls. The left sensorimotor face and mouth region (see Figure 6.1b) was also underactive in the two affected family members compared to the controls, as was a region of the middle temporal lobe. Although underactive, these regions were significantly activated during word repetition relative to baseline in both affected family members. The head and tail of the left caudate nucleus (see Figure 6.1c), the left premotor cortex with a ventral extension into Broca's area (Brodmann's area (BA) 44; Figure 6.1d), and a left ventral prefrontal area (BA 47/45) were significantly overactive in the affected family members compared to the controls, as was the left angular gyrus.

Table 6.1 Results of SPM analysis of PET data

| Anatomical Region | Coordinate (x,y,z) | | | Z score |
|--|--------------------|-----|----|---------|
| <i>Underactive in affected family members</i> | | | | |
| L. SMA / cingulate cortex (BA 6/24) | -10 | 12 | 48 | 6.05 |
| | -6 | -2 | 56 | 6.05 |
| | -2 | -4 | 48 | 6.05 |
| L. Sensorimotor cortex (face, lips) (BA 3/4) | -50 | -20 | 36 | 4.77 |
| L. Middle temporal cortex (BA 21) | -56 | -54 | 4 | 3.12 |
| <i>Overactive in affected family members</i> | | | | |
| L. Ventral prefrontal cortex (BA 47/45) | -46 | 32 | -4 | 3.27 |
| L. Premotor cortex (BA 6) | -26 | 18 | 36 | 3.49 |
| | -24 | 18 | 48 | 3.32 |
| L. Caudate nucleus (head) | -2 | 14 | 8 | 3.77 |
| L. Broca's area (BA 44) | -46 | 10 | 20 | 3.27 |
| L. Caudate nucleus (tail) | -18 | -32 | 16 | 3.01 |
| | -28 | -38 | 16 | 3.23 |
| | -22 | -42 | 12 | 3.96 |
| L. Angular gyrus (BA 39/19) | -42 | -72 | 32 | 3.37 |
| | -36 | -76 | 36 | 3.40 |
| SMA, supplementary motor area; BA, Brodmann's area; L, left; | | | | |

SMA, supplementary motor area; BA, Brodmann's area; L, left;

Areas underactive in affected family members



Areas overactive in affected family members

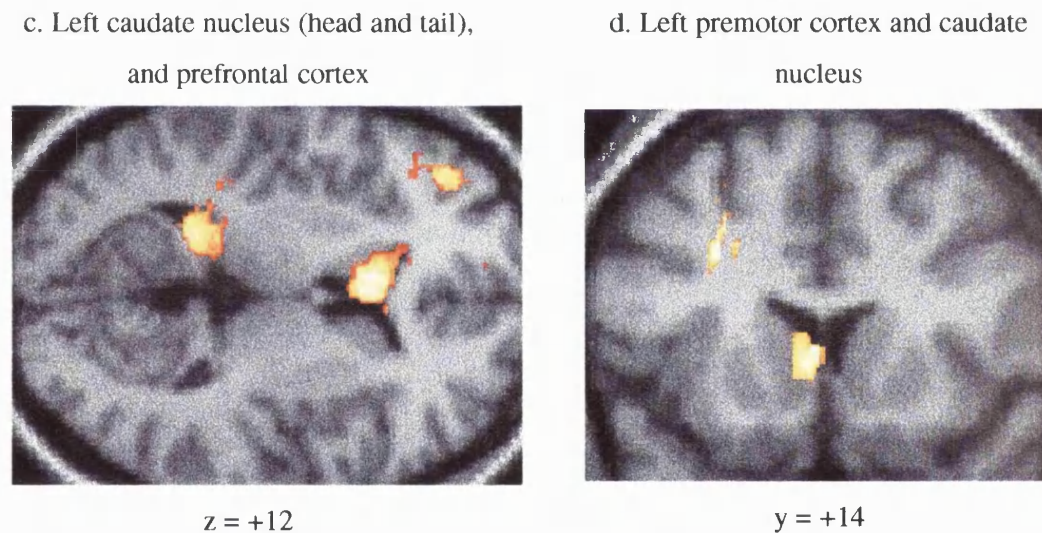


Figure 6.1 Results of SPM analysis of PET data. Coloured areas are regions that are either *underactive* (a. and b.) or *overactive* (c. and d.) in the affected family members compared to the activation seen in the control subjects.

- a. Parasagittal section through left hemisphere, 6 mm from midline.
- b. Transverse section, 36 mm above the transverse plane through the AC-PC line.
- c. Transverse section, 12 mm above the transverse plane through the AC-PC line.
- d. Coronal section, 14 mm in front of the coronal plane through the AC.

6.4 Discussion

Two affected family members were scanned with PET during word repetition and a control condition (baseline). Although these individuals have difficulty repeating words, in that their articulation is not as clear as that of controls (see previous chapters), they were able to meet the requirements of both conditions and repeated all the words presented.

Price *et al.* (1996; Experiment 2) reported the PET results obtained in normal subjects during word repetition versus the control conditions (i.e. saying “crime” to reversed words). Significant activations were reported in the SMA, anterior cingulate cortex, Broca’s area (BA 44), sensorimotor cortex (lateral and medial), inferior temporal cortex, and posterior middle temporal cortex (BA 21) of the left hemisphere, in the thalamus of the right hemisphere, and in the cerebellar vermis. The report of Price *et al.* (1996) also described further experiments that compared either repeating or listening to words with rest rather than with repeating one word while listening to reversed words. Under such conditions bilateral activations were seen, principally in the temporal lobe, which were linearly related to the rate of word presentation.

Underactivation of medial and lateral motor cortex

The most significant finding in the present study was the lack of activation of the SMA and adjacent cortices (see Figure 6.1a) in the affected family members during word repetition compared to baseline. Normally the SMA is significantly activated during tasks requiring volitional action (Passingham, 1993) and, indeed, all of the controls in this study showed significant activation of the SMA in the word repetition condition compared to baseline. In this experiment and others, the SMA is consistently activated whenever articulation occurs, and this activation increases in conditions where different words are repeated, compared to conditions requiring automatic responses such as saying the same word repeatedly. The failure to see significant activation of the SMA in the two affected family members could be due either to an absence of activation in both conditions or to activations that were not statistically different in the two conditions; and, in the latter case, either there could have been a failure to show increased activation during the repetition of different words or the SMA may have been overactive (compared to controls) during the baseline condition, i.e. during repetition of the same word.

The left sensorimotor cortex was also found to be underactive (see Figure 6.1b) in the two affected family members relative to the controls, although this region

was activated by word repetition relative to baseline in both groups. This region is commonly activated bilaterally during conditions requiring articulation of words, whereas it is not activated on either side during listening conditions when no articulation is required (Price *et al.* 1996). Murphy *et al.* (1997) also showed significant bilateral activation of a region of sensorimotor cortex (Talairach co-ordinates -42, -18, 32 and 46, -16, 32) during conditions requiring articulation of speech whilst controlling for breathing and language content. This region on the left is very close to the one that was underactive in the affected family members (Talairach co-ordinates -50, -20, 36).

Overactivation of the caudate nucleus and frontal cortex

The head and the tail of the caudate nucleus were overactive during word repetition (see Figure 6.1c) in the two affected family members. Although the role of the caudate nucleus in learning and sequencing motor programs is well known, an increasing number of reports suggest that it also has a role in the regulation of speech and language (Ullman *et al.* 1997; Lieberman *et al.* 1992; Pickett *et al.* 1998). The caudate nucleus receives projections from many cortical areas and projects to other basal ganglia nuclei and back to frontal cortical areas via the thalamus. Lesions of thalamic nuclei belonging to these circuits have also been shown to interfere with speech and language. Further, electrical stimulation of both the caudate nucleus and the thalamus have produced vocalisations in patients during surgical procedures (Ojemann, 1983; c.f. electrical stimulation of cortical areas which usually produces speech arrest).

Pathology of the basal ganglia is known to cause overactivation of the premotor cortex and other frontal cortical areas in patients with dystonia (Ceballos Baumann *et al.* 1995). In the affected family members, overactivation of three frontal cortical areas was observed. These were a premotor area and anterior and posterior parts of the left inferior frontal gyrus. Case reports, functional imaging studies and intra-operative stimulation investigations suggest these areas are involved in motor tasks both related and unrelated to speech, as described in further detail below.

Graff Radford *et al.* (1986) reported a single case of an acquired foreign "accent" following a stroke which led to infarction of premotor cortex (Brodmann's area 6) and the white matter anterior and superior to the head of the caudate nucleus of the left hemisphere. The patient demonstrated a transcortical motor aphasia. Price *et al.* (1996) reported that, in the normal subjects, the posterior part of the left inferior frontal gyrus (BA 44) was activated, often with adjacent premotor cortex, by

repetition and reading aloud. Contrasting repeating and listening suggested that activity in BA44 is related to speech production. This area extends 15-20 mm caudal to the anterior part of the left inferior frontal gyrus, which is possibly associated with speech perception. Thompson Schill *et al.* (1997) suggested that the activation in the left inferior frontal gyrus was qualitatively and quantitatively different under conditions in which the subject was required to generate a verb when presented with a noun for which there are a number of commonly associated verbs (e.g. for "ball", kick, roll, bounce, throw, etc.) compared to a noun that has just one typical verb association (e.g. for "kite", fly). In short, this area of the left inferior frontal gyrus shows greater activation when the subject is engaged in search among a number of competing verbal responses than when the response is a more "automatic" association. The posterior region of the left inferior frontal gyrus has also been shown in PET studies to be activated during motor tasks that are unrelated to speech, e.g. in the normal execution of hand or arm movements (Schlaug, Knorr & Seitz, 1994), as well as during movement of a paralysed hand in patients with subcortical infarctions (Chollet *et al.* 1991). Finally, Ojemann (1983) has shown that electrical stimulation of this area impairs the mimicry of orofacial movements.

Abnormal activation of temporal and parietal cortex

The middle temporal gyrus was found to be significantly underactivated in the two affected family members during word repetition compared to listening to reversed speech. Price *et al.* (1996) reported that, when contrasted with rest, listening to or repeating words activated dorsal temporal regions bilaterally in normal subjects, but that these activations were largely abolished when the contrast was with listening to reversed speech, as in our study. The latter contrast produces significant activation of the temporal lobe with a peak in the middle temporal gyrus, and this activation is associated with the lexical and semantic processing of heard words. A possible explanation of why this region was significantly underactive in the two family members is that their poor articulation may be associated with a low level or deviant semantic processing of heard words (although see previous chapters).

Finally, the left angular gyrus was significantly more active in the two family members than in the four controls. Although this is a region known to be involved in language processing, particularly reading (Menard *et al.* 1996), it is not activated in normal subjects during word repetition contrasted with listening to reversed speech (Price *et al.* 1996). Perhaps in the affected family members, the activation of language

areas that are not normally activated by word repetition is due to increased demands that this task makes on their impaired language system.

Overactivation and skill

The relationship between the level of activity of a region and a particular ability or skill is not known. Modayur *et al.* (1997) reported that female patients of low verbal ability show disruption of speech when stimulated electrically over a greater number of perisylvian sites than female patients with high verbal ability. This suggests that ability, or mastery of a skill, at a behavioural level is reflected in the amount of cortex needed for the behaviour. In line with this notion, Raichle *et al.* (1994), using PET, demonstrated that mastery or “automatisation” of a skill may actually result in a reduction in the amount of cortex activated during performance of such a skill (see Toni *et al.* 1998, for a discussion of activation in motor sequence learning). The pattern of overactivity seen in the two affected family members could thus be compensatory, reflecting more effortful speech by these individuals. Alternatively, the overactivation could reflect a primary functional abnormality that interferes with their speech.

6.5 Summary

In conclusion, the PET study demonstrated functional abnormality in a number of components of the affected family members' motor system, including (but not limited to) SMA, caudate nucleus, motor cortex, and inferior frontal cortex. It is likely that this abnormal pattern of activation is related to their poor motor control of speech as indicated by their impaired performance on tests of word and nonword repetition and of oral praxis (see previous chapters). The task selected for the PET study, however, is known to probe only left hemisphere language areas. Whether the right hemisphere of the affected family members is functionally abnormal remains to be investigated.

7. Abnormal brain structure in the KE family: a voxel-based morphometry study

A new method of analysing structural magnetic resonance images was used to compare the amounts of grey matter in the brains of three groups of subjects: the affected members of the KE family, the unaffected members, and a group of age-matched controls. It was hypothesised that because of the nature of the disorder observed in the affected family members, brain regions associated with motor control and expressive language would be the ones to show a structural abnormality. Also, because this disorder persists throughout development and into adulthood, it was hypothesised that the underlying neuropathology would be bilateral; otherwise reorganisation or recovery of function could have been mediated by the intact hemisphere. Whole-brain morphometric analyses revealed a number of areas in which the affected family members had significantly different amounts of grey matter compared to the unaffected and control groups, who did not differ from each other. These areas included ones which had also been found to be functionally abnormal in the PET study, namely, motor- and speech-related brain regions. Several areas were bilaterally abnormal as hypothesised. One of the regions found to be bilaterally abnormal was the caudate nucleus, which is of particular interest because this structure was also found to show functional abnormality in the PET study. It is suggested that abnormal development of this nucleus is critically related to the presence of oral dyspraxia and poor articulation of speech, which are the principal deficits underlying the disorder shown by the affected members of this family.

7.1 Introduction

Magnetic resonance imaging (MRI) of the KE family revealed no structural abnormalities on visual inspection that could be correlated with the disorder seen in the affected family members. As described in Chapter 1 (see Section 1.4), this is a typical finding in developmental disorders, particularly those with a suspected genetic origin. The brain abnormalities are likely to take the form instead of anomalies in such variables as neuronal size and number, and these may be detectable only by studies of brain morphometry. There have been a number of brain morphometric studies of developmental disorders using either postmortem methods or analysis of in vivo structural images. These were reviewed in Chapter 1.

In the present study of the KE family, a relatively new technique was used to analyse structural images, namely voxel-based morphometry (VBM; Wright *et al.* 1995). Validation of the most striking findings was sought by performing direct volumetric measurements on structures of interest identified by the VBM analyses, because this is a new technique (see Chapter 8). VBM draws on statistical methods that were originally developed for positron emission tomography (PET) studies. It compares regional grey matter volume on a voxel-by-voxel basis, thereby generating a large number of comparisons and the need for statistical correction. It was important, therefore, to generate hypotheses that predicted in advance the regions of the brain that would be structurally abnormal in the KE family.

The most obvious feature of the disorder in the affected members of the KE family, evident even to the naive observer, is the unintelligibility of their speech. In some instances, such as when using rehearsed and overlearned phrases, and in comfortable, stress-free situations, speech can be clear, although even then intelligibility varies greatly among affected family members. In most situations and on behavioural testing, however, every affected family member can be identified as such on the basis of impaired control of the oral musculature for both speech and nonspeech movements (see earlier chapters, and Vargha Khadem *et al.* 1998). This impairment in motor control is evident throughout development and persists into adulthood. It was therefore hypothesised that the underlying neuropathology would involve one or more components of the motor system, particularly one or more of those that showed functional abnormality in the PET study.

When a focal lesion to the dominant hemisphere is acquired during childhood, gross or persistent disturbance of speech and language is rarely seen (Hecaen, 1976), presumably because of a capacity for reorganisation of these

functions in the undamaged hemisphere. When language functions fail to reorganise following childhood insults, bilateral pathology is therefore suspected (Vargha Khadem, Watters & O'Gorman, 1985). Indeed, as indicated earlier in Chapter 1 (see Section 1.4), some of the previous morphometric studies, including the early postmortem findings in dyslexia, reported bilateral abnormalities in the brains of developmentally disordered populations. Therefore, a second hypothesis was proposed, namely, that the underlying neuropathology would be bilateral.

7.2 Methods

7.2.1 Participants

Ten affected and seven unaffected family members were scanned. Of the affected family members, four were adults from the first and second generations of the family, and the remaining six were third generation members ranging in age from 9 to 21 years. The unaffected family members were from the third generation and ranged in age from 9 to 27 years. Age- and sex-matched controls were selected from a database of scans of volunteers. For two affected family members it was not possible to select sex-matched controls; the distribution of sexes, however, within the family and control groups was the same (9 female and 8 male in each). Only one affected family member (III-5) was left-handed.

7.2.2 Data acquisition

Family members and controls were scanned using a 1.5 Tesla Siemens system with a standard quadrature head coil. Three-dimensional (3-D) data sets of the whole head were collected using a T1-weighted MPRAGE (magnetisation prepared rapid acquisition gradient echo; (Mugler & Brookeman, 1990) sequence (TR = 10 ms, TE = 4 ms, TI = 200 ms, flip angle = 12°, matrix size = 256 × 256, field of view = 250 mm, partition thickness = 1.25 mm, 128 sagittal partitions in the 3rd dimension, acquisition time = 8.3 min). The neuroradiological reports based on these scans stated that there were no overt focal abnormalities detectable on visual assessment. The scans of III-9, however, showed a noticeable hemispheric asymmetry, with the left hemisphere being much larger than the right posteriorly.

7.2.3 Image analysis

Before statistical analyses were carried out on these 3-D data sets, the images were processed using methods implemented in the statistical parametric mapping (SPM) '96 software (Wellcome Department of Cognitive Neurology, London, UK) running in MATLAB (Mathworks Inc., Sherborn, MA).

Template construction

The 34 3-D data sets (from the 17 family members, 10 affected and 7 unaffected, and 17 age-matched controls) were spatially normalised by minimising the sum of squared differences between each one and a template image (Montreal Neurological Institute template) according to the basis function approach described by Friston *et al.* (1995). The mean image of these spatially normalised scans was smoothed to 8 mm full width at half maximum (FWHM) in order to generate a new template.

Image processing

The original 3-D data sets were processed in three stages: normalisation, segmentation and smoothing (see Figure 7.1). The first stage involved spatial normalisation to the new template, which was constructed as described above. This normalisation (transformation) involved a 12 parameter affine registration followed by a nonlinear registration using 756 parameters. The images were resampled to produce voxels of 1.5 x 1.5 x 1.5 mm using nearest-neighbour interpolation to preserve the original voxel intensities. In the second stage, the normalised images were segmented (partitioned) into grey, white, cerebrospinal fluid, and scalp images (Ashburner & Friston, 1997). The segmented images were probability images which classified each pixel based on both its signal intensity and its spatial location. Finally, in the third stage of image processing, the resulting grey matter images were smoothed using a 12 mm FWHM isotropic Gaussian kernel. This method creates a spectrum of intensities which can be thought of as images representing the local volume, or local regional density, of grey matter.

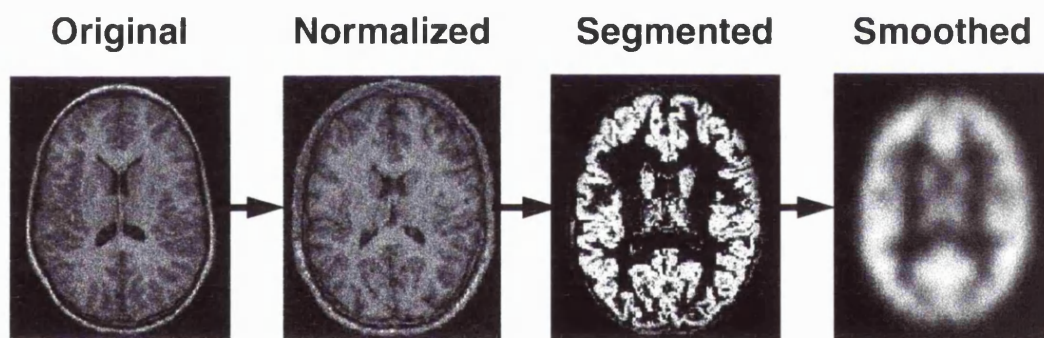


Figure 7.1 *The processing stages of image analysis. Note: original image is not in the same plane as other images and has a different magnification.*

Statistical Analysis

The processed images of the third-generation family members and their controls were analysed using the SPM software. The first- and second-generation family members were excluded from this analysis because there were no unaffected family members in this age group with whom they could be compared. An analysis of covariance (ANCOVA) with six planned linear contrasts was run with three groups, affected family members (n=6), unaffected family members (n=7), and an age-matched control group (n=13). The global amount of grey matter was used as a covariate in this analysis. Thus, the data underwent normalisation for the amount of grey matter in each data set, thereby allowing regional differences between data sets to be detected irrespective of the global differences in the total

amount of grey matter. For each of the three group comparisons, i.e. affected family members vs. unaffected, affected family members vs. controls, and unaffected family members vs. controls, there were two contrasts, one identifying regions in which a given group had more grey matter than their comparison group, and one identifying regions in which they had less grey matter. The results were displayed in statistical parametric maps of the t statistic for voxel values for each contrast. These t maps were transformed to the unit normal distribution (Z) and thresholded at 2.33 ($p=0.01$). The significance of the difference for each region was estimated using distributional approximations from the theory of random Gaussian fields. This characterisation is in terms of the probability that the peak height observed (or higher) could have occurred by chance over the entire volume analysed (i.e. a corrected p value of <0.05). An uncorrected p value of <0.0005 was used for regions that had been predicted in advance. These regions were those that showed functional abnormality in the PET study, or were in other known anterior language or motor regions, or were the contralateral, homologous regions to any of the regions already identified. Regions that survived an uncorrected $p<0.0005$, but were not predicted in advance, are listed in the Appendix.

7.3 Results

The contrasts between the unaffected family members and the control group did not reveal any areas of significant difference in grey matter volume that survived a correction for multiple comparisons. There were no hypotheses about structural differences between these two groups and therefore no regions were predicted in advance to be structurally abnormal. Even so, regions that survived an uncorrected statistical threshold of $p < 0.0005$ are listed in the Appendix, and none of these was a region that either showed functional abnormality in the PET study, or was a known anterior language or motor region (i.e. a region predicted in advance for the comparisons involving the affected family members).

In the comparison of the affected family members and controls, a number of regions were found to be abnormal. Those in which the affected group have significantly less grey matter than the controls include the head of the caudate nucleus, areas within the sensorimotor cortex, the posterior inferior temporal cortex, and the cerebellum. All of these areas show bilateral abnormality (see Table 7.2; also Figure 7.2 a-c). The affected family members have significantly more grey matter than controls in anterior insular cortex bilaterally, the left inferior frontal operculum, the putamen and motor cortices bilaterally, the right cerebellum, and medial occipito-parietal cortex, clearly on the left but perhaps bilaterally (see Table 7.2; also Figure 7.3 a-f).

In the most critical comparison, that between the affected and unaffected family members, again a number of regions were found to be abnormal. The affected family members have significantly less grey matter than the unaffected in the regions listed in Table 7.3 (see also Figure 7.2 d-g). These include two regions in the left inferior frontal cortex dorsal to the operculum, the head of the caudate nucleus bilaterally, and a region within the SMA. Finally, the affected family members have significantly more grey matter than the unaffected in the left frontal operculum, including anterior insular cortex and pars triangularis, the superior temporal cortex, including the planum temporale bilaterally, the putamen bilaterally, a region within right sensorimotor cortex, and the tail of the right caudate nucleus (see Table 7.3; also Figure 7.3 g-l).

Table 7.2 *Results of VBM analyses: affected family members versus controls*

| <i>Anatomical Region</i> | <i>Coordinates (x,y,z)</i> | | | <i>Z score</i> |
|---|----------------------------|-----|-----|----------------|
| <i>Less grey matter in affected family members</i> | | | | |
| Right caudate nucleus (head) ¹ | 14 | 20 | 9 | 4.93 |
| Left caudate nucleus (head) ¹ | -9 | 15 | 9 | 5.64 |
| Left caudate nucleus (head) ^{2,3} | -12 | 6 | 15 | 4.18 |
| Right sensorimotor cortex (BA3/4) ^{3,4} | 42 | -10 | 51 | 3.33 |
| | 52 | -14 | 36 | 3.53 |
| Left sensorimotor cortex (BA3/4) ³ | -39 | -20 | 45 | 4.07 |
| Right cerebellum ¹ | 33 | -39 | -52 | 4.82 |
| Left cerebellum ⁴ | -33 | -42 | -54 | 3.49 |
| Right inferior temporal gyrus (BA37) ¹ | 64 | -51 | -14 | 4.67 |
| Left inferior temporal gyrus (BA37) ⁴ | -66 | -38 | -18 | 4.21 |
| <i>More grey matter in affected family members</i> | | | | |
| Right anterior insular cortex ^{3,4} | 40 | 30 | -2 | 3.53 |
| | 33 | 26 | -2 | 3.37 |
| Left inferior frontal gyrus (BA45) ³ | -52 | 26 | 4 | 3.73 |
| Left anterior insular cortex ³ | -36 | 24 | 2 | 3.66 |
| Right putamen ³ | 27 | -8 | -3 | 4.50 |
| Left putamen ^{3,4} | -28 | -12 | -3 | 4.34 |
| Left motor cortex (BA4) ³ | -18 | -28 | 75 | 4.39 |
| Right motor cortex (BA4) ^{3,4} | 18 | -28 | 76 | 3.65 |
| Right cerebellum ¹ | 30 | -40 | -36 | 4.74 |
| Medial occipito-parietal cortex (BA19/7) ¹ | -3 | -75 | 27 | 4.72 |

BA, Brodmann's area; ¹ corrected $p < 0.05$; ² uncorrected $p < 0.0005$, but showed abnormal activation in the PET study; ³ uncorrected $p < 0.0005$, but a known motor or anterior language area; ⁴ uncorrected $p < 0.0005$, but symmetrical to one of the regions labelled with the superscripts 1, 2 or 3.

Table 7.3 Results of the VBM analyses: affected versus unaffected family members

| Anatomical area | Co-ordinates (x,y,z) | | | Z score |
|--|----------------------|-----|----|---------|
| <i>Less grey matter in the affected family members</i> | | | | |
| Left inferior frontal cortex (BA46) ³ | -50 | 27 | 20 | 3.78 |
| Left inferior frontal cortex (BA9/44) ^{2,3} | -50 | 22 | 28 | 4.09 |
| Right caudate nucleus (head) ^{3,4} | 14 | 20 | 9 | 3.78 |
| Left caudate nucleus (head) ¹ | -9 | 15 | 9 | 4.73 |
| Left SMA (BA6) ² | -10 | 10 | 48 | 4.04 |
| <i>More grey matter in the affected family members</i> | | | | |
| Left anterior insular cortex ³ | -36 | 24 | 2 | 3.76 |
| Left inferior frontal gyrus (BA45) ³ | -48 | 24 | 6 | 3.33 |
| Right putamen ³ | 27 | -8 | -3 | 3.88 |
| Left putamen ³ | -34 | -15 | -4 | 4.18 |
| Right tail of caudate nucleus ³ | 36 | -22 | -8 | 3.38 |
| Right superior temporal gyrus (BA22) ⁴ | 58 | -32 | 9 | 3.56 |
| Left superior temporal gyrus (BA22) ¹ | -57 | -38 | 9 | 4.89 |
| Right sensorimotor cortex (BA 3/4) ³ | 33 | -38 | 60 | 3.76 |

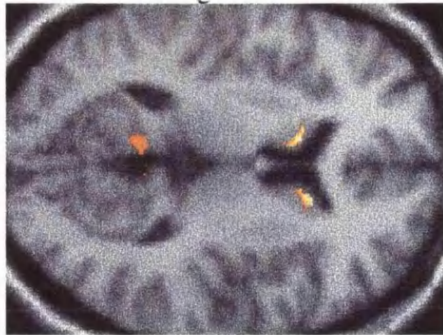
BA, Brodmann's area; ¹ corrected $p < 0.05$; ² uncorrected $p < 0.0005$, but showed abnormal activation in the PET study; ³ uncorrected $p < 0.0005$, but a known motor or anterior language area; ⁴ uncorrected $p < 0.0005$, but symmetrical to one of the regions labelled with the superscripts 1, 2 or 3.

In summary, the results of the VBM analysis showed that the affected family members have significantly less grey matter in the caudate nucleus bilaterally, when compared to both the unaffected family members and the age matched controls. The affected family members also have less grey matter than the unaffected members in the SMA region and in two regions within the left inferior frontal cortex. In addition, comparison with the age-matched controls revealed that the affected family members have significantly less grey matter in regions of the sensorimotor cortex, the posterior inferior temporal cortex, and the cerebellum, all bilaterally. The affected family members have significantly more grey matter in the left inferior frontal operculum and in the putamen bilaterally when compared with both unaffected family members and controls. When compared with just the unaffected

group they have significantly more grey matter in the planum temporale bilaterally, right tail of caudate nucleus, and a region of the right sensorimotor cortex. Finally, when compared with the control group only, they have significantly more grey matter in the anterior insulae and regions of the motor cortices bilaterally. The unaffected family members and the controls did not differ significantly in the amounts of grey matter in any region.

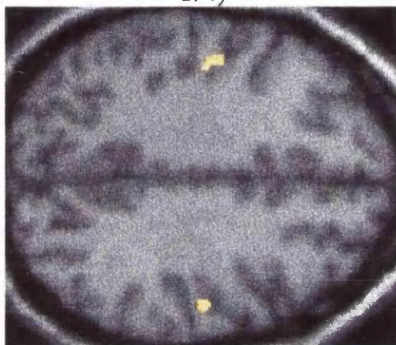
Affected vs. Controls

a. Left and right caudate nuclei



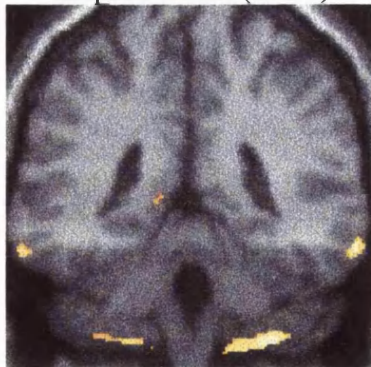
$z = 9$

b. Left and right sensorimotor cortex (BA 3/4)



$z = 45$

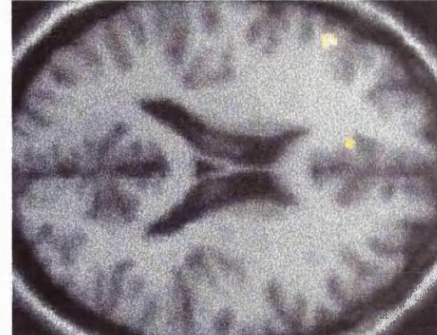
c. Left and right cerebellum and inferior temporal cortex (BA37)



$y = -39$

Affected vs. Unaffected

d. Left inferior frontal cortex (BA46)



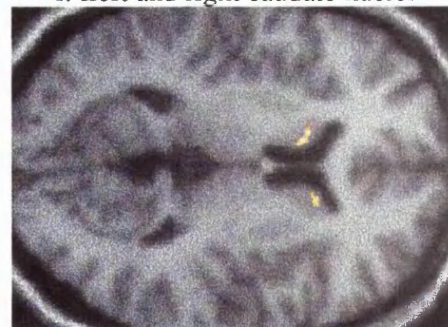
$z = 20$

e. Left inferior frontal cortex (BA9/44)



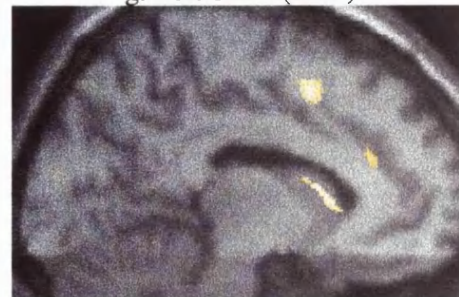
$x = -50$

f. Left and right caudate nuclei



$z = 9$

g. Left SMA (BA6)

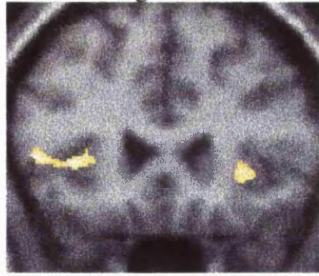


$x = -10$

Figure 7.2 Results of VBM analyses: regions where the affected group has significantly less grey matter than the controls (a to c) and unaffected group (d to g)

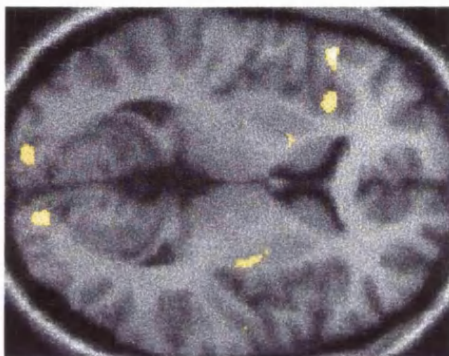
Affected vs. Controls

a. Left and right anterior insula



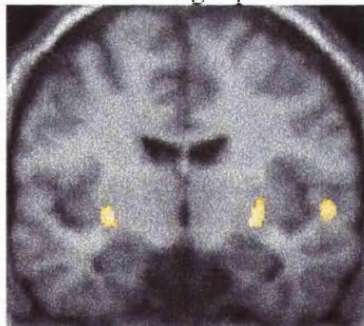
y = 20

b. Left inferior frontal cortex, left anterior insula and right putamen



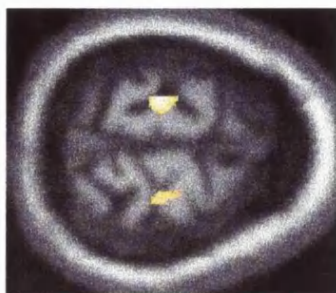
z = 4

c. Left and right putamen



y = -8

d. Left and right motor cortex (BA4)

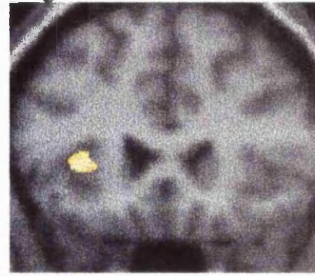


z = 75

(figure continues on next page)

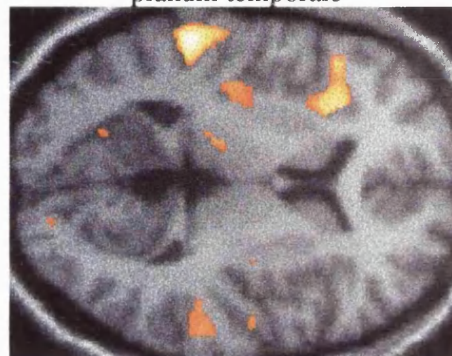
Affected vs. Unaffected

g. Left anterior insula



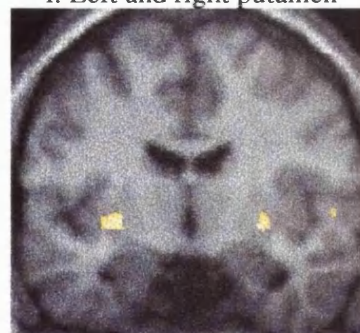
y = 20

h. Left inferior frontal cortex (BA45), left anterior insula and right and left planum temporale



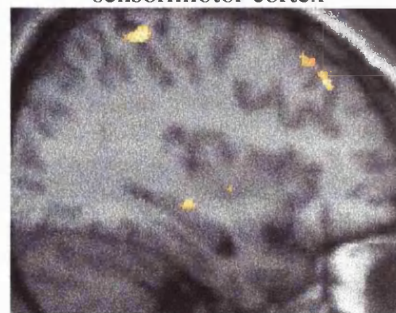
z = 4

i. Left and right putamen



y = -8

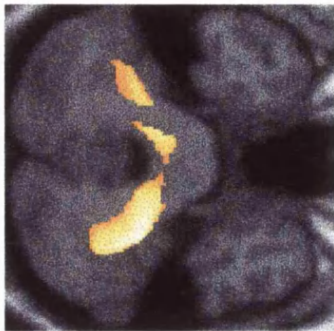
j. Right tail of caudate nucleus and sensorimotor cortex



x = 36

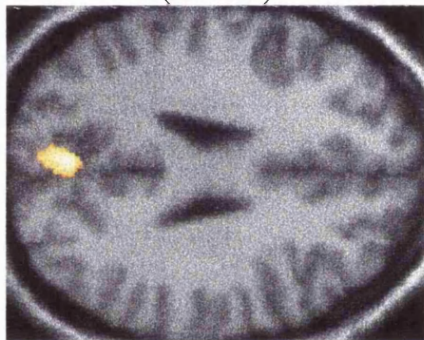
Affected vs. Controls

e. Right cerebellum



$z = -36$

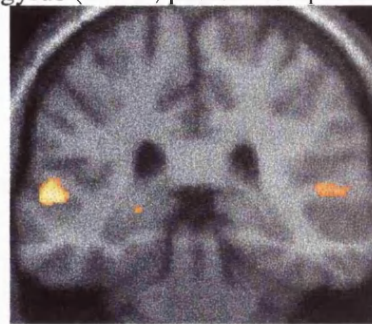
f. Right occipito-parietal cortex (BA19/7)



$z = 27$

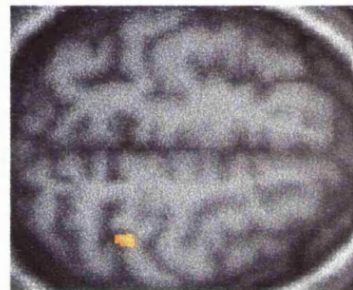
Affected vs. Unaffected

k. Left and right superior temporal gyrus (BA22; planum temporale)



$y = -38$

l. Right sensorimotor cortex (BA3/4)



$z = 60$

Figure 7.3 Results of VBM analyses: regions where the affected group had significantly more grey matter than the controls (a to f) and unaffected group (g to l). Coloured regions indicate significant differences; images thresholded at $p < 0.05$. For sagittal sections, x is the distance in millimetres from the vertical plane through the longitudinal fissure; for coronal sections, y is the distance in millimetres from the VAC plane; for transverse sections, z is the distance in millimetres from the horizontal plane through the AC-PC line.

7.4 Discussion

7.4.1 Discussion of morphometric methods using MRI

The use of MRI protocols now permits morphometric studies to be carried out *in vivo* and longitudinally, neither of which was possible with previous morphometric studies that relied on analysis of postmortem tissue. There are limitations to this method, however. For example, the spatial resolution of MR images obtained with a clinical imaging system for morphometric studies is typically one millimetre, which is several orders of magnitude less than the resolution required for visualisation of neuronal circuitry. There are also many problems with both measurement and analysis of MRI data for morphometric studies that deserve consideration.

Problems with morphometric analyses of MR images

It is now possible to obtain images of thin, contiguous, slices of the whole head with good in-plane resolution in a relatively short time. After suitable MR images have been collected, most morphometric studies require that the pixels be classified accurately into grey matter, white matter, and cerebrospinal fluid. This process is often referred to as image segmentation. Manual techniques of segmenting tissue boundaries are complicated by the fact that these boundaries are usually convoluted, and therefore the techniques are not only time-consuming but also error-prone. Automatic computer-based algorithms that speed up this process are largely reliant on the signal intensity of pixels, but this intensity is not an absolute measure. One of the major problems is signal intensity inhomogeneity. Identical regions of grey matter can have different signal intensities depending upon where in the head-coil they are situated, because of the inhomogeneity of the radiofrequency field of the head-coil in an MR system. Thresholding algorithms may therefore overestimate the amount of grey matter in some regions whilst underestimating it in others. The segmentation process is also hampered by the fact that not all intensity-based borders have sharp edges. Depending upon the resolution of the image, and in particular the thickness of the slice, many regions may contribute to the signal in a given pixel, leading to "partial volume effects". Thus, a pixel at an intensity border (and there are many such pixels) needs to be considered carefully, particularly if the slices are thick. Many previous methods of image segmentation either have been totally investigator-operated or have combined semi-automated methods with investigator input. Obviously, the greater the human

input, the greater the amount of subjectivity introduced into the study. The use of totally automated segmentation routines therefore has a number of advantages. The segmentation is reproducible, blind to subject identification, and also blind to the hypothesis being tested. It is dependent, however, on the quality of the raw data, and therefore the problems relating to field inhomogeneity and partial volume effects, described above, still apply.

Selection of subjects and controls for morphometric analyses

Proper selection of subjects for a morphometric study is important, particularly if group data are being analysed. In this case, the disorder under investigation must be clearly defined so that one can be confident that the sample is homogeneous. Proper selection of the control group is equally important, particularly in studies of familial disorders where controls are often drawn from the patient's immediate family and are presumed not to have the disorder under investigation. Other factors to consider are the morphological changes that occur during development and with ageing. Morphological differences that may be related to sex and handedness are also important considerations and may be confounded with variables of interest. Ideally, controls should be matched for all of these factors.

Voxel-Based Morphometry using SPM

The morphometric technique that was used in the present study required construction of a template image from the data sets to be analysed. The data sets were all obtained from the same clinical imaging system, thus minimising the system differences discussed above. The images were processed in three steps (see Figure 7.1): normalisation to the template, segmentation to produce grey matter images, and smoothing of these segmented images. The statistical analysis was then run in SPM to identify regional differences in the relative local amounts (or local volume density) of grey matter between groups of subjects.

The first step of image analysis was normalisation. The reason for normalising the data is to bring the individual data sets into a common anatomical reference frame within which the images can be statistically compared. Interindividual differences in brain size and shape need to be corrected so that regional differences in structure may be detected. The technique used here was fully automated and therefore much quicker than more traditional methods, which use manual measurement of regions-of-interest and correction for differences in cerebral size or volume. The technique, however, is not without criticism. In particular, the transformations that are applied to bring the data sets into register with a template

could conceivably correct differences between data sets that are of interest. In future studies it may be possible to obtain quantitative measures of the transformations required to map an abnormal data set onto a normal template, thereby quantifying the anatomical variability and structural changes associated with the disorder being investigated.

The segmentation step is perhaps the most important stage of the VBM analysis. Unlike previous implementations of this technique (see Wright *et al.* 1995), the current one is fully automated and the resulting images are not binary, as previously, but are continuous probability maps. The intensity of each voxel in a probability map reflects the probability that the voxel belongs to a particular tissue class. The T1-weighted images had good grey-white matter contrast with fairly high resolution. The segmentation process would be improved, however, if the variations in contrast due to radiofrequency field inhomogeneities were removed. The use of global normalisation at the analysis stage reduces the likelihood of detecting regional differences due to errors in the segmentation process. An example of such an error is global overestimation of the amount of grey matter due to poor contrast in the image. A problem for the segmentation process used in our study is presented by the tissue of the cerebellum. The relative amounts and thickness of cerebellar cortex and of cerebral cortex are quite different. The segmentation of the images is dependent upon the resolution of the images. At a resolution of approximately one millimetre, therefore, although good segmentation of cerebral cortex is achieved, that of cerebellar cortex is poor. However, poor segmentation of cerebellar tissues should not necessarily result in artifactual group differences. The analyses may be improved either by masking the signal from cerebellar tissue manually, or by applying a smoothing filter to this region of a different size from that used in cerebral cortex.

Smoothing the images creates a spectrum of grey matter intensities and facilitates the detection of regional differences in the relative amounts (or densities) of grey matter. The statistical model used in the analysis stage also requires that the data be smoothed. The paradox here is that having optimised imaging protocols in order to collect high resolution MR images, the smoothing stage of image analysis reduces that resolution. The higher resolution of the images (because of reduced partial volume effects), however, improves the segmentation stage of the image analysis, and smoothing after the segmentation stage allows for the statistical detection of differences in the thickness and regional dispersion of the grey matter.

The analysis treats the global amount of grey matter as a potential confound, and therefore the data are globally normalised for the amount of grey matter (i.e. the amount of grey matter is treated as a covariate). Thus, regional differences between scans are detectable irrespective of the global differences in the total amount of grey matter. The analysis is carried out on a voxel-by-voxel basis, so a large number of comparisons are made, many of which would reveal significant differences between data sets by chance. A correction for the number of comparisons is therefore necessary. SPM generates two statistics for each region identified as statistically different, one corrected for multiple comparisons and the other uncorrected. With an *a priori* hypothesis that a particular region is implicated in the disorder under investigation, it is appropriate to report uncorrected statistical differences between the groups.

In summary, a relatively novel technique for analysis of abnormalities in brain structure was used to examine the MRI data collected from members of the KE family. The technique was fully automated and implemented in SPM96 software, which is widely available. Since it was fully automated (i.e. noninteractive), it is completely reproducible, and does not involve many labour-intensive hours. The aim of using this technique is to identify statistically those regions of anatomical variation between groups of subjects that differ by a variable-of-interest, such as disease state, sex, or age. The technique uses a whole brain approach and is of particular use, therefore, in guiding the investigator to more specific region-of-interest analyses. While there are many questions that remain to be answered concerning this technique, its applications are potentially numerous and powerful.

7.4.2 Discussion of results

The results of the VBM analysis in the KE family and controls accord well with those from the PET study. A robust and highly significant result of these analyses was that the caudate nucleus had less grey matter bilaterally in the group of affected family members compared either to the group of unaffected members or to controls. Importantly, the caudate nucleus was also found to be functionally abnormal in the PET study, as was the SMA and areas within inferior frontal and sensorimotor cortices, all of which were revealed to be structurally abnormal in the VBM analyses. It is worth noting that the two affected family members studied with PET were not included in the VBM analyses reported here. Thus, there is converging evidence from different individuals drawn from the same population that these regions are abnormal with respect to both function and structure. The relationship

between the amount of grey matter in a region and its relative activity, however, is unknown and remains to be investigated. A simple explanation for the findings described is that areas with less than the normal amount of grey matter must increase activity above normal levels to produce behaviour similar to that produced by the normal area. Another possible explanation is that a behavioural impairment, such as poorly articulated speech, could result in underdevelopment of a region, thereby rendering its grey matter volume abnormally small. In the case of the caudate nucleus, however, reduced volume was associated with increased activity, whereas in the case of the SMA, reduced volume was associated with decreased activity. The two sets of results thus point to two different types of pathology.

Basal ganglia and language

The present finding that abnormal caudate nucleus structure and function are associated with developmental language disorder receives corroboration from other studies. Jernigan *et al.* (1991) performed a morphometric analysis using MRI scans and reported the caudate nucleus to be bilaterally reduced in volume in a group of children with SLI compared to matched controls. Also, Tallal, Jernigan & Trauner (1994) reported bilateral damage to the head of the caudate nucleus in a ten-year-old boy with a history of SLI and behavioural difficulties. Expressive language and articulation had been severely impaired in this boy at the age of four, although by age eight his expressive language had improved considerably.

In addition to the reduced amount of grey matter in the caudate nucleus, the affected family members were found to have increased amounts of grey matter in the putamen relative to the unaffected group and the controls (see Figure 7.3). Pathology of the putamen and caudate nuclei has been reported in association with aphasic symptoms in adult patients (Alexander, DeLong & Strick, 1986; Lieberman *et al.* 1992; Ullman *et al.* 1997) and some with this combined pathology also show oral and verbal dyspraxias. Aglioti *et al.* (1996) described a bilingual patient who, following a stroke that affected the putamen and the caudate nucleus of the left hemisphere, suffered aphasia of her mother tongue but not of her less practised second language. The patient also exhibited oral dyspraxia but performed normally on a test of ideomotor gestural apraxia. Prior to her stroke, the patient had hardly ever used her second language in speech, although she could understand it. Following the stroke, she spoke her second language with a foreign accent, a phenomenon that has been described previously in a patient with a lesion of the putamen (Blumstein *et al.* 1987). Aglioti *et al.* (1996) proposed that their patient's

basal ganglia lesion predominantly affected the more automated language of her mother tongue, whereas her second, less practised, language relies on other cortical and subcortical areas that were spared. Speedie *et al.* (1993) reported a bilingual patient who suffered a right basal ganglia lesion. This patient was impaired in producing, but not in understanding automatic speech, and was no longer able to sing, swear, use conventional social greetings and conversational fillers, or recite over-familiar verses and rhymes. This deficit affected both languages spoken by the patient. Further evidence of basal ganglia involvement, in particular of the putamen, in the articulation and motor control of speech comes from functional imaging studies. In normal healthy volunteers who were bilingual but had acquired their second language after the age of five, Klein and colleagues (Klein *et al.* 1995; 1994) reported increased PET activation of the left putamen during repetition in the second language, and during translation from the first language to the second. These authors attributed this increased activation to the increased articulatory demands, in particular motor timing, of word repetition and word generation in the second as compared with the first language.

Inferior frontal cortex and language

Many regions of left inferior frontal cortex have been implicated in the neural control of language, in particular Broca's area located in the posterior part of the left inferior frontal gyrus. The homologue of this region in the monkey is believed to be the rostral part of the ventral premotor cortex (F5; Rizzolatti & Arbib, 1998). This area in the monkey contains "mirror" neurons that fire both when the monkey carries out a specific action or gesture and when the monkey observes the experimenter making a similar gesture. Rizzolatti & Arbib (1998) suggest that a system for gesture recognition exists in humans and is located in left inferior frontal cortex (Broca's area), and also that this system may have evolved to include the orofacial movements necessary for speech and therefore human communication.

The analysis of the MRI scans of the KE family showed that the affected family members had an abnormally large amount of grey matter in the left frontal opercular regions (pars triangularis and anterior insular cortex; see Figure 7.3), and, in the comparison with controls, this abnormality was present in the right operculum as well. Further, when the affected group was compared with the unaffected group of family members, two regions of the left inferior frontal gyrus, located more dorsally than the previous regions, were found to have less grey matter volume (see Table 7.3 and Figure 7.2). As mentioned previously, PET studies have revealed two

areas of activation in the left inferior frontal gyrus during word repetition. Price *et al.* (1996) suggested that the more anterior area is involved in speech perception, whereas the posterior area is associated with production, since the latter area was activated in repetition conditions but not in listening conditions. The regions of the left inferior frontal cortex that had less grey matter in the affected compared to unaffected family members (see Table 7.3) are located more dorsally than both of the areas described by Price *et al.* (1996). The pars triangularis, however, had more grey matter in the affected family members than in both the unaffected group and the controls (see Table 7.2 and Table 7.3); this region is located close to the area that Price *et al.* (1996) suggested is involved in speech perception, and 14 mm anterior to the inferior frontal region that they found to be involved in speech production. Rather than having a role in speech perception, the former area may be active during inner speech, or subvocal articulation, which would be present during both listening and repetition, and therefore would not be differentially activated when these two conditions are compared. This latter interpretation seems preferable, since this area is structurally abnormal in the affected family members, and poor speech production implies impaired inner speech rather than impaired perception.

Insular cortex and speech

In addition to the structurally abnormal regions within inferior frontal cortex, a region of the insular cortex located close to the pars triangularis was also found to be abnormal in the affected family members. This group has significantly more grey matter in the left anterior insular cortex than the unaffected group, and more grey matter in the same region bilaterally than the control group. Dronkers, (1996) reported that a lesion to a specific area of left anterior insular cortex was necessary to produce an apraxia of speech in adult patients who had suffered stroke. Aphasic patients without apraxia of speech all had lesions sparing this part of the insula. Also, in a postmortem study of a young girl with language impairment, Cohen, Campbell & Yaghai (1989) reported a dysplastic gyrus in the insular cortex of the left hemisphere. This girl was described as having delayed expressive language and oromotor apraxia. Her brother, but no other close family members, was also diagnosed with language impairment (specifically the dysphonetic subtype of dyslexia) and was impaired at speech repetition.

Medial and lateral motor cortex and speech

The affected family members had significantly less grey matter than the unaffected members in the left SMA. This region in the affected members was also found to be functionally abnormal in the PET study, in that it did not show a difference in activation between the baseline and the word repetition condition. In classic intraoperative cortical stimulation studies (Penfield & Welch, 1951), stimulation of this medial frontal region was reported to interfere with voluntary limb and speech activities, findings recently corroborated by Lim *et al.* (1994). Also, stimulation of the SMA can produce complex, repetitive patterns of vocalisation (Woolsey, Erickson & Gilson, 1979). Patients with lesions of the left medial frontal cortices often have a period of muteness post-operatively. Following recovery they are able to repeat words and respond to questions, but residual deficits in spontaneous expression have been reported (Ziegler, Kilian & Deger, 1997; Jonas, 1981). For example, Jonas (1981) described four patients with medial frontal lesions who had dysfluent language, and two of the patients stuttered. The results of systematic experimental studies in animals (Ziegler, Kilian & Deger, 1997) are consistent with the view that the SMA plays a role in the preparatory aspects of sequential movements, especially in conditions involving short-term buffering of the motor response. Such conditions obviously apply to fluent speech, and Alcock (1995) demonstrated that affected members of the KE family had particular difficulty with the production of simultaneous and sequential orofacial nonspeech movements, but not with simple nonspeech movements.

The VBM analysis in the affected members of the KE family revealed still other structural abnormalities of the motor system. Two regions of primary motor cortex were identified as being bilaterally abnormal in the comparison of affected family members with the unaffected and control groups. The region with reduced grey matter in the affected group corresponds to the region identified in the PET study as functionally underactive during word repetition. This is a region identified by Murphy *et al.* (1997) as one that is activated bilaterally during speech, when breathing and language content are controlled for. The other region, which had increased grey matter in the affected group, is located dorsal and caudal to the first region. The literature provides no suggestions as to how this abnormality might be related to the behavioural and cognitive impairment of the affected members of the KE family.

Temporal and parietal cortex and language

A relationship between the posterior perisylvian cortex (Wernicke's area) and language function was suggested initially by Wernicke's description of patients with verbal comprehension deficits following lesions to this region (see Kolb & Wishaw, 1990, for review). In our study also, regions typically associated with receptive language function were found to be abnormal in the affected family members. They had significantly more grey matter in the *plana temporale* bilaterally. The coordinates for the abnormal region in the right hemisphere are 6 mm more anterior than those for the region on the left, reflecting the usual asymmetry of the auditory regions (Penhune *et al.* 1996). *En bloc* regions of interest which include the *planum temporale* have been found to be abnormal in many studies of children with developmental disorders, including language impairment (Plante *et al.* 1991). As described earlier, the *planum temporale* has been found to be structurally abnormal at the macroscopic and microscopic level in the brains of individuals with dyslexia. It should be noted, however, that in these studies the abnormality was usually due to a unilateral increase in the size of the *planum temporale* of the right hemisphere. Just as for other findings of abnormally large volumes of grey matter, the relevance of an increased size of the *planum temporale* is still unclear, but it has been speculated upon extensively. Geschwind proposed that, normally, a fixed amount of cortical language substrate develops to produce a structural asymmetry, typically with the left *planum temporale* larger than the right. He predicted that exposure to a delaying influence in the intrauterine environment differentially retards the growth of the left *planum* and produces a compensatory increase in the area of the right (Geschwind & Behan, 1982). Galaburda, however, rejects the notion of a fixed amount of language substrate, and proposes that a teratogenic agent acts to decrease the typical neuronal loss that results in the size asymmetry, thus allowing survival of cortical neurons that in normal development are reduced in number. This leads to an increased size of the right *planum temporale* and atypical symmetry.

The posterior inferior temporal gyrus (BA37) has less grey matter bilaterally in the affected family members than in the controls. In the left hemisphere this area has been related to reading and naming. The supporting evidence is based on lesion (Damasio & Damasio, 1983), electrocorticography (Nobre, Allison & McCarthy, 1994), stimulation (Luders *et al.* 1986), and functional imaging studies (Price *et al.* 1996).

Like the finding of increased activation of the angular gyrus in the PET study (see Section 6.4.1), the finding of increased amount of grey matter in the *planum*

temporale bilaterally was unexpected, because the disorder in the KE family is primarily one of expressive rather than receptive language. The bilateral nature of the abnormality in these areas, however, and the frequent association of this abnormality with other developmental disorders raises questions about cause and effect. It has been suggested (see earlier chapters) that, in cases with a primary expressive language impairment, other deficits may be a result of the adverse effect that such an impairment has on the development of language as well as on cognition generally. The findings described above of structural abnormalities in regions typically associated with receptive language suggest an extension of this hypothesis to include the structural level. Thus the development of cortical areas usually associated with receptive language may be adversely affected secondarily by the maldevelopment of cortical and subcortical structures typically associated with expressive language. However, until longitudinal studies are carried out starting at very early ages, it is not possible to determine whether functional impairment can indeed cause structural abnormality.

7.5 Summary

In summary, a relatively novel technique of image analysis was applied to the MRI scans of matched groups of affected and unaffected family members and controls. The results of this analysis revealed a number of areas with either significantly more or significantly less grey matter in the affected family members compared to the other two groups. The unaffected family members and controls did not differ significantly from each other. Many of the abnormalities were bilateral and located in motor-related areas known to be involved in the expressive aspects of speech and language. One region found to be bilaterally abnormal was the caudate nucleus, which was also found to show functional abnormality, in the form of overactivity, in the PET study of two affected family members (see previous chapter). These findings confirmed both of our initial hypotheses derived from a consideration of the affected members' behavioural profile. Further, the finding of both bilateral structural abnormality and functional abnormality in the caudate nucleus suggests that its abnormal development is critical to the development of oral praxis and articulation, the main deficits of the affected family members. Structural differences were also present, however, in areas more commonly associated with receptive language. It is clear that the defect at the genetic level gives rise to abnormal brain development, which leads to a functional impairment expressed mainly as an impairment in the articulation of speech sounds, but also in expressive language generally and even in receptive language. These several impairments and the underlying structural abnormalities will require a considerable amount of further study, particularly longitudinal study, to disentangle cause and effect among their interactions.

8. Morphometry of the caudate nuclei in the KE family: a quantitative volumetric study

The PET study and the whole brain morphometric analyses provided converging evidence of functional and bilateral structural abnormality of the caudate nucleus in the affected members of the KE family. The results of the morphometric analyses were further examined using a more detailed volumetric analysis of this structure. Pixel counting methods were used to measure the cross-sectional area of thin transverse slices throughout the caudate nucleus, allowing quantification of the volume and examination of volume changes as a function of slice position within the nucleus. The results confirmed that the volume of this nucleus was reduced bilaterally in the affected family members compared to the unaffected ones and a group of age-matched controls. This reduction in volume was found to be most evident in the dorsal slices through the nucleus. The volume of the caudate nucleus was significantly correlated with the performance of the affected family members on a test of oral praxis and a test of nonword repetition, providing further evidence of a relationship between the abnormal development of this nucleus and the impairments in oromotor control and articulation reported in the KE family. Further studies are needed, however, to establish the specific regions of frontal cortex that are related to the abnormal regions within the caudate nucleus, and to guide hypotheses about the abnormal neural circuitry that gives rise to the behavioural syndrome in the affected members of the KE family.

8.1 Introduction

The positron emission tomography (PET) study of two affected family members revealed functional abnormalities of several regions including the left caudate nucleus. In addition, one of the most robust findings of the whole brain morphometric analysis, known as voxel-based morphometry (VBM; see previous chapter), was that compared to either the unaffected group or the control group, the affected family members had significantly less grey matter in the caudate nuclei bilaterally. Thus, there is converging evidence from two separate studies that the caudate nucleus is a critical site of pathology in the KE family. This chapter examines the structural abnormality of the caudate nucleus in further detail using a quantitative method.

The method used to measure the volume of the caudate nucleus was region-of-interest pixel counting. Most morphometric brain analyses use this method (see Chapter 1, Section 4.1), however, as previously discussed, the results of these studies are often conflicting. The method is well suited for measuring the volume of the caudate nucleus, however, because this nucleus is anatomically well defined and discrete, i.e., most of its boundaries are with either white matter or cerebrospinal fluid.

By using this method, quantitative data for individual datasets are available. These data were used in correlation analyses with the scores of the affected family members on behavioural and cognitive tests. These analyses allowed direct testing of the hypothetical claims previously made based upon the results of the PET and whole brain morphometric studies. Specifically, these claims were that pathology of the caudate nucleus was related to the observed deficits of the affected family members in expressive language, particularly in articulation, and in oral praxis.

The specific method of region-of-interest pixel counting used in this study has previously been used successfully to quantify the volume of the hippocampus in studies of patients with temporal lobe epilepsy (van Paesschen *et al.* 1995). The method is simple and makes use of Cavalieri's principle (Gundersen *et al.* 1988) for estimating the volume of an irregularly shaped object. Using this method, it is possible to obtain a slice-by-slice comparison of data sets, which allows visualisation of regional differences within the caudate nucleus, and provides information not only about its size but also about its shape.

8.2 Methods

8.2.1 Participants

The participants in this study were those who participated in the previous analysis (VBM; see Section 7.2.1), namely, groups of affected and unaffected family members plus a group of age-matched controls.

8.2.2 Cavalieri's volume estimator

Cavalieri showed that the volume of any object can be estimated from parallel sections separated by an equal distance, if the areas of all cross-sections of the object are summed and multiplied by the distance between them. The estimate is completely independent of the orientation of the set of sections and of the shape of the object (see Gundersen *et al.* 1988).

8.2.3 MRI data acquisition

The MRI data sets used in this analysis were those used in the VBM analysis described above (see Section 7.2.2). As stated previously, each original three-dimensional (3D) data set consisted of 128 sagittal slices, 1.25 mm thick. The original data sets were manually reformatted into one millimetre thick contiguous transverse slices parallel to the horizontal plane through the anterior and posterior commissures (AC-PC line) and orthogonal to the vertical plane through the longitudinal fissure. The approximate orientation of the slices with respect to the caudate nucleus and other basal ganglia structures is shown in Figure 8.1.

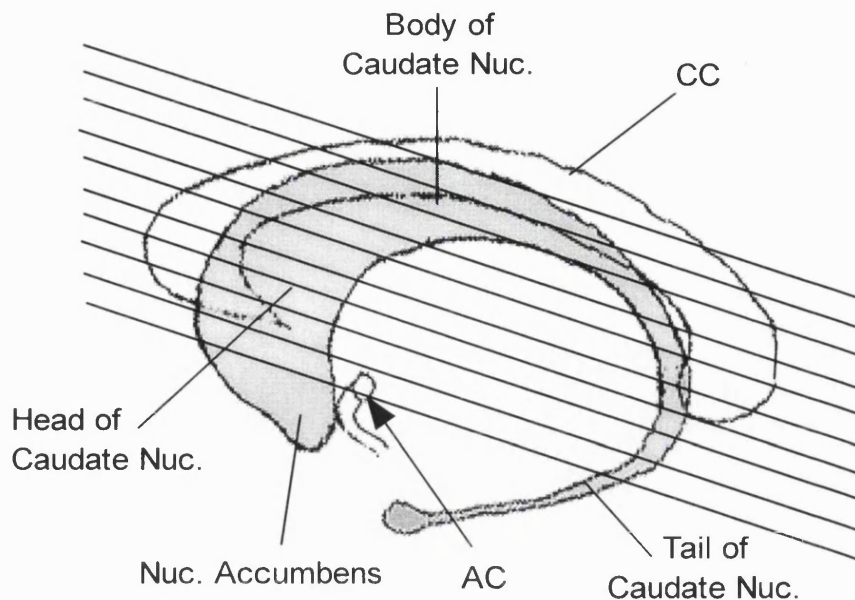


Figure 8.1 Drawing of the right caudate nucleus viewed from medial to lateral. The approximate orientation of the reformatted slices (shown here at ~3 mm thickness) is superimposed. The corpus callosum (CC) and anterior commissure (AC) are shown for reference. Nuc., nucleus.

8.2.4 Volume measurement

All volume measurements were made while blind to the classification of each data set. The data were transferred to a SUN workstation for measurement using XDisPlm software (Plummer, 1992). With this software, the investigator delineates the limits of the object of interest by drawing a line around it using the cursor. The software automatically counts the number of pixels inside this line.

Caudate nucleus volume

The cross-sectional areas of the caudate nucleus were measured for each slice from the dorsal surface of the nucleus, where it appears lateral to the lateral ventricles to its ventral limit at about the level of the anterior commissure (AC), where it merges into the nucleus accumbens (see Figure 8.2). Although the body and head of the caudate nucleus were easily seen on all slices, the tail was often indistinguishable from the nearby ventricle and hippocampus/amygdala and so was not measured. The volumes were calculated (according to Cavalieri's principle) by summing the cross-sectional areas measured on each slice, in pixels, and multiplying by the slice thickness (1 mm), and pixel size (calculated from the matrix size: 256 x 256 pixels; and field-of-view: 250 mm; pixel size = 0.9537 mm²).

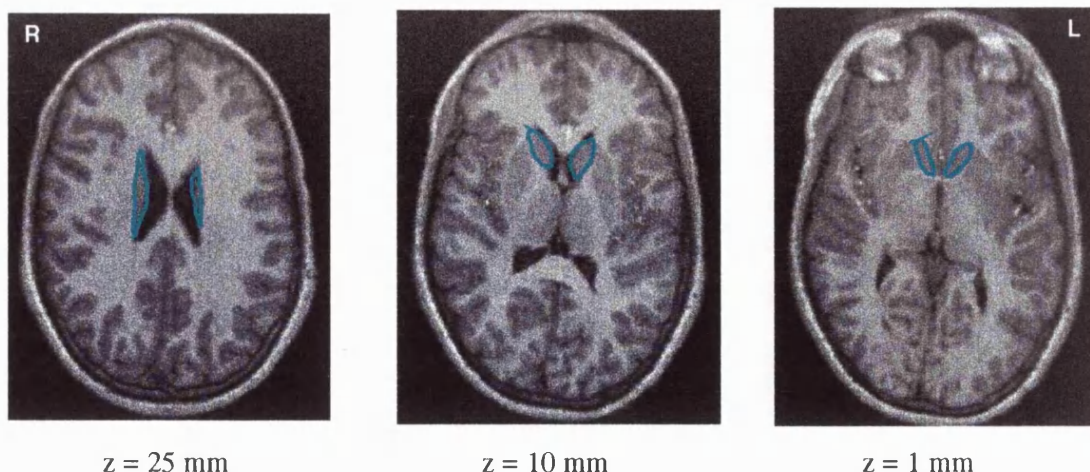


Figure 8.2 *Measuring cross-sectional areas of the caudate nuclei from its dorsal surface to the level of the AC (i.e. at $z=0$). z , approximate vertical distance from the transverse plane through the AC-PC line.*

Intracranial volume

Absolute caudate nucleus volumes were corrected by reference to intracranial volumes (ICVs), which were estimated from the original sagittal slices of the 3-D data sets as described by van Paesschen *et al.* (1995; see Figure 8.3). These data sets contained 128 slices, each 1.25 mm thick, and a sampling strategy was applied such that the volume was estimated from measurement of the cross-sectional area of every tenth slice starting with a randomly selected slice within the first set of 10. The volumes were calculated as above but with a distance between slices of 12.5 mm. The limits of the cross-sectional area measured were defined on most slices superiorly and posteriorly by the dura mater, or the inside of the skull if the dura was not visible; inferiorly by the lower surfaces of the frontal and temporal lobes, excluding the petrous bone; ventrally in the mid-line by the clivus ventral to the brain stem; and caudally by attachment of the dura to the anterior and posterior arch of the first cervical vertebra.

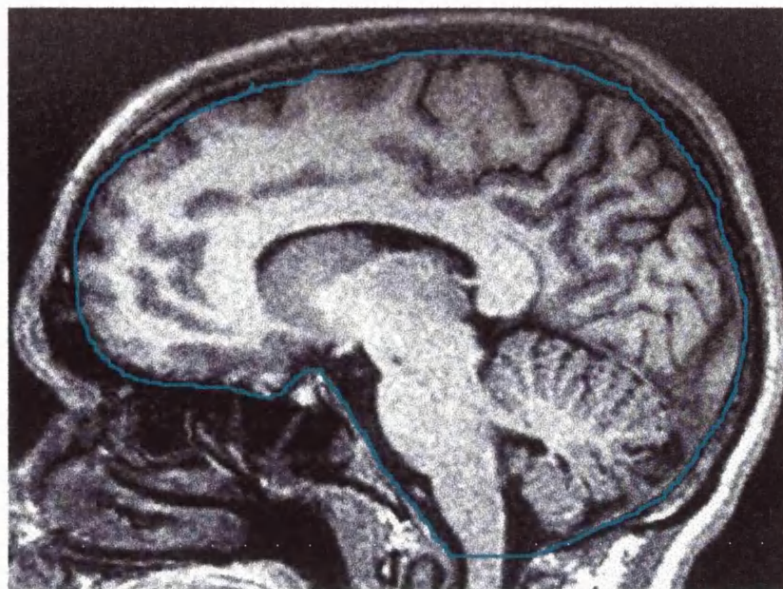


Figure 8.3 *Measurement of ICV. The cross-sectional area is measured on a parasagittal slice close to the midline (see text for details)*

8.2.5 Repeatability of volume measurements

Caudate nucleus volumes and intracranial volumes of all family members (affected and unaffected) and the control subjects were measured twice. The mean of the two volume measurements was then used in the analysis. Repeatability coefficients between the first and second measurements were calculated for both groups. Repeatability coefficients are two standard deviations (SD) of the distribution of differences between two measurements, expressed as a percentage of the mean of all the measurements. Bland & Altman (1986) suggest this as the best method to assess agreement between two clinical measurements. The repeatability coefficient for the caudate nucleus measurements was 4.16% (i.e. 95% of the remeasurements were within 4.16% of the first measurement) and that for the ICV was 1.03%.

8.2.6 Correction of caudate nucleus volumes for ICV using the covariance method

There was a significant correlation between ICV and caudate nucleus volume measurements for the comparison group, which consisted of the entire normal control group ($n=17$) and the unaffected family members ($n=7$). The Pearson's correlation coefficients between ICV and caudate nucleus volume were 0.48 ($p=0.018$) for the left caudate nucleus and 0.42 ($p=0.041$) for the right. Two regression lines, one for each caudate nucleus volume and the ICV, were calculated, and the slope of each line (B) was used to calculate a corrected caudate nucleus volume (CNV_{Corr}) for each subject based on their measured caudate nucleus volumes (CNV_{Uncorr}) and ICV using the following equation:

$$CNV_{\text{Corr}} = CNV_{\text{Uncorr}} + B (ICV_{\text{Mean}} - ICV)$$

The mean ICV (ICV_{Mean}) for the group of unaffected family members and controls was 1445 cm³. The value of B for the regression of the left caudate nucleus volumes with ICV was 0.0022 and that for the regression of the right caudate nucleus volumes with ICV was 0.0020.

8.2.7 Behavioural and cognitive testing

Chapter 3 described procedures for a number of behavioural and cognitive tests, which were administered to the affected and unaffected members of the KE family. The scores for the tests that revealed the affected family members to be significantly impaired relative to the unaffected family members were used in correlation analyses with the corrected caudate nucleus volume measurements for left and right caudate nuclei separately. Scores for the following tests were analysed: performance intelligence quotient (PIQ) and Coding subtest score of the intelligence scale, Lexical Decision, Test for Reception of Grammar (TROG), Word and Nonword Repetition, Object Naming, Verbal Fluency (Phonemic, Semantic and Written), Morphological Production (Words and Nonwords), Past Tense Production, Nonword Reading and Spelling, and Oral Praxis.

8.2.8 Statistical Analysis

The volume data were analysed by a one-way analysis of variance (ANOVA) comparing the groups of affected family members, unaffected family members, and controls. This was carried out twice, first with the affected family members of all three generations versus the unaffected and control groups, and then with the affected members of the third generation only versus the unaffected and control groups. The second analysis was run because there are no age-matched unaffected family members to compare with the affected family members from the first and second generations. Because the results of the two analyses did not differ, only those for the third-generation family members (affected, n=6; unaffected, n=7) and their age-matched controls (n=13) are reported here.

The analyses looked at absolute caudate nucleus volumes, intracranial volumes, caudate nucleus volumes that had been corrected for ICV (as described in Section 8.2.6), and asymmetry coefficients. The latter were calculated from the absolute caudate nucleus volumes using the following equation:

$$\text{Asymmetry coefficient} = 2 (\text{Left} - \text{Right}) / (\text{Left} + \text{Right})$$

The caudate nucleus volume data corrected for ICV by the covariance method were entered into correlation analyses with the behavioural and cognitive test results

obtained for the same affected family members. Spearman's correlations were used because these nonparametric tests made the fewest assumptions about the data, the number of subjects was small, and the number of comparisons was large.

8.2.9 Caudate nucleus volume distribution

In addition to the above analyses, the cross-sectional areas of the slices through the caudate nucleus were plotted as a function of slice position as described by Cook *et al.* (1992) for a similar analysis of the hippocampus. The cross-sectional areas were first corrected for ICV using a correction factor for each individual subject. This factor was calculated from the values for CNV_{Corr} (derived from the equation in Section 8.2.6) and CNV_{Uncorr} using the following equation:

$$\text{Corrected area} = \text{Uncorrected area} (CNV_{Corr} / CNV_{Uncorr})$$

The control data were plotted for the left and right caudate nucleus separately, with each graph having three curves, one representing the mean caudate nucleus cross-sectional area for each slice position, and two representing the mean \pm 2SD (see Figure 8.4). The total areas under these curves were equated to the mean caudate nucleus volume and to this volume \pm 2SD of the mean, respectively. In order to construct the curves for the mean \pm 2SD, the mean and SD of the cross-sectional area (SD_a) at each slice position were calculated. The sum of the mean areas at each position of the one-millimetre-thick slices equals the mean volume. The sum of the SDs of the cross-sectional areas (i.e. ΣSD_a), however, does not equal the SD of the mean volume (SD_v); in fact, it yields a much greater value. The ratio of the SD of the mean volume (SD_v) to the sum of the SDs (ΣSD_a) is used, therefore, to adjust the SD at each slice position (SD_a) to produce a new SD (SD_p) as summarised in the following equation:

$$SD_p = SD_a (SD_v / \Sigma SD_a)$$

Using the same method, the data for family members (corrected for ICV as above) can be plotted with the control graphs to allow visualisation of where, in terms of slice position, the volume differences occurred.

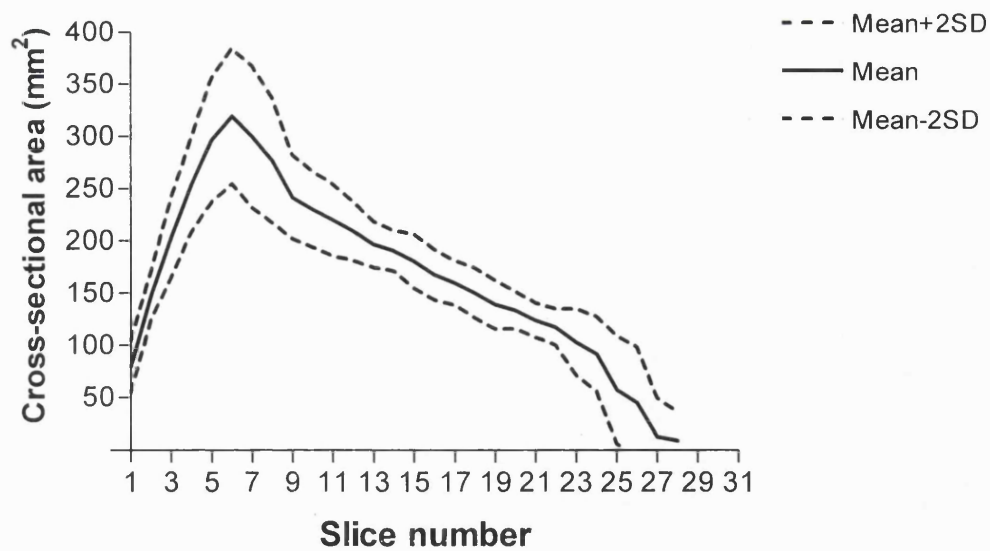


Figure 8.4 Graph showing the change in cross-sectional area with slice position for the control data. (This graph shows the values for the left caudate nucleus). Note: Figure 8.1. shows the approximate orientation of the slices with respect to the caudate nucleus. Slice number 1 is the most dorsal slice and number 31 the most ventral.

8.3 Results

8.3.1 Volume measurements

The absolute caudate nucleus volumes (CNV), ICV, corrected CNV, and asymmetry coefficients of the affected family members ($n=6$), their unaffected siblings ($n=7$) and a group of age- and sex-matched controls ($n=13$) were compared using one-way ANOVAs.

For the ICVs, there were no significant differences ($F(2,23)=0.32$, $p=0.73$) among the three groups (see Table 8.4 and Figure 8.5).

For the absolute CNVs, however, the affected family members were found to have significantly smaller volumes for both left ($F(2,23)=8.71$, $p=0.002$) and right ($F(2,23)=9.07$, $p=0.001$) caudate nuclei compared to both the unaffected group (left caudate nucleus: $t(11)=3.30$, $p=0.007$; right caudate nucleus: $t(11)=3.58$, $p=0.004$) and the controls (left caudate nucleus: $t(17)=3.88$, $p=0.001$; right caudate nucleus: $t(17)=3.91$, $p=0.001$) (see Figure 8.6).

For the corrected CNVs, an identical pattern of results was observed. The one-way ANOVA revealed a significant group difference for both left ($F(2,23)=9.95$, $p<0.001$) and right ($F(2,23)=9.18$, $p=0.001$) corrected CNVs. The affected group had significantly smaller volumes than the unaffected (left: $t(11)=3.97$, $p=0.002$; right: $t(11)=3.88$, $p=0.003$) and control (left: $t(17)=3.91$, $p=0.001$; right: $t(17)=3.87$, $p=0.001$) groups. There were no significant differences between the unaffected and the control groups (left: $t(18)=1.40$, $p=0.178$; right: $t(18)=0.70$, $p=0.494$).

There were no significant differences among the three groups for the asymmetry coefficients ($F(2,23)=1.89$, $p=0.17$; see Figure 8.8), although there was a trend towards smaller mean laterality coefficients in the affected group than in the other two groups, because three out of the six affected members showed positive asymmetry coefficients (i.e. left caudate volume greater than right, or reverse asymmetry). One of these three affected family members was the only left-hander. In contrast, all but one member of the unaffected group, and all of the controls, showed the expected negative asymmetry coefficients (i.e. right caudate volume greater than left). The asymmetry coefficient of one affected family member, although negative, was larger than that seen for any of the unaffected family members and controls. A test of homogeneity of variance between the affected group and the controls was significant ($p=0.024$) but a t-test for the difference in the means was not significant, even after adjustment for unequal variance in the two groups. The means and standard deviations for each group are given in Table 8.4.

Table 8.4 Group means \pm standard deviations for volume measurements.

| Measurement | Affected <i>n</i> =6 | Unaffected <i>n</i> =7 | Controls <i>n</i> =13 |
|--|-------------------------|---------------------------|--------------------------|
| Intracranial Volume (cm ³) | 1451 \pm 60 | 1475 \pm 136 | 1436 \pm 100 |
| Absolute Left CNV (cm ³) | 4.11 \pm 0.42 | 5.13 \pm 0.65 | 4.78 \pm 0.31 |
| Absolute Right CNV (cm ³) | 4.20 \pm 0.49 | 5.30 \pm 0.60 | 5.06 \pm 0.43 |
| Corrected Left CNV (cm ³) | 4.10 \pm 0.35 | 5.07 \pm 0.51 | 4.79 \pm 0.37 |
| Corrected Right CNV (cm ³) | 4.19 \pm 0.44 | 5.24 \pm 0.52 | 5.08 \pm 0.48 |
| Asymmetry Coefficient | -0.02 \pm 0.06 | -0.03 \pm 0.03 | -0.06 \pm 0.03 |

CNV, caudate nucleus volume

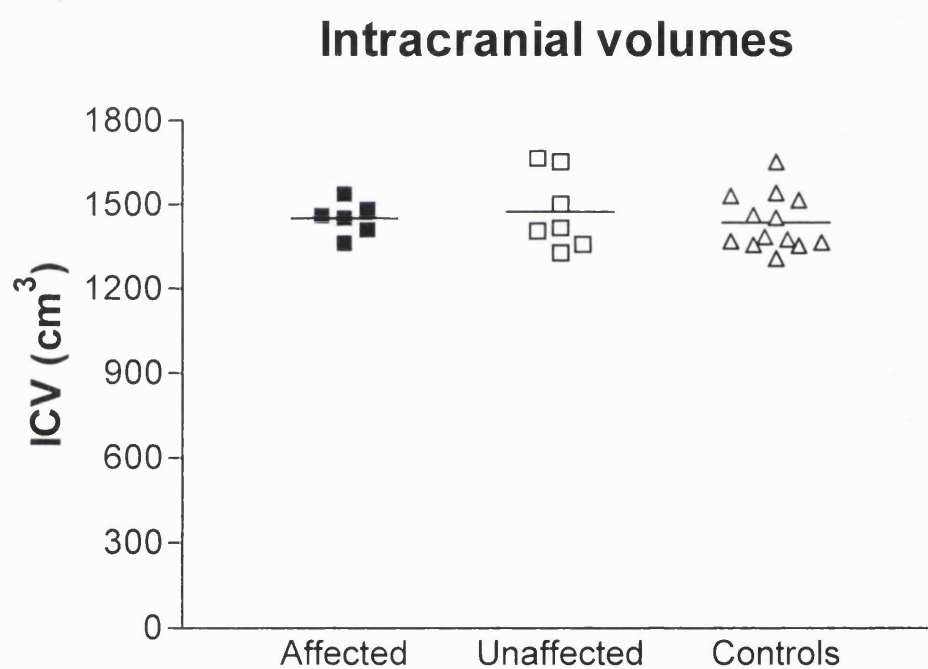


Figure 8.5 Intracranial volumes. Bar, group mean; filled squares, individual affected family members; unfilled squares, individual unaffected family members; triangles, individual controls; ICV, intracranial volume.

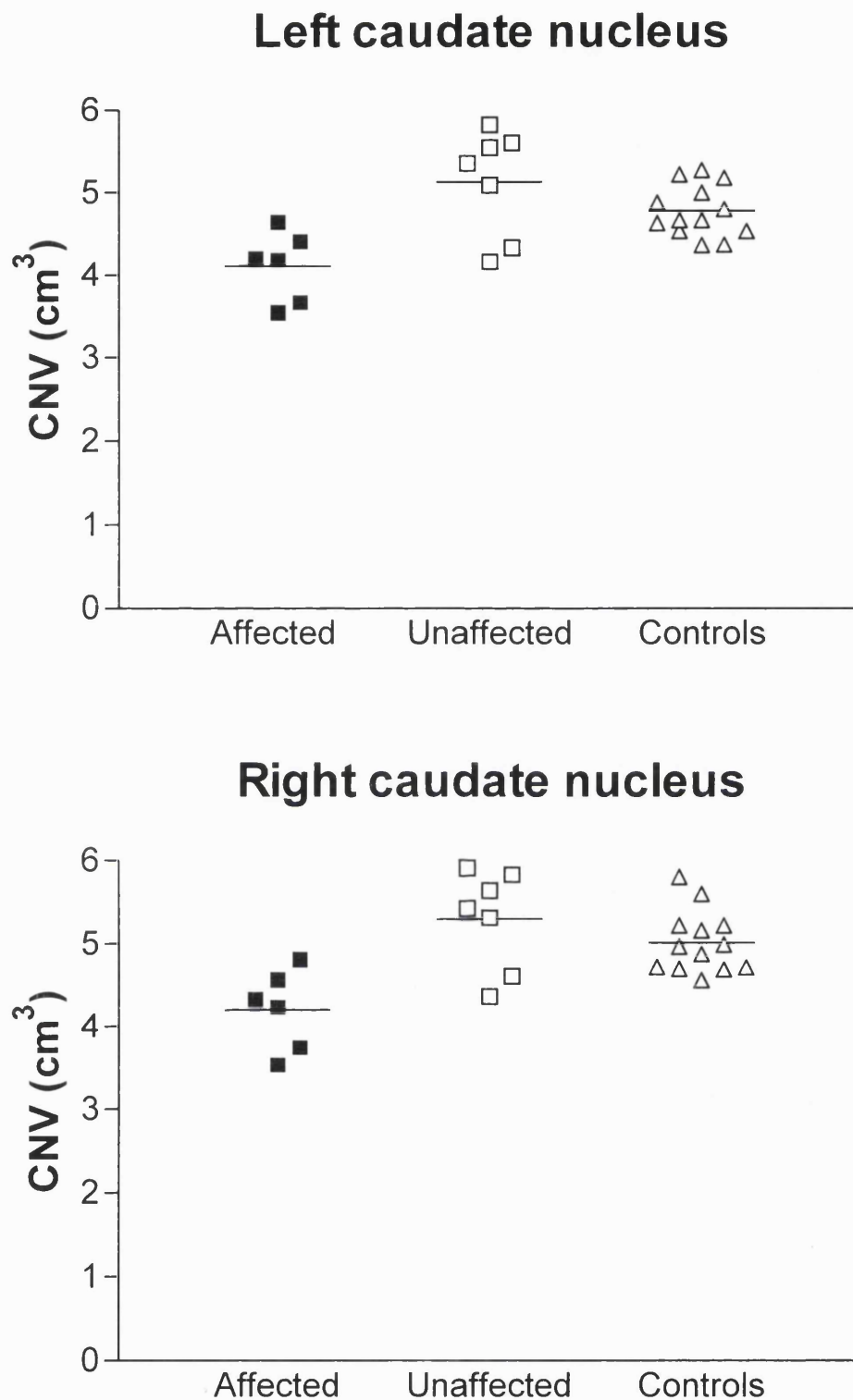
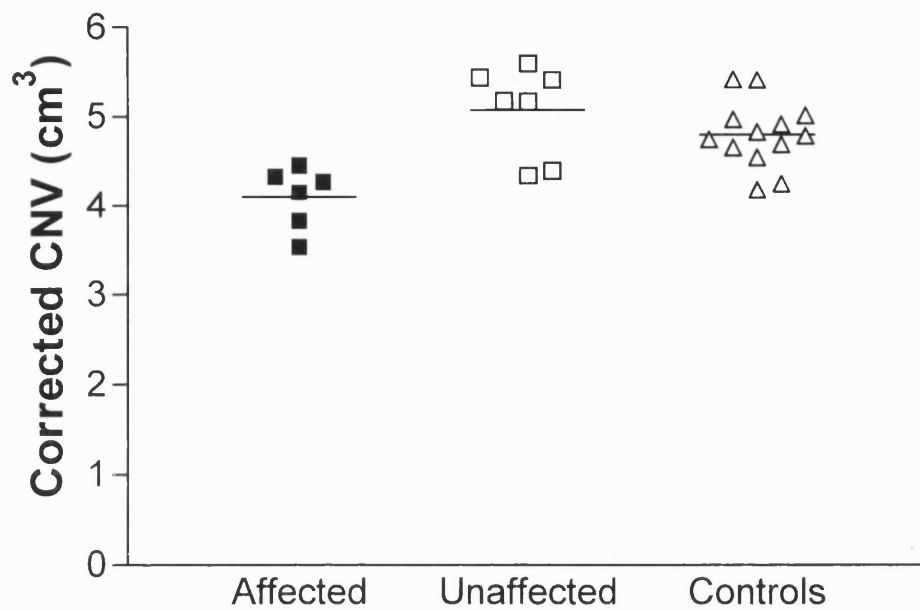


Figure 8.6 Left and right absolute caudate nucleus volumes. Bar, group mean; filled squares, individual affected family members; unfilled squares, individual unaffected family members; triangles, individual controls; CNV, caudate nucleus volume.

Left caudate nucleus



Right caudate nucleus

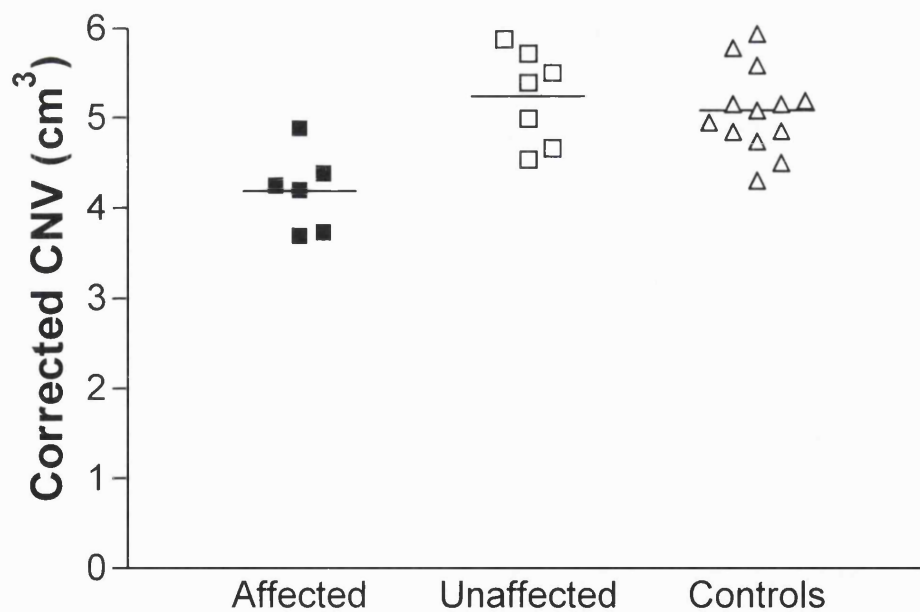


Figure 8.7 Left and right caudate nucleus volumes corrected for intracranial volume using the covariance method. Bar, group mean; filled squares, individual affected family members; unfilled squares, individual unaffected family members; triangles, individual controls; CNV, caudate nucleus volume.

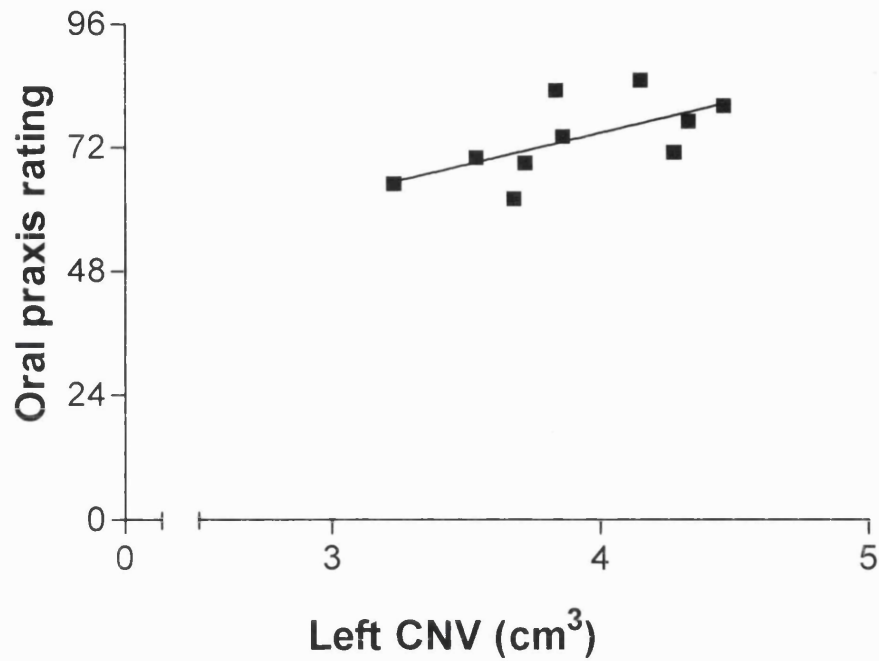


Figure 8.9 Graph showing relationship between the corrected left caudate nucleus volume and the score on a test of oral praxis. Filled squares, individual affected family members; line, regression line.

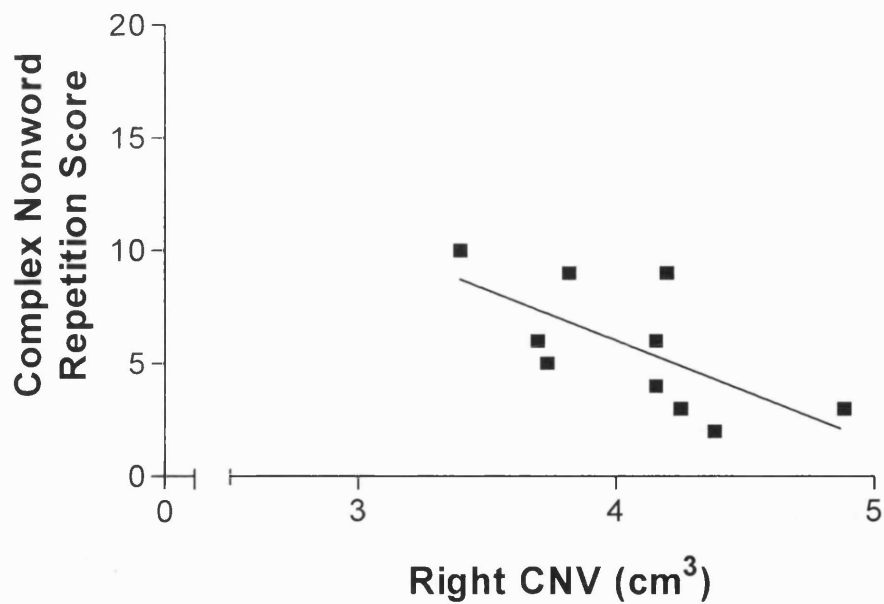


Figure 8.10 Graph showing relationship between the corrected right caudate nucleus volume and the score on a test of nonword repetition with complex articulation. Filled squares, individual affected family members; line, regression line.

8.3.3 Caudate nucleus volume distribution

The cross-sectional areas of the left and right caudate nuclei are plotted as a function of slice position in Figure 8.11 and Figure 8.12 respectively. Examination of the graph for the left caudate nucleus (Figure 8.11) shows that the affected family members of all three generations have reduced caudate nucleus volume in the more dorsal slices compared to both the unaffected family members and the control group. Starting approximately half way through the slices, however, the cross-sectional areas of the affected third generation fall within the 2SD limit of the control mean, then, in more ventral slices, they match the mean of the control groups, and, finally, in the most ventral slices, they slightly exceed the upper 2SD control limit. An almost identical pattern is seen for the right caudate nucleus measurements (Figure 8.12).

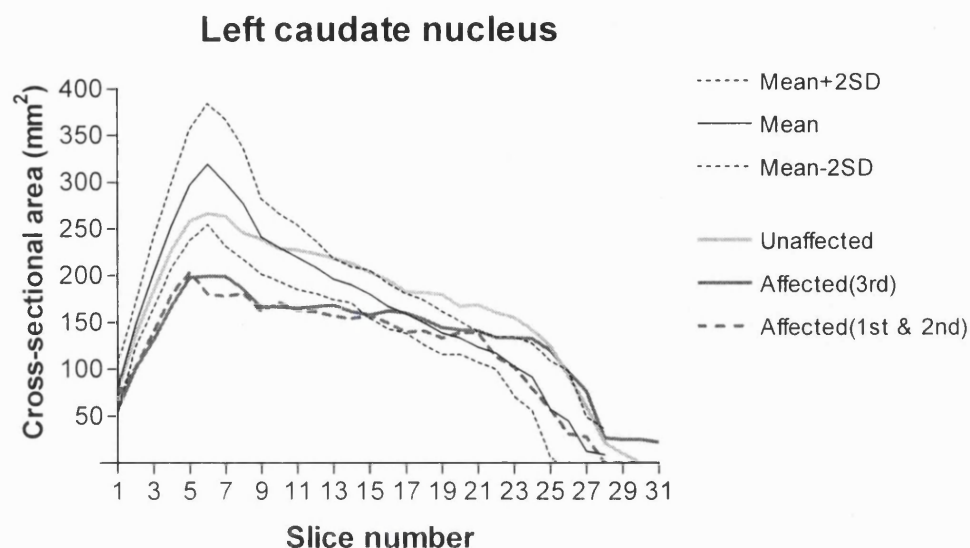


Figure 8.11 Cross-sectional area of the left caudate nucleus as a function of slice position. Thin black line, control group mean ($n=17$); grey dotted lines, control group mean $\pm 2SD$; thick dark solid line, 3rd generation affected family members mean ($n=6$); thick dark dotted line, 1st and 2nd generation affected family members mean ($n=4$); thick grey line, unaffected family members mean ($n=7$).

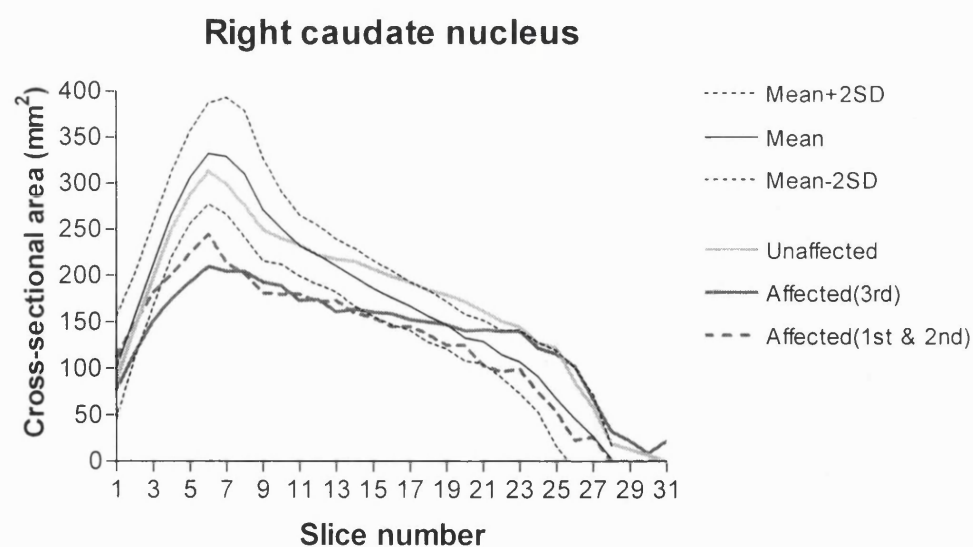


Figure 8.12 Cross-sectional area of the right caudate nucleus as a function of slice position. See legend to above figure.

8.4 Discussion

Before discussing the results, some issues concerning the methodology used in this study will be described.

8.4.1 Methodological issues

The method used to quantify the volume of the caudate nucleus was region-of-interest pixel counting. Most previous morphometric analyses of structural MRI data (reviewed in chapter one) have used such a method. Morphometric studies of the planum temporale demonstrate that different research groups often produce conflicting results (see chapter one and references therein); this is probably because of difficulties in defining anatomical boundaries and in visualisation of this structure on MRI. The caudate nucleus, by comparison, is more easily defined anatomically and well visualised on MRI. It is therefore a more suitable structure than the planum temporale for quantification using this method. Decisions are required, however, concerning the axis along which to obtain parallel sections, so as to obtain best visualisation of the nucleus. Transverse sections, parallel to the horizontal plane through the AC-PC line, were used in this study as these give a greater cross-sectional area for the caudate nucleus and fewer slices for measurement compared with coronal sections. In coronal sections, however, the inferior boundary of the nucleus is more easily identified than in transverse sections. Also, in this study, the tail of the caudate nucleus was not measured because it was often not visualised; this is also a problem for coronal sections. In sagittal sections, however, it might be more easily identified. Ideally, a method that allowed simultaneous visualisation of all three planes is required. Then, once all the pixels containing signal from the caudate nucleus were identified, systematic slices along any axis throughout the nucleus would allow further localisation and visualisation of volume changes as a function of these slice positions.

Although the pixel-counting method used in this study is simple, it is labour-intensive and relies on some subjective judgements, which may differ from one investigator to another. Repeatability (i.e. intra-rater reliability) is important, as well as inter-rater reliability. For the caudate nucleus, repeatability was good. In another analysis, which measured the putamen using similar methodology to that described for the caudate nucleus, repeatability was unacceptably poor and therefore, these data were not reported. The main difficulty in measuring the volume of the putamen or of the lentiform nucleus (putamen and globus pallidus) is that the globus pallidus lies medial to it and, in T1-weighted images, has a signal intensity that lies

somewhere between that for subcortical grey matter and white matter, making boundaries difficult to visualise.

The construction of graphs, which allow visualisation of changes in cross-sectional area as a function of slice position, is useful in order to further localise the reduction in volume within the caudate nucleus. This method is limited, however, to two dimensions. The third dimension represents the length of the structure along the axis orthogonal to the plane of the slices. Since shorter lengths along this axis would result in fewer slices, these graphs should be normalised for the same number of slices per subject. In future studies it might be preferable to carry out a three-dimensional adjustment for volume.

8.4.2 Discussion of results

Caudate nucleus volume

Analyses of quantitative volumetric data for the caudate nuclei confirmed the results of the VBM, in that the affected family members have significantly reduced caudate nucleus volumes relative to both unaffected and control groups, and these two groups were not significantly different. There were no significant differences among the three groups in terms of intracranial volume, suggesting that the caudate nucleus volume differences do not result from differences in total brain volume.

Although the caudate nucleus was shown by the above analyses to be reduced in volume in the affected family members as a group, this is not true for each of the individuals in the group; that is, some affected family members have caudate nucleus volumes equal to or greater than some unaffected family members or controls. A small caudate nucleus cannot be said, therefore, to be characteristic of the disorder that the affected family members share (i.e. a neurobiological phenotype). It is possible, however, that the caudate nucleus, even if apparently normal in size and shape in some affected members, is nevertheless functionally abnormal. The PET study carried out with II-2 and II-9 showed overactivation during word repetition when compared to normal controls. It remains to be examined, whether the other affected family members, including those with normal or near normal volumes for the caudate nuclei, also demonstrate a functional abnormality for this nucleus.

Caudate nucleus asymmetry

Asymmetry coefficients were not significantly different, among the three groups, for although three of the affected family members showed greater volumes

on the left than on the right, i.e. a trend towards reverse asymmetry, one of the affected family members showed a laterality coefficient in favour of the right caudate nucleus that was even larger than that seen in any of the controls. The typical pattern of asymmetry in the caudate nuclei is that the right is larger than the left (Frazier *et al.* 1996; Castellanos *et al.* 1996; but see Hynd *et al.* 1993). This was the pattern observed in all of the controls, all but one of the unaffected family members and three affected family members.

A loss of caudate nucleus asymmetry has been reported in association with ADHD (Castellanos *et al.* 1996) and childhood-onset schizophrenia (Frazier *et al.* 1996). The symptomatology of both of these disorders is highly suggestive of basal ganglia pathology, yet in ADHD this pathology takes the form of reduced caudate nucleus volume, whereas in childhood-onset schizophrenia increased volume is seen. These results emphasise the need to consider the relationship between the relative size of a structure and its function with caution. This is discussed in further detail towards the end of this chapter.

The development of cerebral asymmetries has been investigated using animal models. Strains of mice with autoimmune disease have neuronal migration defects that result in cortical ectopias (Sherman, Galaburda & Geschwind, 1985). In addition, these animals showed alterations in the usual pattern of asymmetry at the cortical level (Rosen *et al.* 1989), suggesting the possibility that the same sort of developmental errors also result in unusual asymmetry at the subcortical level.

Relationship between caudate nucleus volume and behaviour

The relationship between the size of the caudate nucleus and performance on a number of behavioural and cognitive tests was examined directly using correlation analyses. The only significant positive relationship found was that between the volume of the left caudate nucleus and performance on a test of oral praxis. Another significant relationship was found between the volume of the right caudate nucleus and performance on a test of nonword repetition with complex articulation. However, this relationship was negative, since the smaller the right caudate nucleus the better the performance on this test. Repetition of nonwords with complex articulation is thought to be a measure of the primary deficit of the behavioural phenotype in the affected family members (see Chapter 3). Thus, this unexpected finding is intriguing.

These results provide the first direct evidence of a relationship between a brain abnormality and the behavioural phenotype in the KE family. The causal

nature of this relationship, however, has yet to be determined, and the finding of a negative correlation between the right caudate nucleus volume and nonword repetition implies that this relationship is not straightforward. As elaborated in the previous chapter, the possibility remains that failure to master a behaviour, such as oromotor control, could result in underdevelopment of the brain region controlling that behaviour, for example the left caudate nucleus. In addition, the finding of overactivity of the caudate nucleus during word repetition in two affected family members suggests that a functional abnormality of this nucleus interferes with acquisition, and possibly learning of articulation patterns necessary for coherent speech.

The literature concerning the relationship between basal ganglia structures and language was reviewed in Section 7.4.2. The report of a patient with a lesion of the putamen and caudate nucleus of the left hemisphere, which produced an oral dyspraxia as well as an aphasia (Aglioti *et al.* 1996), supports the findings in the KE family.

Volume reduction within the caudate nucleus

The graphs of the mean cross-sectional area as a function of slice position indicate that, as a group, the affected family members have a smaller than normal volume in more dorsal slices of the caudate nucleus. The projections to the caudate nucleus from frontal cortices in nonhuman primates are complicated and, in humans, unknown, so an explanation of the selective effects resulting from cell loss in specific regions of the caudate nucleus is premature. This pattern of volume loss, however, is similar to that reported in Huntington's disease. Vonsattel *et al.* (1985) describe neuronal loss in the neostriatum of Huntington patients as proceeding from medial to lateral and from dorsal to ventral. In Huntington's disease, the paraventricular portion of the caudate nucleus, in particular, displays early neuronal loss (Vonsattel *et al.* 1985).

Relating size and function

In the previous chapter, the affected family members were demonstrated to have differences in the relative amounts of grey matter in a number of brain regions, compared to the unaffected and control groups. These differences took the form of both relative reductions and increases in grey matter. In this chapter, the reduced amount of grey matter in the caudate nucleus for affected family members was confirmed using a quantitative method. Further, the greater the reduction on the left, the poorer the performance on a test of oral praxis and the greater the reduction

on the right, the better the performance on a test of nonword repetition with complex articulation. The precise nature of the relationship between the size of a structure and its function, therefore, is unclear, and so caution is called for in interpreting these results.

The volume of a brain structure is not necessarily a reflection of the number of neurons in that structure, but is likely to be influenced also by the size and density of both neurons and glia. The density of neurons and glia in a brain structure is influenced by hydration, extracellular volume, and the degree of vascularity. Genes, hormones, growth factors, and nutrients also affect the development of neurons, glia and density, and therefore, brain size. In addition, environmental factors such as diet, stress, and the richness of the environment affect brain development and size.

During development of the brain there is an overproduction of neurons, reaching maximum numbers *in utero* (Cowan *et al.* 1984). This is followed by a selective elimination of cells. The size of an individual neuron generally increases with age (Blinkov & Glesner, 1968). Also, as neighbouring neurons undergo apoptosis or cell death, those remaining sprout greater numbers of dendrites and increase the number of synaptic boutons. Bourgeois & Rakic (1993), however, estimated that the total loss of all boutons in the visual cortex of the macaque monkey would account for only a 1-2% decrease in volume. The increase in synaptic pruning during the first decade of life is unlikely to have a large influence on brain size. The loss of synapses, however, may affect dendritic and axonal growth and thereby the volume of a particular structure.

Glial cells outnumber neurons in the brain by a factor of up to ten and, unlike neurons, go through a constant cycle of proliferation and cell death. The influence of glia on brain size is mostly due to myelination by oligodendrocytes, particularly during the first decade of life and even longer in some parts of the brain.

All of these factors call for caution in interpreting a larger volume in a particular structure as imparting an advantage, or a smaller volume as imparting a disadvantage, to the individual.

8.5 Summary

The caudate nucleus was measured in the KE family and controls using a quantitative method. This method allowed examination of individual data sets, calculations of asymmetry, correlation analyses with behavioural measures, and visualisation of the volume reduction within the caudate nucleus. The results of these analyses confirmed those of the whole-brain morphometric analyses, namely that the caudate nucleus was bilaterally reduced in volume in the affected family members relative to the unaffected family members and controls. Asymmetry coefficients were not significantly different among the three groups but showed a trend in the affected family members towards either symmetry or reverse asymmetry. The reduction in the volume of the caudate nucleus in affected family members was associated with poor performance on a test of oral praxis, thus providing the first direct evidence of a relationship between the behavioural and neurobiological findings in the KE family. The volume of the right caudate nucleus, however, significantly correlated with performance on a test of nonword repetition with complex articulation, which suggests that these relationships require cautious interpretation. Finally, the reduction in volume of the caudate nucleus was localised to its more dorsal regions. The functional significance of this finding awaits further study.

Part Four : Discussion

9. General discussion and summary of findings in the KE family

The investigations reported in this thesis examined the disorder of speech and language that affects half of the members of the KE family. There were two main aims. The first was to characterise the functional deficits common to the affected members of the KE family. The second was to identify the structural and functional neurobiological abnormalities associated with the disorder. To these ends, a number of different techniques were used.

A genetic linkage analysis, in the KE family, identified a region on chromosome 7 (7q31) that co-segregated with the disorder (Fisher *et al.* 1998), confirming autosomal dominant inheritance with full penetrance. This locus was designated SPCH1. It is likely that the disorder segregating in the KE family is the result of the disruption of a single gene. The alternative possibility, however, that different components of the phenotype are the consequence of a contiguous microdeletion involving several genes in 7q31 cannot be ruled out.

Relating genes to behaviour is a controversial topic. To say that there is a gene for a physical feature, such as eye colour, or for a disease, such as Huntington's disease, is acceptable, but to say that there is a gene for a behaviour, such as homosexuality, or for a specific aspect of cognition, such as grammar, is less acceptable. This is probably because in the case of eye colour, or a metabolic disease, the underlying biology is understood and the gene is known to code for a pigment, or an enzyme. However, behaviour and cognition do not develop directly from, and are not solely under the influence of genes since environmental factors also have significant influence. Until behavioural phenotypes are better understood in terms of their development and underlying neurobiology, it will not be possible to explain exactly what the gene directly codes for. In developmental disorders, such as that seen in the KE family, it is important to determine which aspects of the behavioural phenotype are directly related to the underlying neurobiological abnormality and which are indirect, secondary effects, arising from the interaction between the primary deficit and cognitive development.

In the neuropsychological studies of the KE family, therefore, attempts have been made to determine a possible core deficit that, through interactions during development might give rise to other deficits that constitute descriptions of the full behavioural phenotype. Similarly, in studying the underlying functional and

structural neurobiological abnormalities that correlate with this disorder, bilateral abnormalities were predicted, because the disorder persists into adulthood, with little or no recovery of language function as is seen following unilateral childhood pathology. These two ideas can be considered as the main themes of this thesis.

The explanation of the disorder in the KE family that arises from the results of the studies presented in this thesis is detailed in this chapter. Alternative explanations are also described. As yet, these studies have not advanced enough to rule out these alternative explanations. Directions for further studies are therefore described.

9.1 Summary of results in the KE family

9.1.1 Cognitive and behavioural deficits

Three chapters in Part 2 of this thesis described studies of the functional abilities of the affected family members. A series of neuropsychological tests was used to compare the performances of affected and unaffected family members and a group of adult aphasic patients. Experimental psycholinguistic methods were used to examine, in greater detail, morphological and syntactic processes in a preliminary study of four affected family members. Finally, auditory processing abilities were investigated in the KE family, in view of work in children with SLI linking impaired auditory processing to language impairment.

The affected family members were impaired in relation to the unaffected family members on a number of measures of language, praxis and nonverbal intelligence. These included nonverbal intelligence quotient (PIQ), the Coding subtest of the intelligence scale, lexical decision, receptive grammar, repetition of words and nonwords, object naming, verbal fluency (both oral and written), production of morphemes in word and nonword conditions and for both regular and irregular past tense, reading and spelling of simple nonwords, and orofacial praxis. A discriminant function analysis revealed that the affected family members were best discriminated from the unaffected members by their score on a test of nonword repetition, in particular the score relating to nonwords with complex articulation. In view of this finding, it was suggested that the deficit in articulation, which is so evident in the speech of affected individuals, is the core deficit, or primary impairment, in this family.

Grammatical morphology and syntactic processing were examined in further detail in preliminary studies of four affected family members. The mental representation of regular and irregular past tense verb forms was compared using a priming paradigm. Normal controls show priming for both regular and irregular past tense conditions. However, in the affected family members, there was no significant priming effect for regular past tense. In addition, the affected family members were impaired in processing auxiliary verb syntax. Both of these findings were discussed in relation to the secondary effects of an articulation disorder in the affected family members.

The affected and unaffected family members were compared on a test of auditory perception (Tallal Auditory Repetition Test), because this type of processing ability has been shown to be impaired in populations of children with SLI. Contrary

to expectations, the affected family members did not demonstrate a deficit on this measure. It was argued that this test was possibly inadequate for detecting a deficit in the affected family members. Further testing using a modification of the Tallal paradigm should be carried out before it can be firmly concluded that there is no deficit in auditory processing.

9.1.2 Neurobiological abnormalities

Three chapters in Part 3 of this thesis described brain imaging studies of the KE family. A functional imaging technique, namely positron emission tomography (PET), was used to examine brain function during word repetition in two affected family members. A whole brain morphometric analysis of magnetic resonance imaging (MRI) scans was used to compare regional brain volume in affected and unaffected family members and age-matched normal controls. Following on from the whole brain analysis, a quantitative region-of-interest method was used to measure the volume of the caudate nucleus from MRI scans.

The PET study revealed a number of components of the affected family members' motor system to be either functionally underactive or overactive. These included the supplementary motor area (SMA) and motor cortex, which were underactive, and the caudate nucleus and inferior frontal cortex, which were overactive. All these areas were in the left hemisphere; no right hemisphere activation was seen in either affected family members or controls using a word repetition paradigm.

The whole-brain analysis of structural MRI scans of affected and unaffected family members and matched controls revealed a number of areas of abnormality. Compared to the unaffected family members or age-matched controls, the affected family members had abnormal amounts of grey matter, either significantly more or significantly less, in many regions bilaterally and located in motor or speech related areas. Of particular significance was the finding that the caudate nucleus was bilaterally reduced in volume in affected family members and had been found to show significant overactivity in the PET study.

In view of these findings, the caudate nucleus was quantified in terms of volume using a region-of-interest pixel counting method. This confirmed that the caudate nucleus was bilaterally reduced in volume in the affected family members relative to the unaffected family members and matched controls. Significant correlations were found between the size of the caudate nucleus in the affected

family members and performance on the tests of oral praxis and nonword repetition for complex articulation.

9.2 Relating genes to behaviour

In summary, in the affected members of the KE family, a genetic abnormality on chromosome 7 has caused brain development to deviate from its normal path, resulting in abnormal brain structure and function. These abnormalities, in turn, have prevented normal development of many aspects of behaviour and cognition, including, but not limited to, oromotor control (verbal and nonverbal), expressive and receptive language, and nonverbal intelligence. In order to understand the relationship between these brain abnormalities and the range of deficits that constitute the full behavioural phenotype it is important to examine the evidence for possible developmental interactions between and within cognitive domains.

9.2.1 Interactions during cognitive development

As described in Chapter 3, the performance of the KE family was compared with that of a group of adult aphasic patients, on a series of tests assessing language, nonverbal intelligence and praxis. The level of impairment on many of the tests in both the affected family members and the patients with aphasia were strikingly similar. However, the benefit of a normal developmental course in the patients with aphasia was highlighted on several tests. These patients performed significantly better than the affected family members on tests of nonverbal intelligence, receptive vocabulary and repetition of familiar word patterns. These results suggest, therefore, that a developmental disorder, no matter how selective, might have consequences for the development of other aspects of cognition, in addition to the ones that are directly affected. Further evidence of the adverse effects of the language disorder on nonverbal cognitive development in the affected members of the KE family was provided by the longitudinal data reported in Chapter 2. The possibility, however, that the reduction in PIQ is not caused by the articulation disorder must be considered. It is possible that the same brain abnormalities that give rise to the impaired speech and language production in this family also constrain cognitive development at a particular level. Once this level is reached by an individual, further nonverbal cognitive development does not occur and a decline in abilities relative to the normal population is observed. Even so, this restriction appears to have been overcome by at least one individual (III-20) who has achieved normal nonverbal intelligence, perhaps via compensatory mechanisms and despite the severity of his speech and language disorder.

Through interactions during development, an articulation deficit can explain the other linguistic deficits seen in the affected family members. The deficit is

manifested during speech in impaired phonology. Phonological processes, which normally disappear from the speech of young children, persist in the affected family members into adulthood in the form of reduced consonant clusters, final consonant devoicing, or deletion. These preclude production of final position morphemes such as -ed and -s, which mark tense and number, respectively, resulting in an apparent morphological deficit. Impaired phonology was demonstrated not just in speech, but also in written form, suggesting that the early abnormal development has impaired phonological representations. This impairment, in turn, could result in poor working memory and might explain deficits in receptive vocabulary and grammar. Impaired phonology could also explain the lack of priming for the affected family members for regular past tense verb forms, as described in Chapter 4.

9.2.2 Interactions between brain and cognition

There are at least three possible explanations for the interactions between brain and cognition resulting in the disorder seen in the KE family, and cosegregating with the genetic abnormality in chromosomal band 7q31. The first explanation proposes a cascade of effects from the genetic anomaly to brain abnormalities to behavioural impairment. The genetic abnormality in the KE family might directly and selectively affect the development of the caudate nucleus or, perhaps, the basal ganglia more generally. Either way, it has resulted in both structural and functional abnormalities of the caudate nuclei bilaterally. The development of cortical areas that project to the caudate nucleus and the thalamo-cortical loops that originate in the caudate nucleus would also be affected by this abnormal development. This, in turn, might prevent normal development of motor learning specifically related to articulation and, thereby, result in a deviant form of articulation and speech. The interaction of the deviant articulatory abilities with language learning during development would also be abnormal, thereby giving rise to the range of deficits seen in the behavioural profile of the affected family members. Impaired language representation itself might also give rise ultimately to a restriction in nonverbal cognitive development, as described above.

The second explanation proposes a more general effect of the genetic abnormality on brain development. This would, in turn, produce a general and mild developmental delay resulting in restrictions in both verbal and nonverbal development, and associated with an articulation disorder that affects language development. On this view, the articulation deficit interacts with language development as described above, but does not cause the nonverbal intelligence

deficit. Instead, the latter arises itself directly from the general effect of the genetic abnormality on brain development.

The third explanation is that the genetic abnormality affects several brain structures and their function. Each brain region itself might then separately contribute to an impairment of the behavioural phenotype of the affected family members without interaction. This explanation is hard to reconcile with a developmental disorder of the type seen in the KE family, both from a biological and from a psychological point of view.

In this thesis, the first explanation has been given greatest emphasis. There is no firm evidence for any of the explanations, however. Further studies are required, therefore, to develop and to test these hypotheses. Identification of the gene responsible for the disorder in the KE family, would possibly allow understanding of its function and its effect on brain development.

9.3 Future directions

There are a number of directions for future research that have arisen from the studies reported in this thesis. Throughout, the emphasis has been on developmental interactions. It seems important, therefore, that further longitudinal studies are conducted with populations of children and adults with developmental speech and language disorders. A critical aspect of science is replication of findings. Unfortunately, with case studies this is often not possible. However, if other families could be identified, ideally with the same genetic abnormality as in the KE family, and closely matched in terms of the behavioural phenotype, it would be important to examine their articulation, oral praxis and morphology in detail and, if possible, to replicate the structural and functional brain abnormalities. With respect to articulation and oral praxis, further detailed studies of these functions need to be carried out, extending those presented here. It is unlikely that nonverbal articulation would be completely unimpaired in this disorder, but at present there is no test of nonverbal articulation that mimics the range, organisation and speed of movements required for speech. The results of the priming study of morphology were interesting but limited to only four affected family members. It is important to extend these studies to the unaffected family members, as well as to additional affected family members, before drawing firm conclusions. It would also be interesting to know how patients with impaired articulation, as a result of a peripheral rather than a central deficit, would perform on the morphological priming study. As already mentioned, further tests of auditory perception are required before it can be concluded that the affected family members do not have a deficit in this domain. Similarly, a more robust test of hemispheric specialisation for language is required.

With respect to the functional imaging, the availability of functional magnetic resonance imaging (fMRI) techniques will allow longitudinal studies to be carried out in groups of patients with developmental disorders. These are important advances. For the study of the KE family, it is important that other cognitive and behavioural paradigms are applied because the PET study reported here was limited only to showing activation of the left hemisphere during word repetition. The contribution of the right hemisphere to speech and language processing in the affected family members remains to be determined. It is expected that these studies will be extremely fruitful for further defining the nature of the deficit in the affected family members.

Morphometric analysis of structural MRI is a rapidly developing and exciting area of research. Methods are being improved rapidly to address some of the issues raised in this thesis. However, validation and replication are important in this area. The size of the data sets being analysed is such that the possibility of identifying brain regions as abnormal is quite large. True validation will only come from post mortem studies of the same individuals. This approach may also address specific questions relating to neurotransmitter and receptor density in the brains of the affected family members. At present, without the use of invasive techniques, it is not possible to identify abnormalities at these levels.

The findings of this thesis have implications for the study of other developmental disorders of speech and language. Within the diagnostic category of specific language impairment (SLI), better definitions of subtypes are required. The genetic studies reviewed in Chapter 1 (Section 1.2) revealed a number of findings which suggest strong heritability for disorders affecting expressive language, in particular phonological and articulation disorders. There is a strong possibility that within SLI there is a subtype that is related to a genetic abnormality that affects the development of articulation and phonology. The disorder in children with SLI with predominantly receptive language deficits, including those with auditory processing impairments, may not have a genetic aetiology but instead may be related to environmental factors. This suggestion is supported by a study by Bishop *et al.* (1999), which reported strong heritability for performance on nonword repetition and no evidence for heritability of performance on a test of auditory processing. The children in that study showed a very similar pattern of impairment to that described in the KE family, namely significant difficulty with nonword repetition for complex articulation and an impairment on the Tallal Auditory Repetition Test related to increasing sequence length but not to rate of presentation. The disorder in the KE family may not be, therefore, very different from that seen in SLI. It may be that the KE family have a particularly persistent and severe deficit at an extreme end of the spectrum of developmental language disorders known as SLI.

Further to this are the findings of two imaging studies which described abnormalities of the caudate nucleus in children with SLI. The first study (Jernigan *et al.* 1991) found significantly reduced caudate nucleus volume in a group of children diagnosed with SLI at age four. These children subsequently failed to meet diagnostic criteria for SLI, because of low nonverbal intelligence. The second is a case study of a child diagnosed with SLI who was shown to have bilateral pathology of the head of the caudate nucleus on magnetic resonance imaging (Tallal, Jernigan &

Trauner, 1994). It is important to extend the imaging studies to other well-defined SLI populations in order to confirm that pathology of the caudate nucleus is implicated in these disorders.

9.4 Concluding remarks

The investigations of the KE family described in this thesis made use of a number of different techniques. Although these studies have increased the understanding of the disorder in this family, they have also highlighted the complexity and dearth of understanding of the relationship between genes, brains and behaviours. Certainly, it was not assumed that this relationship was straightforward or simple, but the possibilities for interaction at multiple levels during development seem endless. Doubtless, the disorder of the affected members of the KE family is a remarkable one. Nevertheless what is most remarkable is that speech and language usually develop along a normal yet incredibly complex path with little apparent effort.

As Professor Marcus Pembrey said in reference to mapping the gene in the KE family:

*“Just because the cause of a watch stopping can be simple,
does not mean that the cause of it working is simple.”*

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Appendix to Chapter 4

The results of analyses of a group of four individuals were presented in Chapter 4 for two experiments. Experiment one employed an auditory lexical decisions paradigm to examine priming effects in four conditions: regular and irregular past tense, semantic and phonological. Experiment two employed a word monitoring paradigm to examine processing of three types of syntax and, as control conditions, two types of semantics. Below the results of analyses for each individual are presented for interest.

Results of experiment one: inflectional morphology

ANOVAs were run for each participant separately with the repeated measure of priming (2 levels: related vs. unrelated prime) and factors of condition (4 types: regular past tense, irregular past tense, phonological overlap and semantic) and version (primed in version A vs. primed in version B). Separate analyses for each condition with the repeated measure of priming and the factor of version were also run.

Analyses of the data for participant II-2 showed no significant effects of priming in any of the conditions. There was a significant effect of version for the phonological condition only ($F(1,17)=5.75$, $p=0.028$), but the interactions were not significant.

Analyses of the data for participant II-9 showed no significant effects of priming nor of version in any conditions. The interactions of priming and version were also not significant.

Analyses of the data for participant III-5, revealed a close to significant effect of priming for the irregular past tense condition only ($p=0.067$). There were no other significant effects or interactions in any of the conditions.

Analyses of the data for participant III-20 revealed a significant main effect of priming in the large ANOVA ($F(1,113)=4.30$, $p=0.040$) but no other significant effects or interactions. The separate analyses revealed a significant effect of priming for the irregular past tense condition only ($F(1,37)=4.44$, $p=0.042$), a significant effect of version for the regular past tense condition only ($F(1,37)=5.09$, $p=0.030$) and a significant interaction between version and priming for the semantic condition only ($F(1,18)=4.49$, $p=0.048$).

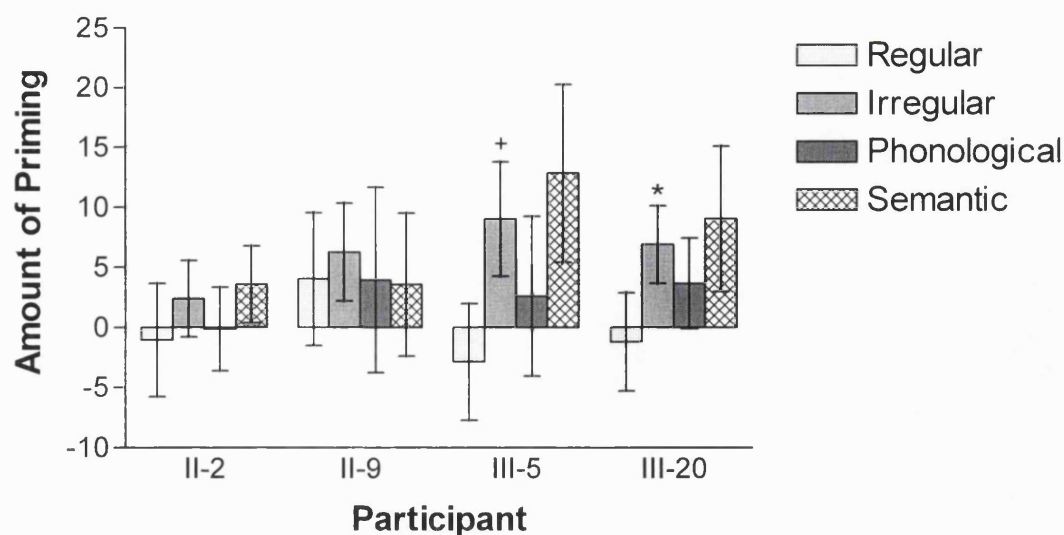


Figure A4.1 Amount of priming by condition in individual participants. Priming effects are expressed as percentages of the mean RT for each condition separately to normalise across sessions and participants. * $p < 0.05$, + $p < 0.1$

Results of experiment two: syntactic processing

For the conditions testing syntactic processing the normalised RT data were analysed as follows. ANOVAs were run for each participant separately with grammaticality as a repeated measure (2 levels: good vs. bad), and factors of condition (3 types: phrase structure, subcategory constraints, and wrong auxiliary) and version (good in version A vs. good in version B). Separate analyses for each condition with the repeated measure of grammaticality and the factor of version were also run for each individual.

For participant II-2, the effect of grammaticality was significant ($F(1,58)=10.74$, $p=0.002$), but there were no significant effects of condition or version and no significant interactions. Grammaticality was significant for phrase structure ($F(1,20)=4.74$, $p=0.042$) and subcategory constraints ($F(1,20)=12.81$, $p=0.002$) separately, but not for wrong auxiliary violations.

For participant II-9, there was a significant effect of grammaticality ($F(1,53)=5.00$, $p=0.03$), but the effects of condition and version and the interactions among these factors were not significant. Separate ANOVAs for each of the types of syntax violation revealed significant effects of grammaticality for subcategory constraints only ($F(1,19)=7.07$, $p=0.016$).

For participant III-5, the effect of grammaticality was not significant, nor were the effects of condition and version. The interaction between condition and version

was significant ($F(2,51)=3.36$, $p=0.042$). Separate ANOVAs revealed a significant effect of grammaticality for phrase structure ($F(1,16)=4.75$, $p=0.045$) only. There was a significant effect of version ($F(1,16)=7.87$, $p=0.013$) for phrase structure only.

For participant III-20, there were significant effects of grammaticality ($F(1,57)=5.83$, $p=0.019$) and condition ($F(2,57)=3.90$, $p=0.026$). The effect of version and all interactions were not significant. Separate ANOVAs revealed a significant effect of grammaticality for phrase structure ($F(1,20)=6.21$, $p=0.022$) only. The effect of version was also significant in the analyses of phrase structure items ($F(1,20)=7.77$, $p=0.011$); this was due to shorter RT for version A. There were no other significant main effects or interactions in any of the other conditions.

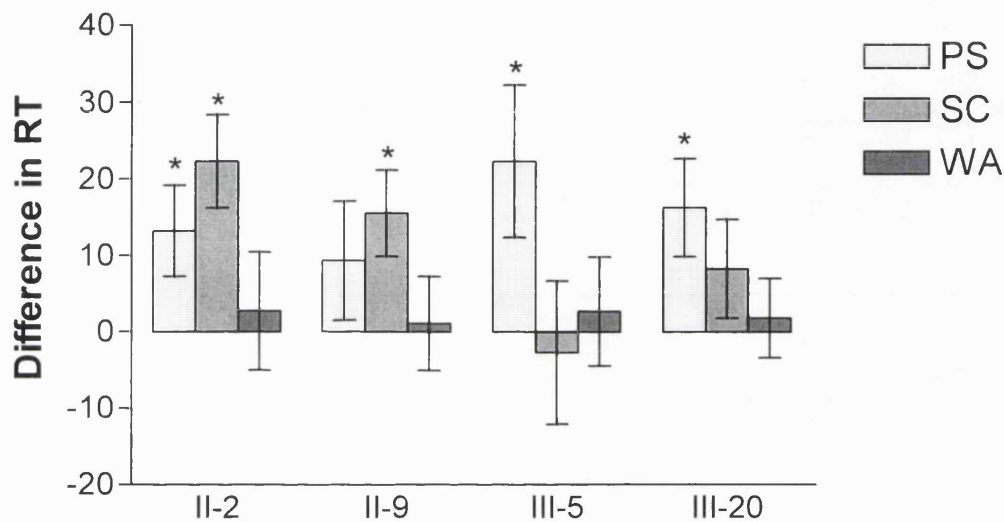


Figure A4.2 Difference in RT for good and bad items by condition in individual participants. PS, phrase structure; SC, subcategory constraints; WA, wrong auxiliary, * $p<0.05$.

For the conditions testing semantic processing the normalised RT data were analysed as follows. ANOVAs were run for each participant separately with semantic appropriateness as a repeated measure (2 levels: good vs. bad), and factors of condition (2 types: pragmatics, and semantic anomalies) and version (good in version A vs. good in version B). Separate analyses for each condition with the repeated measure of semantic appropriateness and the factor of version were also run for each individual.

For participant II-2, there was a significant effect of semantic appropriateness ($F(1,35)=9.57$, $p=0.004$), but the effects of type and version and the interactions were not significant. Separate analyses for each type revealed that the effect of semantic

appropriateness was close to significance for pragmatics ($p=0.097$) and was significant for semantic anomalies ($F(1,18)=7.35$, $p=0.014$).

For participant II-9, the effect of semantic appropriateness was not significant for either condition. There was a significant effect of condition ($F(1,34)=4.89$, $p=0.034$). Examination of the means revealed that II-9 produced significantly shorter RT to items testing pragmatics than to those testing semantic anomalies.

For participant III-5, there were no significant main effects or interactions for any of the analyses carried out.

For participant III-20, there was a significant effect of semantic appropriateness ($F(1,34)=8.65$, $p=0.006$), but the effects of type and version were not significant. The separate analyses for each condition revealed a significant effect of semantic appropriateness for items testing pragmatics ($F(1,17)=5.60$, $p=0.030$) and a close to significant effect for items testing semantic anomalies ($p=0.097$).

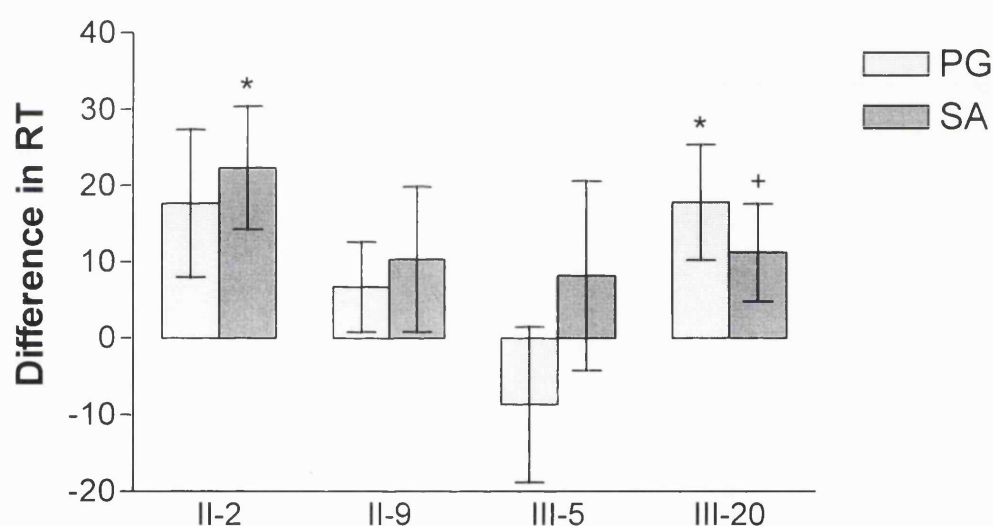


Figure A4.3 Difference in RT for good and bad items by condition in individual participants. PG, pragmatics; SA, semantic anomalies, * $p<0.05$, + $p<0.10$.

Appendix to Chapter 7

The tables below report all the regions identified in the voxel-based morphometry (VBM) analyses described in Chapter 7, which were significant at an uncorrected $p < 0.0005$, but were not predicted in advance.

Table A7.1 *Results of the VBM analyses: affected versus unaffected family members*

| <i>Anatomical area</i> | <i>Co-ordinates (x,y,z)</i> | | | <i>Z score</i> |
|--|-----------------------------|-----|-----|----------------|
| <i>Less grey matter in the affected family members</i> | | | | |
| Right superior frontal gyrus (BA9) | 10 | 58 | 24 | 3.46 |
| Right orbito-frontal cortex (BA11) | 33 | 52 | -20 | 4.26 |
| Medial orbito-frontal cortex (gyrus rectus) (BA11) | 3 | 50 | -24 | 3.73 |
| Right inferior frontal cortex (BA46) | 50 | 48 | 2 | 3.60 |
| Right anterior cingulate cortex (BA24) | 8 | 48 | 2 | 3.60 |
| Left anterior cingulate cortex (BA24) | -9 | 33 | 22 | 3.50 |
| Left middle frontal gyrus (BA8) | -21 | 27 | 44 | 3.53 |
| Right medial orbital gyrus (BA15/25) | 22 | 20 | -18 | 3.47 |
| Right inferior temporal gyrus (BA38) | 48 | 18 | -40 | 4.24 |
| | 56 | 15 | -33 | 4.13 |
| Left inferior temporal cortex (BA38) | -51 | 4 | -45 | 3.40 |
| Left inferior temporal cortex (BA20) | -46 | -8 | -45 | 4.10 |
| Right inferior temporal gyrus (BA20) | 62 | -12 | -28 | 4.36 |
| Left inferior temporal cortex (BA37) | -66 | -38 | -18 | 4.21 |
| <i>More grey matter in the affected family members</i> | | | | |
| Left pulvinar | -21 | -28 | 2 | 4.12 |
| Left striate cortex (BA17) | -12 | -84 | -4 | 4.16 |
| | -24 | -63 | 0 | 3.40 |
| Right pulvinar | 22 | -28 | -2 | 4.00 |
| Left middle frontal gyrus (BA9) | -27 | 28 | 56 | 3.77 |
| | -20 | 36 | 54 | 3.37 |
| Right superior temporal gyrus (BA41/42) | 58 | -14 | -2 | 3.76 |
| | 56 | -22 | 0 | 3.58 |
| Right parietal cortex (BA7) | 32 | -68 | 50 | 3.63 |
| Right lateral occipital cortex (BA18/19) | 46 | -68 | -8 | 3.52 |
| Right occipital pole (BA17) | 20 | -92 | 0 | 3.32 |
| Right middle frontal gyrus (BA9) | 34 | 33 | 40 | 3.43 |

| | | | | |
|---|-----|-----|-----|------|
| Right medial parietal cortex (BA31) | 8 | -51 | 50 | 3.41 |
| Left inferior insular cortex | -45 | -6 | -15 | 3.39 |
| Left medial occipito-parietal cortex (BA19) | -3 | -78 | 27 | 3.34 |

Table A7.1 *Results of the VBM analyses: affected versus controls*

| <i>Anatomical area</i> | <i>Co-ordinates (x,y,z)</i> | | | <i>Z score</i> |
|--|-----------------------------|-----|-----|----------------|
| <i>Less grey matter in the affected family members</i> | | | | |
| Left orbitofrontal cortex (BA11) | -26 | 60 | -16 | 3.50 |
| | -32 | 54 | -18 | 3.31 |
| Right orbitofrontal cortex (BA10) | 33 | 52 | -20 | 4.13 |
| Left inferior frontal cortex (BA46) | -24 | 50 | 15 | 3.42 |
| Right anterior cingulate cortex (BA24) | 9 | 46 | -2 | 3.73 |
| Left anterior cingulate cortex (BA24) | -10 | 32 | 24 | 3.62 |
| | -6 | 24 | 20 | 3.29 |
| Left superior frontal gyrus (BA8) | -20 | 26 | 45 | 3.45 |
| Right superior frontal gyrus (BA8) | 20 | 24 | 46 | 3.30 |
| Right superior temporal gyrus (BA38) | 51 | 21 | -32 | 3.37 |
| Right inferior temporal gyrus (BA38) | 45 | 18 | -42 | 3.48 |
| Right superior frontal gyrus (BA6/8) | 22 | 12 | 56 | 3.51 |
| Left inferior temporal gyrus (BA20) | -32 | -4 | -48 | 3.47 |
| | -40 | -8 | -46 | 3.64 |
| | -48 | -9 | -39 | 3.87 |
| Left superior frontal sulcus (BA6) | -15 | -8 | 58 | 3.37 |
| Right anterior fusiform gyrus (BA20) | 46 | -15 | -39 | 4.02 |
| Right inferior temporal gyrus (BA37) | 68 | -34 | -20 | 3.77 |
| Left gyrus fasciolaris | -9 | -38 | 2 | 3.44 |
| Right cerebellum | 18 | -40 | -57 | 3.76 |
| Left cerebellum ⁴ | -24 | -40 | -54 | 3.52 |
| | -18 | -45 | -58 | 3.62 |
| Left posterior cingulate cortex (BA30) | -9 | -48 | 6 | 3.69 |
| Right anterior calcarine sulcus | 6 | -50 | 6 | 3.31 |
| <i>More grey matter in the affected family members</i> | | | | |
| Right cerebellum | 24 | -38 | -32 | 4.54 |
| Medial cerebellum | -9 | -43 | -28 | 4.19 |
| Right pulvinar /lateral geniculate nucleus | 24 | -28 | -3 | 4.24 |
| Right parietal cortex (BA7) | -32 | -62 | 56 | 3.60 |

| | | | | |
|--|-----|-----|-----|------|
| Left parietal cortex (BA7) | -50 | -40 | 57 | 3.44 |
| Left parallel sulcus of posterior temporal cortex (BA22) | -63 | -18 | -6 | 4.26 |
| Left pulvinar | -21 | -28 | 0 | 4.06 |
| Left striate cortex (BA17) | -12 | -87 | -4 | 4.19 |
| Left lateral occipital cortex (BA18) | -30 | -93 | -14 | 4.00 |
| Left lateral occipital cortex (BA19) | -36 | -76 | -9 | 3.76 |
| Left superior frontal cortex (BA9) | -6 | 57 | 18 | 4.12 |
| Right intraparietal sulcus (BA7) | 32 | -68 | 50 | 4.09 |
| Left superior frontal cortex (BA8) | -14 | 36 | 56 | 3.83 |
| | -26 | 30 | 56 | 3.58 |
| Left middle frontal cortex (BA8) | -50 | 16 | 39 | 3.51 |
| Right parietal cortex (BA7) | 42 | -48 | 58 | 3.41 |
| Left medial striate cortex (BA17) | -21 | -60 | -4 | 3.38 |

Table A7.3 *Results of the VBM analyses: unaffected family members versus controls*

| <i>Anatomical area</i> | <i>Co-ordinates (x,y,z)</i> | | | <i>Z score</i> |
|--|-----------------------------|-----|-----|----------------|
| <i>Less grey matter in the unaffected family members</i> | | | | |
| Left superior frontal cortex (BA6) | -50 | 16 | 38 | 4.21 |
| Left superior frontal cortex (BA8) | -50 | 21 | 30 | 4.10 |
| Left superior frontal cortex - medial (BA32) | -6 | 57 | 16 | 4.19 |
| Left superior frontal cortex (BA9/10) | -14 | 54 | 33 | 3.38 |
| Left superior frontal cortex - medial (BA32) | -8 | 60 | 6 | 3.37 |
| Right superior frontal cortex (BA9) | 20 | 52 | 24 | 3.44 |
| | 24 | 51 | 16 | 3.37 |
| Left middle occipital gyrus (BA18/19) | -30 | -93 | -15 | 3.39 |
| Right middle temporal gyrus (BA21) | 60 | 3 | -26 | 3.32 |
| <i>More grey matter in the unaffected family members</i> | | | | |
| Left supramarginal gyrus | -50 | -46 | 39 | 4.06 |
| Left thalamus | -14 | -21 | 15 | 4.01 |
| Right thalamus | 8 | -24 | 12 | 3.61 |
| Right superior colliculus | 3 | -32 | 2 | 3.59 |
| Right cerebellum | 38 | -40 | -52 | 3.71 |
| | 22 | -39 | -54 | 3.43 |
| Right lateral occipito-parietal cortex (BA19/7) | 42 | -76 | 21 | 3.71 |