The functional role of sensory attenuation in movement

Thesis submitted for the degree of PhD

Maria Eleni Gkotsi

Institute of Neurology
University College London

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ABSTRACT

Our ability to move in a controlled, precise manner is central to our successful interaction with the world. Conversely, disorders of movement control are amongst the most devastating of human illnesses. The work in my PhD aims to make a meaningful contribution to understanding motor control in humans, work which has a direct link to pathophysiology of movement disorders and which I plan to test in patients with Parkinson's disease. Parkinson's disease is the second most common neurodegenerative disorder in the world, affecting ~7 million people, with ~130,000 patients in the UK. The primary motor symptom of Parkinson's disease is bradykinesia, a slowing and reduction in amplitude of voluntary movement. Though the major anatomical site of neurodegeneration – the basal ganglia - and the main neurotransmitter involved – dopamine – have been known for many years, it has been surprisingly difficult to provide a clear neurobiological mechanism for this fundamental movement deficit in Parkinson's disease.

The key to understand motor control in humans is to investigate how sensory information is related to movement. Previous research has demonstrated that the amplitude of somatosensory sensory evoked potentials elicited by median nerve stimulation are attenuated at prior to and during rest, motor preparation and movement in healthy subjects. My PhD will focus on this neurophysiological sensory attenuation and relate these phenomena to theories of motor control in both healthy subjects and PD patients.

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I would like to thank my family so much for their constant support, encouragement, generosity and especially my dad that he wanted me to achieve this PhD. Therefore, this PhD is a gift to my whole beloved family but firstly and foremost to my loving and caring dad.

Table of Contents

LIST OF FIGURES

LIST OF ABBREVIATIONS

DBS	Deep Brain Stimulation
ECG	Electrocardiogram
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electrooculogram
ERP	Event-related potential
ICA	Independent Component Analysis
ISI	Interstimulus Interval
L2/L3	Layer 2 and 3 neuronal cells
L4	Layer 4 neuronal cells
L5	Layer 5 neuronal cells
LFP	Local field potentials
MCMC	Markov Chain Monte Carlo
MEG	Magnetoencephalogram
MH	Metropolis-Hasting algorithm
MMN	Mismatch negativity
mV	Millivolts
ms	Milliseconds
MEPs	Motor Evoked Potentials

NMM	Neural mass models
PD	Parkinson’s disease
Pinhibit	Probability of inhibition
PF	Particle filter
PMBS	Post-movement beta synchronization
Presponse	Probability of response
Pstop	Probability of stopping
RT	Reaction time
SMA	Supplementary Motor Area
SPM	Statistical Parametric Mapping
SQUID	Superconducting Quantum Interface Device
SSAEPs	Steady state auditory evoked potentials
SSD	Stop-Signal Delay
SSEPs	Steady state somatosensory evoked potentials
SSRT	Stop Signal reaction time task
SSVEPs	Steady state visual evoked potentials
TMS	Transcranial magnetic stimulation
V1	Visual cortex area 1
V2	Visual cortex area 2
V3	Visual cortex area 3
V4	Visual cortex area 4

1 CHAPTER 1: GENERAL INTRODUCTION

1.1 NEUROANATOMY: MEDIAN NERVE AND SSEP COMPONENTS

The work in my thesis centres on the attenuation of somatosensory evoked potentials (SSEPs) measured centrally with EEG and elicited by median nerve stimulation. The recording of SSEPs has been used as a neurophysiological technique to study spinal manipulation intervention but also to investigate neuroplasticity (Passmore et al, 2014). SSEPs have been widely used in neurology to investigate lesions, to identify anatomically impairments along the sensory pathway, to identify the general pathology of patients and to monitor how pathologies change over time. It has been widely reported that SSEP recordings show differential response for different types of neurological diseases. In this thesis, SSEPs have been employed to record primary sensory pathways and to probe the attenuation of the sensory response during different tasks. SSEPs are sensitive, reliable, stable, and an objective measure. For that reason they are used routinely as a part of a clinical examination of neurological disorders (Nuwer et al, 1998). Despite the reliability of SSEP recordings there are a number of parameters in the recording methods that can lead to some variability in the SSEP signal. Variability included stimulus intensity, inter-stimulus interval of SSEPs, electrode impedance and location, recognition of components of SSEPs and the methods used to measure these components. The International Federation of Clinical Neurophysiology generated a report of recommended standards that should be used to measure components of SSEPs and therefore decrease variability in SSEP studies (Passmore et al, 2014).

The somatosensory system is compromised by elements of peripheral and central nervous systems. The somatosensory pathway contains peripheral receptors and afferents that enter the dorsal root ganglion and synapse with the ipsilateral dorsal column nuclei before reaching the medulla. When they reach the medulla, they cross to

the contralateral site of brain and then cross the ventral posterior lateral nucleus of the thalamus. Lastly, they arrive in primary somatosensory cortex (Figure 1-1).

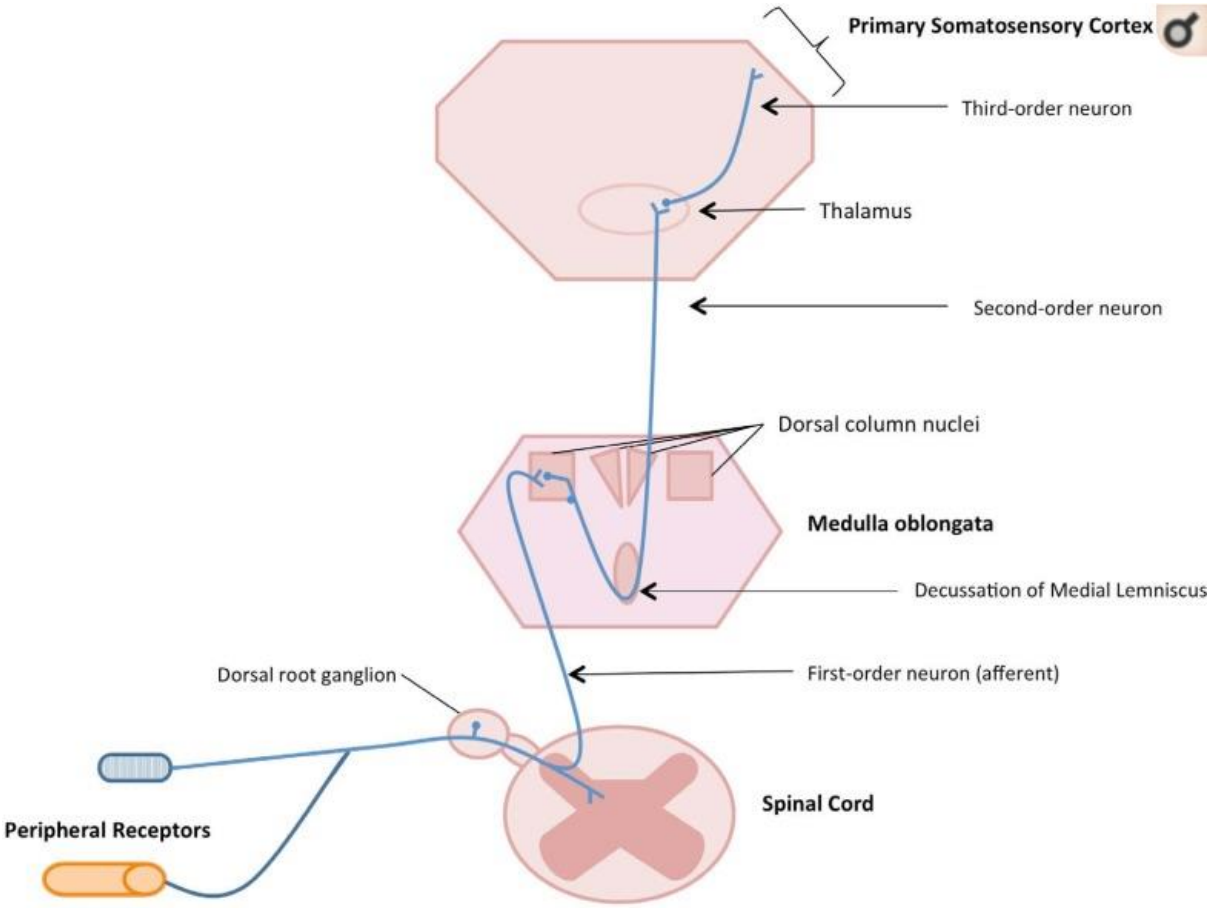

Figure 1-1. ***Figure shows motor and sensory pathways of SSEPs (Passmore et al, 2014).***
To explain the figure in further detail, sensory signals travel from peripheral receptors and afferent neurons to dorsal root ganglion before ascending to the spinal cord and synapsing with ipsilateral dorsal column nuclei at medulla. Once at medulla, they cross in the contralateral site of the brain and reach the ventral posterior lateral nucleus of the thalamus before reaching primary somatosensory cortex.

An evoked potential occurs due to stimulation of peripheral receptors or afferents causing an action potential. Peripheral nerve electrical stimulation induces a somatosensory evoked potential (SSEP; Passmore et al, 2014). The most common electrical stimulation used in clinical and research setting to evoke SSEPs is median nerve or posterior tibial nerve stimulation. Median nerve SSEPs are generated through a transcutaneous electrical stimulation to the wrist and are typically strong enough to cause a thumb twitch whereas tibial nerve SSEPs are generated through electrical

stimulation to the lower limb. Using a tibial nerve stimulation, the equivalent to the N20-P30 primary component of median nerve SSEP is recorded so later and known as N34-P37 (Lee et al, 1998).

For this PhD research, median nerve stimulation was used as the method of choice. Upon delivery of electrical stimulation to the median nerve at the wrist, nerve action volleys travel through sensory fibres up to motor fibres of the shoulder and as it crosses branchial plexus, it produces a peak at the point of the shoulder known as Erb's point or **N9**. This peak **N9,** is a downward wave deflection of a negative polarity that arises 9 ms after stimulation. **N9** could be recorded by applying an electrode channel over the clavicle, lateral to the edge of the sternocleidomastoid muscle. It is generated by afferent action potentials in the branchial plexus. Then sensory fibres cross cervical roots and enter cervical cord. Median nerve pathway joins the posterior columns and its branches synapse with midcervical cord. During this activity, a downward wave deflection with negative polarity is produced after 13 ms of stimulation known as **N13**. **N13** could be measured from the skin on the fifth cervical spine. It is generated by the dorsal root entry in cervical cord and by the cervicomedullary junction. After joining posterior columns, it synapses at the cervicomedullary junction and enters lemniscal decussation. At this point, a positive deflection after 14 ms of stimulation is detected known as **P14.** Then pathway continues from medial lemniscus up to upper midbrain and thalamus where a negative deflection after 18 ms of stimulation is produced, **N18. P14/N18** potential is generated in the upper brain stem and thalamus (sub-cortical) through post-synaptic activity of tectal and pre-tectal nuclei having input from medial lemniscus. Specifically, **N18** represents medial lemniscus. There are both recorded by placing an electrode channel on the ipsilateral centroparietal cortex. Finally, after passing thalamus and cross internal capsule, it reaches the primary somatosensory cortex of the contralateral limb where a negative deflection after 20 ms of stimulation is detected, **N20** (Nuwer, 1998).

Here my interest is in the N20-P25 somatosensory cortical SSEP component response often referred as the 'primary' component. The primary component is known to be modulated by task context (Seki and Fetz, 2012) and most specifically SSEP suppression and SSEP amplitude decrease is seen during the preparation of upcoming movement and during movement execution in all cortical areas and spinal cord in these short-latency primary SSEP components (see next section; Rushton et al, 1981; Starr and Cohen 1985; Abbruzzese et al, 1981; Shimazu et al,1999; Boecker et al, 1993; Voss et al, 2006). In this study, the reason that I chose to look at the primary components of SEP only is that stimulus perception, consciousness and attention do not bias them and they are not thought to be contaminated by afferents evoked through the movement. In contrast, secondary complexes arise later in primary somatosensory, such as P45-N55, in secondary somatosensory cortex and all other cortical areas seem to be biased by other factors involved in attention and stimulus perception that leads to elevated SSEP amplitude and latency response (Shubert et al, 2006; Desmedt et al, 1983). The secondary complexes origin is still obscure but it is evident that arise from different foci and is based on the movement of the stimulated digit (Rushton et al, 1981).

1.2 NEUROPHYSIOLOGICAL THEORY (SENSORY GATING)

The main interest of the work in my thesis is the phenomenon of sensory gating, also referred to as sensory attenuation (Rushton et al, 1981). More specifically the aims of my research are to revisit this sensory gating phenomenon in light of recent theoretical hypothesis about the functional role of movement related sensory attenuation that have been proposed in the active inference framework of movements (Friston et al, 2011). In this section I will review the previous relevant literature on movement related sensory gating.

Every movement a person makes stimulates peripheral sensory receptors that activate neurons in the cortex via ascending sensory pathways (Rushton et al, 1981). However, not all of these afferent signals generated during voluntary movement influence the cortical neuronal activity in the same way and they are known to be heavily modulated by both bottom-up and top-down signals (Rushton et al, 1981; Seki and Fetz, 2012). One such is sensory attenuation.

This sensory attenuation, also called sensory gating, is well documented and is most commonly believed to reflect an active suppression or cancelation of the predicted sensory consequences of an action to make the system more sensitive to unexpected sensations (Seki and Fetz, 2012). However, there are a number of observations about sensory gating, as measured by the reduction in amplitude of the SSEP elicited by a median nerve stimulation at the wrist, that are not easily explained by this proposed functional role. Firstly, SSEPs driven by median nerve stimulation are known to be attenuated not only during active movement but also just prior to the onset of movement (Starr and Cohen, 1985). Secondly, the primary N20-P25 cortical components of the SSEPs as well as the initial N17 response are known to be attenuated during passive as well as active movements (Abbruzzese et al. 1981). In addition this study demonstrated two further interesting results. Firstly, the cervical SSEP responses were not attenuated during active or passive movements, consistent with a mechanism of attenuation that is central, i.e. cortical and/or sub cortical in origin. However, the study also showed that the sensory gating during movement was not present after ischaemic block of large group I afferent fibers from the hand. Thus indicating that the mechanism underlying the sensory gating phenomena is dependent upon the sensory feedback from the periphery in some way (Abbruzzese et al. 1981).

This study by Abbruzzese et al. (1981) provided evidence that sensory gating was dependent both on a central mechanism and on the afferent signal from the periphery. However, there remains the possibility that the sensory gating that is central and the

gating due to the afferent signal are dissociable. This was tested explicitly in a study by Shimazu et al. (1999). In this study, participants were asked to move as quickly as possible after a sound cue, in the form of 70dB auditory clicks. The onset of the sound also triggered the median nerve stimulation. As the movement could not have occurred during the time of the median nerve stimulation due to the simultaneous presentation of the movement cue and the median nerve stimulation the relative contribution of attenuation of the SSEP due to central components and altered afferent signals could be assessed. The results showed that EMG activity were unaffected throughout all conditions, also P14-far fields, N20 in primary somatosensory cortex and P22 in frontal areas remained the same throughout all conditions. This finding indicates that SSEP gating was not caused by muscle afferents activity. Furthermore, SSEP components including frontal N30a/N30b and N60 were shown to be attenuated during movement compared to control conditions. The P30 was also seen to be decreased in some extent during movement (Shimazu et al, 1999).

Further evidence that SSEP attenuation is generated centrally is provided by Bocker et al. (1993). In this study, SSEPs were recorded using EEG in three task conditions, movement execution, movement preparation and rest post movement execution. As expected, and in agreement with previous studies, SSEP gating was shown during all movement execution phases. Gating was also observed during the forewarned movement preparation period. However, SSEP gating was modulated during this foreperiod. The parietal N70-P100 SSEP component showed decreased amplitude at the end of foreperiod compared to rest or the beginning of the foreperiod. The P45-N70 SSEP component also showed a significant decrease in amplitude from the beginning of the foreperiod to the end of foreperiod. In comparison to the SSEP components above, the P100-N140 component showed an increased amplitude at the end of the foreperiod as opposed to a decrease. In distinction from previous studies this study did

not report significant differences in the amplitude of the short latency SSEP components (Shimazu et al, 1999).

To identify if and how motor preparation influence sensory attenuation Voss et al. (2006) applied TMS to delay motor commands output coming from primary motor cortex. Experimentally cutaneous stimulation was applied to left and right index finger. Stimulation to the left finger was taken as a reference. Subjects' were instructed either to sit still or lift their right finger when the last of the 3 auditory tones was presented. On some trials a TMS pulse was sent during the presentation of the last auditory tone that resulted in a delay of the voluntary movement. During this delay period, cutaneous stimulation was applied 70 ms after the TMS stimulus. The results demonstrated a significant sensory suppression of the SSEP elicited during the period when the voluntary movement was delayed by the TMS that was of a similar magnitude to that observed during the movement phase. To eliminate the possibility that the suppression during the delay period was due to the difference in timing, cutaneous stimulation was applied before finger movement in the absence of TMS and no significant sensory attenuation was observed. This study demonstrated that sensory suppression is based on central signals that are related to motor preparation (Voss et al, 2006).

Sensory gating during motor preparation and motor execution has not only been shown in humans but also in primates. A good example of this is the study of Seki and Fetz (2012) where superficial radial nerve stimulation at a constant frequency of 3 Hz was applied and SSEPs were recorded in cervical spinal cord, primary sensory cortex, primary motor cortex and premotor cortex of monkey during a wrist flexion-extension task. The monkeys were trained to generate flexion-extension torques about the wrist. In the beginning of the trial, a cursor was presented at the centre of the screen where monkey stayed at rest. Then flexion and extension targets were shown right and left from the centre of the screen. During the instructed delay period targets were filled

indicating which movement the monkey should make. Then a go signal appeared and the monkey moved the cursor to the target as quickly as possible and the reaction time was measured (active period). Next, the monkeys held an elastic load for 1.5 s, this was defined as the active hold period where after a while a second go trial appeared, and the monkey executed the movement and a second reaction time was measured. After measuring the second reaction time, the wrist was passively returned to rest and the next trial started. During this task SSEPs were attenuated throughout the task. Taking rest condition as a baseline, all three cortices and spinal cord SSEP showed a significant reduction during movements. SSEP attenuation was also observed during the instructed delay period in primary motor cortex and pre-motor cortex but not in primary sensory cortex and cervical spinal cord suggesting a more specific suppression. It should be noted that the reaction time during movement was proportional to the suppression of SSEP magnitude. Shortest reaction times showed greater SSEP suppression than the longer reaction times. In contrast, SSEP attenuation in the instructed delay task was inversely correlated to the reaction times of the subsequent motor execution. SSEP reduction was also seen in all three cortices and spinal cord during active hold condition. This study therefore demonstrated that during active movement SSEP suppression is based on presynaptic and postsynaptic inhibition whereas during active hold condition, lateral inhibition from bottom-up mechanisms could result in the SSEP decrease (Seki and Fetz, 2012)

This neurophysiological attenuation in sensory responses during movement is also believed to affect the sensory percept (Shegill et al, 2003). A seemingly trivial example of this phenomenon is the inability to tickle oneself (Blakemore et al, 1999) but the phenomenon can also be more easily quantified using a force estimation task (Shegill et al, 2003). In such tasks healthy subjects tend to overestimate the force required to match a test force when they press on themselves. Abnormal gating has been proposed to be manifest in schizophrenic and dystonic patients. Indeed it has been

shown that, schizophrenic patients suffering from hallucinations are unable to estimate sensory consequences of their self-induced actions (Shegill et al, 2005). In addition, patients with dystonia showed abnormal pre-movement gating that was not observed in healthy subjects. These results were interpreted as the inability of these patients to correctly integrate the motor program that is essential for a movement to be performed with the sensory input (Murase et al, 2000).

The previous research on the perceptual sensory attenuation made the assumption that the neurophysiological sensory attenuation of the SSEP and the perceptual sensory attenuation had a common cause. However, whether neurophysiological attenuation affects sensory percept known as perceptual sensory attenuation is not entirely known. Palmer et al. (2016) tested whether there is a relationship between neurophysiological and perceptual sensory attenuation using a force match paradigm. Median nerve stimulation was delivered at the wrist and SSEPs were recorded. In the force-matching task, subjects received a force on their left finger and asked to match the force by pressing with their right finger either robot 1 (‘’self’’ condition) or robot 2 (‘’external’’ condition). They held the matched force until they heard an auditory tone that represented the stop signal. Median nerve stimulation was applied either when they held the matched force or when they replicated the force induced at the left finger. To record whether SSEPs were attenuated during movement, ‘’move’’ instructions were presented in the computer followed by an auditory go signal and subjects tapped their index finger of the wrist being stimulated. Then ‘rest’ instruction was presented in the screen and subjects were asked to remain still. Median nerve stimulation was applied and SSEPs were recorded. The results showed a significant neurophysiological SSEP attenuation of primary and secondary components during movement periods compared with rest. However, primary and secondary SSEP components were not seen to be affected during the force matching task and were not correlated with the perceptual sensory attenuation. Crucially, this study showed that neurophysiological

and perceptual sensory attenuation are dissociable and functional distinct. This has important implications for our understanding and treatment of neurological disorders (Palmer et al, 2016).

Previous accounts of both neurophysiological and perceptual sensory gating have largely interpreted these effects as arising from the active cancellation of a predictable sensory event (Blakemore et al. 1999, Shergill et al. 2003, Seki and Fetz, 2012). However, there are a number of experimental results that are not consistent with this account (Marcerollo et al, 2016). Most notable is the fact that SSEPs are themselves attenuated. SSEPs are the response to an unpredictable somatosensory event and therefore, if the cancellation model were true, then it is unclear how SSEPs driven by median nerve stimulation are attenuated when the event is entirely unpredictable. This suggests that rather than being an active cancellation of predictable sensory events sensory gating/attenuation is more a global phenomenon during active movement. Indeed, consistent with this recent neurophysiological data in the macaque monkey has demonstrated that sensory gating is largely a global effect occurring both cortically and in the spinal cord (Seki and Fetz, 2012). In the following section I will outline an alternative account that can account for SSEP movement related attenuation, active inference (Friston et al. 2016).

1.3 ACTIVE INFERENCE AS AN ALTERNATIVE NEUROPHYSIOLOGICAL THEORY FOR SENSORY ATTENUATION

The active inference framework provides a unifying theory of how we perceive and interact with external stimuli in the world. It applies the predictive coding framework, used traditionally to understand perception, to the sensorimotor system. This provides a novel and neurobiologically plausible theory for sensorimotor control. The active inference framework is grounded in the principles of predictive coding. Predictive coding is based on minimizing prediction error though recurrent or reciprocal

interactions among levels of a cortical hierarchy. In the predictive coding framework, each level of a hierarchy employs a generative model to predict representations in the level below. This generative model uses backward connections to convey the prediction to the lower level where it is compared to the representation in this subordinate level to produce a prediction error. This prediction error is then sent back to the higher level, via forward connections, to adjust the neuronal representation of sensory causes, which in turn change the prediction. This self-organising, reciprocal exchange of signals continues until prediction error is minimised and the most likely cause of the input has been generated. It can be shown that this scheme is formally equivalent to empirical Bayesian inference, in which prior expectations emerge naturally from the hierarchal models employed (Friston 2002, 2003, 2005). Within the cortical hierarchy a prediction error is generated at each level, within the active inference framework the influence of these bottom up prediction errors on higher levels are modulated by the estimate of the certainty or the precision in the prediction. Indeed within the active inference and free energy frameworks the prediction errors are precision weighted. Intuitively this makes sense as the more confident, or precise, you are in a prediction the more sensitive you should be to any difference between the predicted and actual input.

Every movement we make stimulates peripheral sensory receptors that provide sensory feedback of the motor act. It is thought that, when we move, we predict the sensory consequences of that movement (through forward models) and compare this prediction to the actual sensory input (Wolpert & Ghahramani 2000, Adams et al. 2013). As with perceptual inference any difference between the predicted and actual sensory input will result in a prediction error, which is used to update the forward model for more accurate future predictions. This idea of generative and forward models in motor control is well established (Wolpert & Ghahramani 2000) and these models have been successfully employed to account for many observed features of motor control.

However, they do not provide a clear account of why we move. Active inference makes a clear and testable prediction as to why we move. Within this framework the generative models employed are constantly trying to predict the sensory input, for movements, the somatosensory afferent signal from the periphery. As with models of perception we can update our generative models to minimise prediction error between the predicted and actual sensory input. However, with actions we can minimise any prediction error between the predicted and actual sensory input in a second way, we can move so that our actual sensory inputs match our predicted sensory input. Within this framework, therefore, movements occur to minimise the prediction error between our predicted and actual sensory. Within this framework whether we move to minimise our prediction errors or whether we update our generative models to minimise prediction errors is determine by the relative precision weights on the estimate of the sensory input or on the model. According to the active inference framework, when we start to prepare a movement, we generate a prediction of what the sensory input of this movement will be and this creates a prediction error between the current and the predicted sensory states. To minimize this error, an individual can: (i) stay still and update their prior beliefs (within the forward model) so that the predicted sensory input matches the actual sensory input; or (ii) move, so that the actual sensory input matches the predicted sensory input. Modulating the relative uncertainty in these sensory states will determine which option is selected. For example, to initiate movement, the uncertainty in the current sensory state is increased, or the precision is decreased, such that the individual will shift to the predicted sensory state with the lowest uncertainty. Therefore within this account, sensory attenuation is necessary for movement and reflects the reduction of sensory precision to allow the movement to occur (Friston et al., 2011, Friston et al, 2016). Within this framework sensory attenuation is a necessary consequence of reducing the precision (synaptic gain) of sensory evidence during movement to allow the expression of the prior beliefs that incite movement. One consequence of this framework is that in order to be able to

move the prediction errors about the hidden states must be greater than the prediction errors about the somatosensory expectations. In other words, in order to be able to move the gain of the somatosensory prediction error signal must be reduced and this results in the observation of sensory attenuation during active movement. Of particular interest is that within the active inference framework a failure to move can be modeled by a failure to sufficiently attenuate precision on the somatosensory expectations. Indeed, it has been proposed that some of the hypokinetic symptoms of Parkinson's disease, specifically akinesia and bradykinesia, can be recast as a result of a pathology in reducing the precision of the somatosensory expectations (Friston et al. 2012, Macerollo et al, 2016). Furthermore, the attenuation of the precision has been proposed to be mediated by changes in neuromodulators such as dopamine. In other words, hypokinetic movement disorder symptoms could arise from a failure in estimating the correct level of sensory precision. However, the neurophysiological correlates of these estimates are unknown. Recent research has provided evidence that cortical oscillations in the beta-frequency range (~15-30Hz) might be functionally related to these parameters of uncertainty (Torrecillos et al. 2015, Tan et al. 2016).

1.4 SENSORIMOTOR BETA OSCILLATIONS

It has been known for over 50 years that power in the beta frequency range (~15-30 Hz), originating in the sensorimotor cortices in healthy human subjects, is modulated during action execution (Jasper & Penfield 1949, Gastaut 1952). Beta power is reduced just prior to and during the period of movement and is transiently increased subsequent to the end of the movement (Kilner et al. 2000, Baker et al 1999, Baker et al. 1997, Pfurtscheller & Lopes Da Silva 1999, Hari & Salmelin 1997). However, despite extensive research into these neuronal oscillations their functional role, if any, remains unknown. The importance of understanding their functional role is highlighted by the

observation that Parkinson's disease patients have a pathologically higher power of beta oscillations, both in the cortex and sub-cortically in the subthalamic nucleus (Little & Brown 2014, Moran et al 2011, Jenkinson and Brown 2011). It has therefore been proposed that in Parkinson's disease patients pathologically high amplitude of beta oscillations causes bradykinesia and other motor symptoms (Little and Brown 2014). However, there is still discrepancy for and against this notion. Beta oscillatory activity is seemed to be increased prior to and during movement cortically and sub-cortically. To increase dopamine transmission, stop disease progression and potentially reduce beta oscillations, pharmacological agents such as levodopa are used (Little and Brown, 2014, Jenkinson and Brown 2011, Moran et al, 2011). Understanding how electrical properties of the brain change during pathophysiology will increase our understanding of surgical techniques that are used to restore movement through electrical stimulation (Moran et al, 2011). One such technique is deep brain stimulation (DBS) were electrodes are surgically implanted in a PD patient brain and electrical stimulation is given, where it ameliorates 60% of Parkinsonian symptoms. In comparison, levodopa decreases these symptoms around 37-69%. But do these agents actually suppress beta oscillations? There is a discrepancy in the literature as some studies show that only DBS decrease beta oscillations and some others that both levodopa and DBS decrease them. Beta oscillations could be potentially decreased through DBS by the use of high-frequency stimulation (~100 Hz). However, mechanism of DBS action is still unknown (Eusebio et al, 2012), (Giannicola et al, 2010).

It has been proposed that beta oscillations function to maintain existing motor tasks and in compromising new movements. (Engel et al, 2010). Somatosensory, primary motor and parietal cortices are important brain areas for information flow in beta band oscillations. Its dominance has been observed in processing endogenous top-down signals as intended or predicted to preserve status quo in cognitive and behavioural

control (Engel et al, 2010). However, it is unclear how the beta oscillations function to maintain the status quo or by what mechanism they are produced or maintained. Recently, it has been proposed that beta oscillations in the sensorimotor system might be related to the parameters of uncertainty that have been proposed in generative models and motor control (see section above and Palmer et al. 2016). According to the active inference framework, sensory attenuation is a prerequisite for movement and sensory attenuation is realized through a modulation in the synaptic gain, or precision, of the somatosensory prediction error units. However, what the neurophysiological correlates of this change in precision are remains unknown. Prima facie it appears that there is compelling evidence to predict sensorimotor beta power and estimates of sensory precision might be linked (Palmer et al. 2016). For example, 1) sensorimotor beta oscillations are known to be attenuated during motor preparation and execution; active inference would predict a decrease in precision. 2) increases in sensorimotor beta-power are associated with the inhibition of executed actions; active inference would require an increase in somatosensory precision to inhibit an action. 3) sensorimotor beta-power is augmented in patients with Parkinson's disease compared to healthy controls; active inference would predict a high level of sensory precision in Parkinson's disease patients compared to healthy controls. 4) When the motor system is stimulated at 20 Hz frequency of stimulation through transcranial alternating current stimulation (tACs) motor performance was disturbed (Davis et al, 2012). tACs induces an oscillatory electrical field across the two electrodes implanted in the head as alternating current is passed between them (Davis et al, 2012).

Indeed there is some evidence that beta oscillations and precision might be linked. Bhatt et al. (2016) modelled the modulation of beta oscillations in the motor cortex during a simple hand grip. In line with previous results, beta oscillations were attenuated during movement and increased at movement termination. To explain beta power desynchronization during movement, the authors used canonical microcircuit

models and employed dynamic causal modelling to explore different connectivity patterns between the different layers to investigate which model could best explain the data. Strong pathway was identified for intrinsic connectivity between superficial and deep pyramidal layers. Weaker pathways were seen for reciprocal connections between inhibitory and superficial pyramidal subpopulations, also between middle pyramidal and inhibitory subpopulations. To relate these pathways to the modulation observed during the handgrip, an increase was seen in all connections. Release of handgrip resulted in an increase of input in deep layers. At rest, increases between connections was not evident. The authors interpret these results as in line with attenuation of sensory precision based on predictive coding (Bhatt et al, 2016).

One prediction of the proposed link between precision and sensorimotor beta power is that there should be a tight correlation in the task modulation of sensorimotor beta oscillations and the attenuation of the primary component of the SSEP. If the attenuation of the SSEP is realized through a modulation in precision and if precision is related to beta power then there should be an observable relationship between the SSEP amplitude and beta power. To date no studies have investigated this relationship. Pfurtscheller et al (2002) used median nerve stimulation to measure SSEPs whilst subjects manipulated a the cube with the fingers of the right hand that was stimulated. Results showed a marked suppression of beta oscillations during the motor behaviour but a significant enhancement of long latency SSEP components (Pfurtscheller et al, 2002). However, these were long latency component and there has not been any comparison of short latency SSEP components, beta oscillations and sensory gating. This is one of the aims of the research in this thesis.

1.5 FREQUENCY TAGGING

Frequency tagging is an experimental approach has been used in many studies involving different types of evoked potentials such as auditory evoked and visual evoked potential but less used to record SSEPs. Only one study to date by Kourtis et al, 2008 has used this approach and it is the most influential for this thesis as one of the main aims is to show the time-course of SSEPs based on time-frequency analysis.

Frequency tagging and resonance phenomena have been widely described in the scientific literature, mainly in the visual and auditory domains (Klimesh, Basar, Silberstein and others). If a system is capable of oscillation and periodic series of impulses are given at a frequency equal to the natural frequency of the oscillatory system, the system is set for an oscillation with a large amplitude known as resonance phenomenon. An example of this notion, is Tacoma Narrows Bridge that collapsed as wind reached the bridge natural frequency (Bilah and Scanlan 1991).

The logic of this technique is fairly simple. Subjects are presented with a sensory stimuli that is modulated constantly at a particular frequency. The sensitivity of the subjects' response to the sensory stimuli is measured using EEG or MEG. In this way experimenters are either able to study the transmission of this sensory signal as it is processed (Hermann, 2001) or to study whether the primary sensory cortices are particularly sensitive to being driven at particular frequencies. A good example of the latter is the study of Hermann (2001). Here, 10 human subjects were presented with a flickering light at a range of different frequencies from 1 to 100 Hz in 1 Hz steps. Oscillatory EEG activity through repetitive stimulation was presented in the form of steady-state visual evoked potentials (ssVEPs). Neural oscillators such as gamma power could respond more strongly if stimulated at resonance frequencies and this is quite evident from this study as clear resonance phenomena were seen especially at 10,20,40,80 Hz. Therefore, a possible correlation could be seen between evoked

oscillations and EEG activity of ssVEPs responses where synchrony of visual neurons firing is exhibited to the frequency of flickering light known as photic driving (Hermann 2001). Frequency domain analysis and resonance phenomena using 10 Hz of stimulation has also been evident in alpha oscillatory activity (range from 8-12 Hz) during primary sensory coding and memory representations (Schurmann et al, 1997), (Klimesh et al, 1997), (Basar et al, 1997). To evaluate these phenomena, for many studies the key question is how amplitude of ssVEPs changes in relation to stimulation frequency presented and showed that the amplitude of ssVEPs increases when stimulation frequency is the resonant frequency that drives the system (Shurmann and Basar 1994). Presenting a visual stimulus of familiar and unfamiliar objects during object recognition and measuring ssVEPs shows a preferential response for 12 and 15 Hz. When presented at these frequencies ssVEPs amplitudes are the highest towards familiar object presentation (Kaspar et al, 2010). Frequency tagging in ssVEPs has also been recorded in spatial selective attention experiments where range of frequencies from 20-28 Hz were presented. When flicker frequencies of 20.8 and 27.8 were displayed in the right-field and left-field respectively, amplitude of ssVEP was enhanced in either field when attention was directed to other location (Muller et al, 1997). Modulation of ssVEPs and resonant frequencies are also linked with stimulus classification and memory search (Silberstein et al, 1995), (Silberstein et al, 1990), (Wilson and O'Donell 1986).

To test multisensory integration of both auditory and visual stimuli, steady state auditory and visual evoked potentials (ssVEPs, ssAEs) were recorded. For auditory stimulation, 11 Hz frequency was used to tag EEG response and for visual stimulation the frequency of interest was 10 Hz. It showed that temporal harmony play a key role in multisensory integration during the sensory-stages of cortical processing (Nozaradan et al, 2012). Frequency tagging has also been possible in the auditory domain alone through recording of ssAEs. Subjects were presented with 40 seconds sequences of

sound at 1.6 Hz. The results showed a stable amplitude response over repetitions and contrast responses possible (Nozaradan et al, 2017).

However, such frequency analysis in somatosensory SEPs has not been presented widely in experimental studies. Frequency analysis was carried out by Kourtis et al, 2008 to study the time-course of sensory attenuation and cortical excitability changes during selection, preparation and execution of responses. SEPs were recorded through median nerve stimulation using a stimulation frequency of 22.2 Hz. Association of the time-course of SEPs with the time-course of lateralized potentials was made and showed close resemblance. The time course of sensory attenuation was seen as a SEP amplitude decrease greater for contralateral than ipsilateral movement (Kourtis et al, 2008). Although this study gives information about time-course of sensory attenuation, it does not provide published evidence why this frequency was used and does not show whether activity is driven by SEPs or β-oscillations.

1.6 HOW ACTIVE INFERENCE, PREDICTION ERROS AND PRECISION ARE LINKED TO SENSORY ATTENUATION

Active inference is based on the Free Energy principle of the brain. Free energy is a function that is based on our observations and our guesses of the final estimate by combining our prior belief and our new observation (likelihood). Under active inference framework, body homeostasis is achieved by minimizing free energy or surprise through the use of probability theory and Bayes theorem. Minimization of free energy is a result of maximization of our guess to the true posterior and of our model regarding prior belief and likelihood and is in line with predictive coding as prediction error has to be minimized to avoid surprise. In predictive coding, each level of hierarchy produces a generative model based on the probability of different states (hidden-only one observation is made for each state) and their observations, the prior beliefs and new observations. Prediction error is made by comparison of lower cortical level to subordinate level and is fed up to higher cortical areas to adjust representations of sensory causes and update the prediction of the system. This happens multiple times until prediction error is minimized (Friston, 2002; Friston, 2003). Under predictive coding, prior beliefs are controlled by the precision or confidence of the predictions that made in higher cortical areas relative to sensory precision (Lawson et al, 2015).

To understand the mechanism of sensory precision and sensory prediction, studies have used the paradigm of the force-matching task where participants are asked to exert a force that matches either a self-generated or externally generated action. It has been evident that the force exerted by an internal generated cause is greater (Blakemore et al., 1998, 2000). This will lead to a decrease in sensory precision and an attenuation in the amplitude of sensory prediction errors (precision weighted). In turn, this effect is known as sensory attenuation. Schizophrenic patients have shown increased sensory precision and amplitude of sensory prediction and therefore less

sensory attenuation. Because of impaired sensory attenuation, they perform force matching tasks more accurately than controls (Brown et al, 2013).

In terms of sensory precision in movement production, for prediction error to be minimized, movement has to be executed so that actual sensory input matches predicted one, where sensory precision is decreased and sensory attenuation is evident. Therefore, sensory attenuation is necessary for movement to occur (Friston et al., 2011, Friston et al, 2016).

Based on these findings and under the active inference framework, I hypothesized that physiological sensory attenuation that is based on a decrease in SSEP amplitude before and during movement, will follow the same paradigm where amplitude of prediction errors will decrease followed by a decrease in sensory precision and therefore the action will update prior beliefs or representations of body states.

The following figure (Figure 1-2) shows how different sensory prediction errors and expectations are generated in different brain areas. How these sensory prediction errors and expectations are passed in a hierarchical order resulting in sensory attenuation. To explain the diagram in more detail, somatosensory and proprioceptive prediction errors are generated in thalamus whereas expectations and prediction errors of forces (circles) are generated in sensorimotor cortex. Expectations and prediction errors of the causes of the forces (triangles) are placed in prefrontal cortex. Proprioceptive predictions descend to spinal cord through a classical reflex arc. Red connections arise from prediction error units and they are either intrinsic or forward extrinsic connections that arise from superficial principal cells. On the other hand, black connections arise from conditional expectations and present intrinsic and backward connections from deep principal cells. Finally, cyan connections are descending neuromodulatory effects that mediate sensory attenuation. To conclude, expectations

of sensory states can be fulfilled by descending proprioceptive predictions or corrected by ascending sensory prediction errors. Precision of sensory prediction errors must be attenuated.

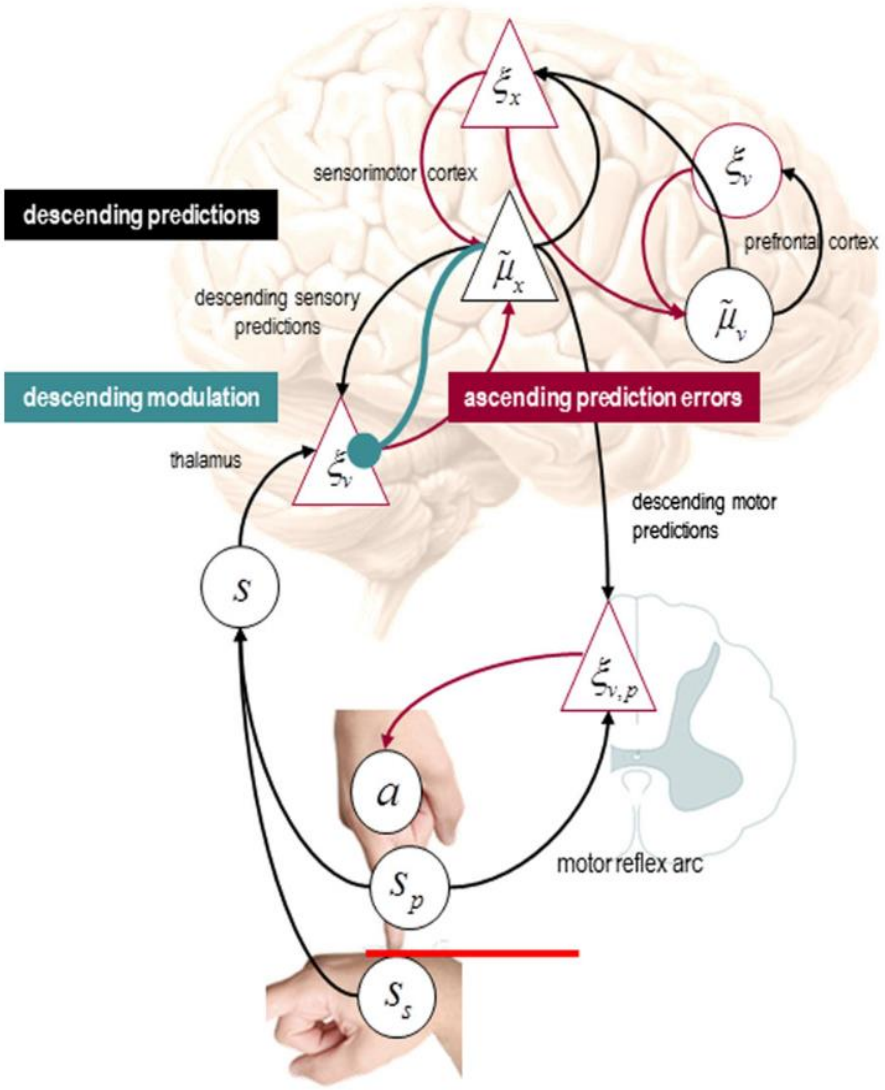

Figure 0-1. ***Figure adapted by Brown et al, 2013***

2 AIMS OF RESEARCH

This thesis consists of three experimental research chapters

The first study was designed to develop the technique of somatosensory sensory frequency tagging that will enable me to study the time course of SEP attenuation prior to and during movement and to test the hypothesis that median nerve SEP attenuation is correlated with modulations in sensorimotor beta oscillatory power.

Therefore, the main aims of the first experiment were to

- Test whether SSEPs elicited through median nerve stimulation are present when the median nerve is stimulated at different frequencies
- Can SEPs elicited through median nerve stimulation be frequency tagged
- If so is their evidence of resonant responses as a function of the frequency of stimulation.

In the second experimental chapter I investigated whether SSEPs were attenuated during a motor task and whether this attenuation was correlated with modulations in beta power.

To this end, the main aims of study 2 were to:

1) Test whether SSEPs elicited through median nerve stimulation are present
2) Whether there are attenuated prior and during rest, motor preparation and movement
3) Whether SSEPs are attenuated with time

4) Identify if beta oscillations are present and whether there are attenuated by task and time

5) Correlated their time courses to identify if there are related to each other

Further to this, a 3rd behavioural experiment was carried out. This study was designed to investigate whether increasing somatosensory through vibration in the periphery altered performance on a stop-signal reaction time task.

The main aims of study 3 were:

1) Test the performance and accuracy of subjects in a go/no-go task by calculating reaction times

2) Test whether performance and accuracy differ significantly when vibration is used

3 FREQUENCY TAGGING: NEW TECHNIQUE OF EVALUATING SSEPs

3.1 INTRODUCTION

According to the active inference framework, sensory attenuation occurs for a movement to be realized. It is known that SSEPs elicited by median nerve stimulation and measured non-invasively at the scalp using EEG are reduced in amplitude, or attenuated both prior to and during movement (see general introduction for a review of this literature). However, the precise time course of SSEP attenuation during movements is not known. One of the most important studies in this field is by Starr and Cohen (1985). Starr and Cohen (1985) measured sensory attenuation by generating auditory clicks of 100 μs-pulses every 3 seconds as a signal for thumb movement and delivering median nerve stimulation at approximately 20 ms after the clicks. The authors showed that sensory attenuation could be observed both prior to and at movement onset. However, this study highlights the practical difficulties of using standard SSEP protocols to investigate sensory attenuation as a function of movement time. To produce reliable SSEPs hundreds of trials are required. Therefore to study the modulation of the SSEP amplitude as a function of time requires hundreds or thousands of trials, hundreds of trials per time point studied. It is for this reason that the results of Starr and Cohen (1985) were based on three subjects and the experiment for each subject lasted for about 6 hours, with 500 stimulations per time point. Most importantly given this methodology it is not practicable possible to measure the time-course of sensory attenuation at a fine time scale (Starr and Cohen, 1985). To be able to test the hypothesis that the time course of SSEP attenuation during movement is related to the modulation of beta oscillations we require a more a subject friendly experiment that still allows us to measure SSEP attenuation.

One possible solution to investigate the time course of SSEP attenuation is to develop a novel SSEP protocol that would allow for the study of the time course of SSEP modulation during movement tasks. One possibility would be to use frequency tagging. Frequency tagging has been widely used in studies to record auditory and visual evoked potentials, to either study the transmission of sensory input as it is being processed (Klimesh et al. 2012) or to study whether primary cortices are sensitive to be driven at particular frequencies (Hermann et al, 2001). In contrast to the visual and auditory domains very little work has been carried out investigating whether frequency tagging is a viable methodology for SSEP research. One previous study that has used frequency tagging in somatosensory domain to record SSEPs was by Kourtis et al. (2002). In this study SSEPs were induced by median nerve stimulation. In this study they stimulated the median nerve only at 22.2 Hz and showed that is was possible to study a modulation in SSEP amplitude as a function of task. However, it was not clear as to why this frequency was used or whether this was the optimal stimulation frequency. Therefore the aims of this experiment were to test firstly whether frequency tagging of SSEPs was a reliable methodology and secondly whether there were resonant frequencies of stimulation within the sensorimotor system.

Therefore, the main aims of Experiment 1 were to:

- Test whether SSEPs elicited through median nerve stimulation are present when the median nerve is stimulated at different frequencies
- Provide evidence that SSEPs elicited through median nerve stimulation be frequency tagged
- If so is their evidence of resonant responses as a function of the frequency of stimulation.

3.2 MATERIAL AND METHODS

3.2.1 DATA ACQUISITION

3.2.1.1 PARTICIPANTS

19 healthy subjects took part in this study (12 males, 7 females, mean 32.5 age years, range 22-43 age years), 3 subjects were excluded from the analysis due to the poor quality of the EEG recordings. All were right-handed, had normal or corrected-to-normal vision and were naive with respect to the purpose of the experiment. The experiment was performed with the approval of the ethics committee of University College London, and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

3.2.1.2 STIMULI

To elicit an SSEP response, stimulating electrodes were placed over the median nerve of the right wrist. The intensity of the electrical stimulus was 80% of the motor threshold. The motor threshold was determined separately for each participant by unilaterally applying discrete electrical square wave pulses (0.5 ms duration each) at the median nerve inside of the wrist. The lowest value which produced a twitch of the thumb (observed by the experimenter) was taken as the motor threshold.

SSEPs were tested in two conditions, standard SSEP and frequency tagging SSEPs. In the standard SSEP condition, 4 minutes of 1 Hz median nerve stimulation was given

and performed twice, once at the start and once at the end of the experiment. This condition was employed to enable us to compare the SSEP production under high frequency conditions with that of standard frequencies of 1 Hz. It also enabled us to choose the electrodes of interest overlying left sensorimotor cortex where SSEP was maximal so as to carry out the analysis of frequency tagging conditions in an independent manner.

In frequency tagging SSEP, median nerve was stimulated for 2 minutes (120 seconds) at 11 different frequencies (5.3, 8.2, 11.1, 14.2, 17.1, 19.7, 23.3, 25.6, 28.4, 32.0, 34.1 Hz) producing 11 different blocks. These frequencies were chosen so as to avoid frequencies that were phase locked to 50 Hz mains noise. Earlier pilot experiments revealed that using integer values for the frequencies produced large 50 Hz noise artefacts. Between blocks subjects were able to rest and the next block was only started at the subject's instruction. The order of these blocks was randomly selected for each subject.

In all conditions the subjects sat in a comfortable chair in a darkened room, with their right arm supported in a cushion. Subjects were instructed to relax and remain still throughout the experiment

3.2.1.3 EEG AND SSEP PROTOCOL

EEG was recorded with a Biosemi system with 128 scalp electrodes at a sampling rate of 2048 Hz. Earlobe electrodes were used as reference. All pre-processing and initial data analysis was performed within SPM12 (http://www.fil.ion.ucl.ac.uk/spm).

3.2.2 DATA ANALYSIS

3.2.2.1 PRE-PROCESSING AND SSEP AMPLITUDE ANALYSIS

EEG data were high band filtered at 0.1 Hz frequency and then epoched in a time-window of -100 ms to 250 ms where 0 ms was the time each median nerve stimulation was given. These filtered and epoched time-series were averaged across all events for each block and each subject. To test the hypothesis regarding frequency tagging, the EEG data were averaged across electrodes of interest and time points were selected for the primary SSEP component (N20-P25) of the standard SSEP condition (always blocks 1 and 13). Note, that this was completely independent to the non-standard frequency condition to avoid bias. This was performed for each subject separately. Electrodes of interest were chosen from grandmean scalp maps where a negative median nerve SSEP response at around 20 ms, overlying left sensorimotor cortex was seen (see Figure 3-1 left central electrodes shown as blue). Electrodes were identified visually through the scalp maps, but their selection was not limited to that. The standard SSEP data was plotted for each subject (Figure 3-3) and based on whether N20-P25 showed the largest deflection, the electrode selection was adjusted accordingly. Only electrodes showing a clear ERP were chosen. In addition, electrodes that produced noisy N20-P25 deflection were eliminated from the analysis. These electrodes were used for all further analysis on the frequency tagged SSEPs.

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From this grand averaged ERP averaged across electrodes, the amplitude of the primary SSEP response was computed through calculating the time-points of N20-P25 complex for the standard SSEP condition. N20 and P25 components represent the minimum and maximum of the waveform and the time points were selected from the ERP plots of each subject and occurred approximately around 20 ms and 25 ms respectively after the time of the median nerve stimulation. These values were different for each subject but the same time points were used within each subject for each frequency of stimulation. The amplitude of the difference in ERP values at these time-points were calculated to produce one value per subject for the standard SSEP condition. These time-points and electrodes of interest were further used to calculate the amplitude of SSEP response in non-standard frequency tagged conditions, producing 11 measures of the N20-P25 amplitude for each subject. These values (corresponding to the magnitude of the SSEP) were used for all statistical testing of the time series data.

To test the hypothesis whether SSEP amplitude changes with frequency and whether there is an optimal frequency where SSEP amplitude appears to be higher, a repeated measures ANOVA was carried out for non-standard frequency tagged conditions. *Repeated measures* ANOVA are also referred to as *within-subject* ANOVA as the factors are measured from the same subjects. F-statistic is used to examine main effects and interactions of factors using the ratio of squared means and assess whether expected values of a quantitative variable differ from each other. Degrees of freedom were calculated as n-1 where n represents the number of the subjects and therefore 16 df were taken. The p-value shows the probability of how random our results are using 0.05 as a cut-off value. As statistical errors could hugely influence the results and due to the presence of abnormal errorbars, outlier removal was carried out

and values above 1 standard deviation were eliminated. Epoched files produced for each block and for each subject were scanned for bad trials.

3.2.2.2 FREQUENCY-DOMAIN ANALYSIS

Frequency-domain analysis was carried out using custom written code in MATLAB. The aim of the frequency-domain analysis was to identify EEG responses that are periodic over time. Specifically I wanted to test a common phenomenon in other forms of sensory frequency tagging, that the response frequency (frequency of response as measured in the EEG) can be driven by the input frequency (the frequency of median nerve stimulation). All analyses here focused on whether I can drive the EEG at the frequency of stimulation. In frequency-domain analyses the most important concept is the transformation that changes time to frequency and vice versa. A classic transformation method is Fourier transform. Classic Fourier transform facilitates the detection and estimation of the signal processing through decomposition by a basis of single periodic functions, sines and cosines. Detection determines the specific signal set present in the observation whereas estimation identifies the values of the parameters from the signal. This Fourier analysis converts the EEG time series into a frequency spectral graph that is known as the power spectrum. Power is a measure of the square of EEG magnitude and magnitude is the average of EEG signal amplitude (Harris, 1978).

A transformation method used here was the Welch spectrum. This method is a modification of Fast Fourier transform that enables power spectrum analysis. It involves record sectioning, modification and averaging of periodograms from the section. The advantages of Welch spectrum are that it involves less computation than other frequently used methods, it transforms sequences that are shorter than the whole

record, it yields resolution in the time dimension that is often necessary when testing and measuring a signals that are non-stationary over time and decreases the noise in the power spectra (Welch, 1967). The precise choice of segment length is a compromise between reliability and frequency resolution. Longer segments give more frequency resolution whereas shorter segment length decrease variance and gives more averages (Harris, 1978).

Here I calculated power spectrum on non-overlapping sections of 2048 data points, here that is equivalent to windows of 1 second. These power spectra were calculated from the filtered data for the electrodes of interest (see above). Power spectra produced from a window of 2048 data points recorded at 2048 Hz produced a power spectrum with 1025 frequencies from 0-1024 Hz. The 2 minutes stimulation period had 120 windows. Windows are weighting functions and are used in harmonic analysis to avoid unwanted effects that are based on spectral leakage. From all possible frequencies, only frequencies that coincide with the basis could represent a single basis vector whereas the others frequencies will present non-zero projections on the basis set. This finite-duration processing is defined as spectral leakage. Application of windows aims to decrease discontinuity at the boundary of the observation by setting the value of derivatives to zero or near to zero so that the data is continuous in many orders of derivative (Harris, 1978; Roach and Mathalon, 2008).

To test the hypothesis that the input frequency was driving the response frequency I reduced the sampling of the 1025 frequency power spectra by only selecting the power at the driving frequency for each subject. The resulted in an 11X11 matrix for each subject where the 11 values corresponded to the 11 stimulation and response

frequencies (5.3, 8.2, 11.1, 14.2, 17.1, 19.7, 23.3, 25.6, 28.4, 32.0, 34.1 Hz). All statistical analysis in the frequency domain was performed on these values.

Here I calculated the average power spectra for three conditions. The first was the raw data. Here the power spectra data were calculated on the 120 s time period for each stimulation frequency. Note that this time series will include both the median nerve artefact and any cortical responses to the stimulation. The second condition was a time series where the median nerve artefact had been removed prior to the frequency analysis. To generate the artefact free data I replaced the 15 time points that covered the stimulus artefact with the 15 data points just prior to stimulation. The data were linearly rotated so that the substituted data matched the original data preceding and proceeding the 15 points of the artefact. In this way I produced a median nerve artefact free data set. The third condition was a time series of only the median nerve artefact. To produce the artefact data set I first produced a noisy time series of the same length as the other data sets by randomly selecting data from a distribution with a mean of zero and standard deviation one for each time point and then adding in the 15 data point artefact at the time of stimulation. I then analysed each of these data sets in the same way as for the raw data (see above)

Logarithmic normalization of the power spectra was carried out in this section.

3.3 RESULTS

3.3.1 SSEP AMPLITUDE ANALYSIS

In the first analysis, to demonstrate that there was a significant primary component in both the standard, where 4 minutes of 1 Hz stimulation was given, and non-standard

SSEP conditions where median nerve was stimulated for 2 minutes (120 seconds) at 11 different frequencies (see methods for details), I averaged over the all the trials for each block for each SSEP condition. Then I computed the grand average by averaging this data across all subjects and blocks for both the standard and non-standard SSEP condition. The resultant grand average scalp maps for standard and non-standard SSEP conditions are shown in Figure 3-1A&B, Figure 3-2A&B respectively. The scalp maps show the grand average at all electrodes at the time point of the N20 and P25 SSEP components (on average these occurred at ~21 and 24 ms respectively in both conditions). Figure 3-1A and Figure 3-2A show a region overlying left somatosensory cortex contralateral to the stimulated right wrist where the magnitude of the SSEP was maximal. Crucially the scalp maps of the N20-P25 component in both conditions are qualitatively and quantitatively consistent and this is clear evidence that an SSEP was present during both low and high-frequency median nerve stimulation.

Having provide face validity that high frequency median nerve stimulation resulted in qualitatively similar scalp maps analysis was performed to identify the electrodes of interest from standard SSEP condition (~1 Hz stimulation) for each subject individually based on where the ERP showed the largest deflections relative to baseline at a post-stimulus time point and scalp position consistent with a median nerve SSEP (~20 ms after stimulation with overlying left central electrodes shown as the blue area in Figures 3-1A&B).Bad electrodes were not selected and were eliminated (Figure 3-1A).

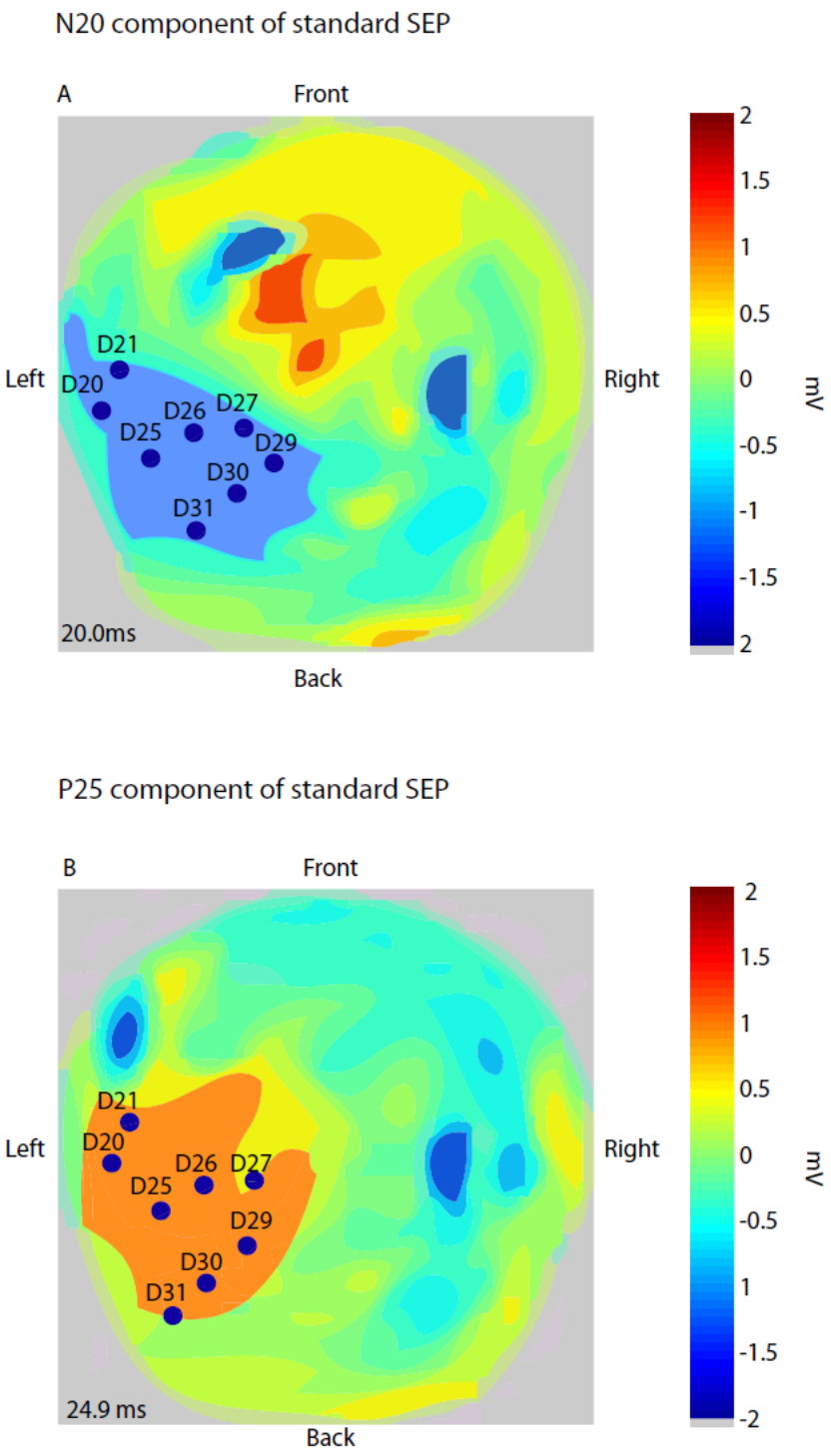

Figure 3-1. ***Scalp maps of standard primary SEP component****.*
A. *Scalp map of all subjects for standard SSEP condition that shows N20 SSEP component as lowest activity in the scalp (**Blue**) at the right. This figure also shows the hotspot of electrodes chosen* ***B.*** *Scalp map of non-standard SSEP condition that shows P25 SSEP component as highest activity in the scalp (Red) at the right similarly to N20 SSEP component of Figure 4-1A.*

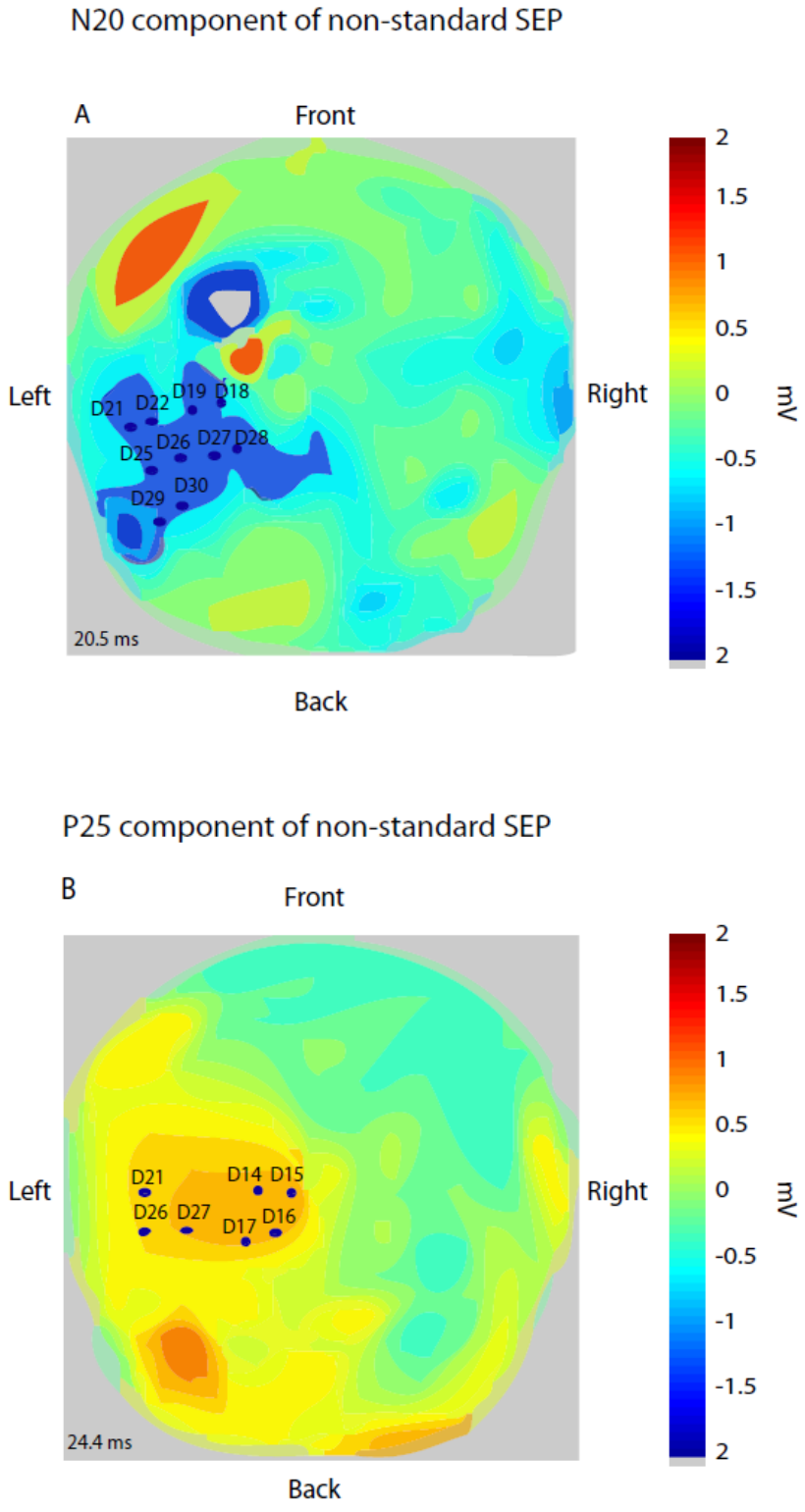

Figure 3-2 ***Scalp maps of non-standard primary SEP components***
A. Scalp map of all subjects for non-standard SSEP condition that shows N20 SSEP component as lowest activity in the scalp (**Blue**) at the right. This figure also shows the hotspot of electrodes chosen **B** Scalp map of non-standard SSEP condition that shows P25 SSEP component as highest activity in the scalp (Red) at the right similarly to N20 SSEP component of Figure 4-2A.

All further analysis of the SSEP focussed on the magnitude of the primary complex defined as the difference between the amplitude of the SSEP at N20 and the P25. To this end the time points of the N20 and P25 components were calculated for each subject in a non-biased way. For each subject the SSEPs were first averaged across the electrodes of interest (see above for methods) and then across standard SSEP condition. The time of the N20 and P25 components were then selected from this SSEP by eye for each subject. The magnitude of the SSEP was defined as the difference in the SSEP amplitude at these two time-points (Figure 3-3A, 3-3B). The spread of N20-P25 timepoints in milliseconds for each subject for the standard SSEP condition are shown in Figure 3-4. The same time-points were used for each subject in the non-standard SSEP condition. The order of frequencies (5.3, 8.2, 11.1, 14.2, 17.1, 19.7, 23.3, 25.6, 28.4, 32.0, 34.1 Hz) were randomized across subjects.

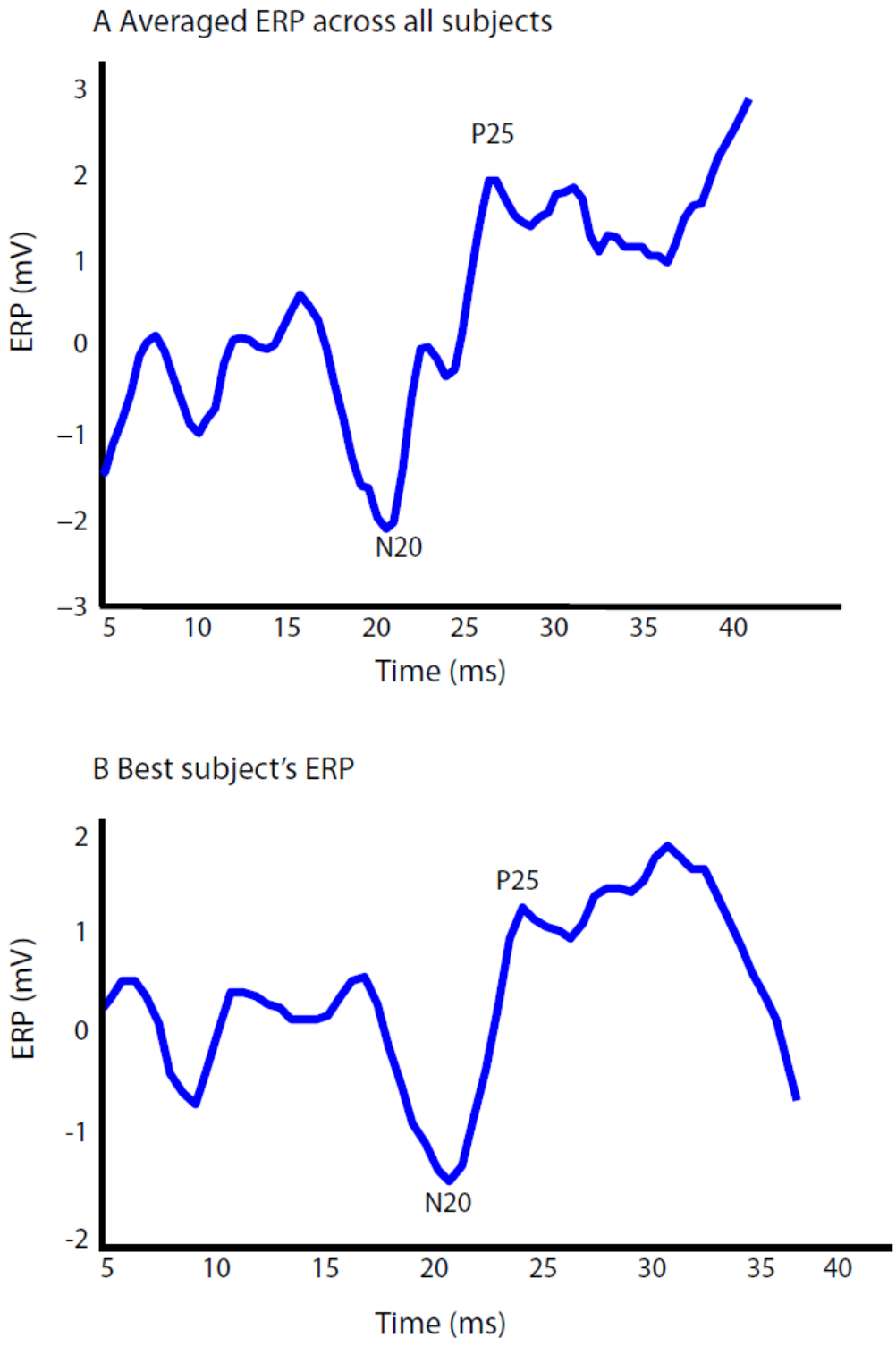

Figure 3-3 ***Averaged and single subject's ERPs for standard SSEP condition***
A. *Shows averaged ERP across all subjects for standard SSEP condition and the selection of N20-P25 timepoints at 20 and 25 ms respectively.* ***B.*** *Shows best subject's ERP for standard SSEP condition and the selection of N20-P25 timepoints at 20 and 25 ms respectively.*

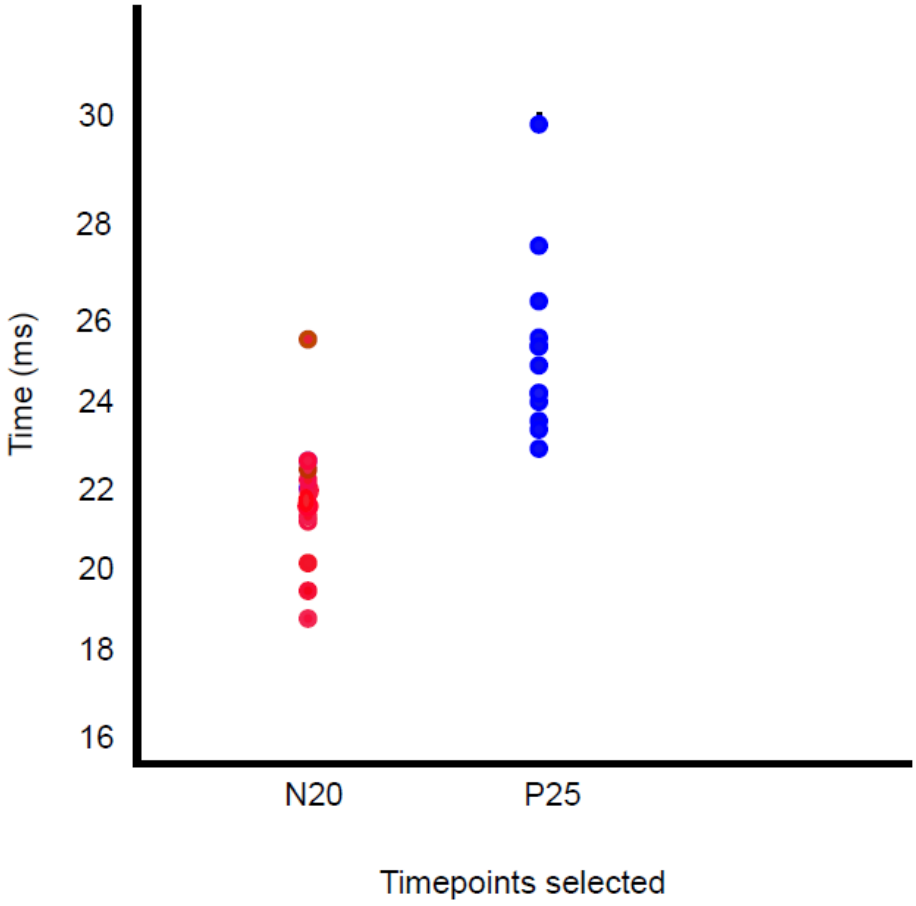

Figure 3-4 ***Spread of N20-P25 timepoints across all subjects***

A repeated measures ANOVA within-subjects design was carried out to test whether SSEP amplitude is modulated by frequency in standard and non-standard conditions and whether there was an optimal frequency that drives the system.

The repeated measures ANOVA showed no significant effect of frequency on SSEP amplitude ($f(15) = 0.8$, $p = 0.4$). Although, the omnibus statistic did not show the p-value was significant suggesting that SSEP amplitude is unlikely to be modulated by frequency, paired t-tests were carried out to explore and see whether there is a difference between conditions and if there is an effect that could have been shadowed by noise in one of the datasets. However, my data cannot survive correction and that is the reason that the t-tests have not been corrected for multiple comparisons.

To this end, the amplitude of the SSEP for each stimulation condition was compared to the null value, here an amplitude of zero (Figure 3-5).

Unsuprisingly, the standard condition, showed a clear SSEP at 1 Hz frequency (t_{15}=2.53) (p=0.02). In the non-standard conditions, significant SSEPs were evident at the theta frequency of 5.3 Hz (t_{15}=-3.41, p=0.003) as well as alpha frequencies including 8.2 Hz (t_{15}=-4.3, p=0.0005), 11.1 Hz (t_{15}=-2.54, p=0.02) and at beta frequencies including 14.2 Hz (t_{15}=-3.01, p=0.008), 17.1 Hz (t_{15}=3.64, p=0.002), 23.3 Hz(t_{15}=-2.43, p=0.02). Near significance was seen for frequency of 28.4 Hz (t_{15}=2.08) (p=0.05). Non-significant SSEP amplitude response was seen at some beta frequencies including 19.7 Hz (t_{15}=-0.11, p=0.9), 25.6 Hz (t_{15}=-0.06, p=0.9). Gamma frequencies showed non-significance including at 32.0 Hz (t_{15}=-0.77, p=0.4) and 34.1 Hz (t_{15}=-0.17, p=0.8).

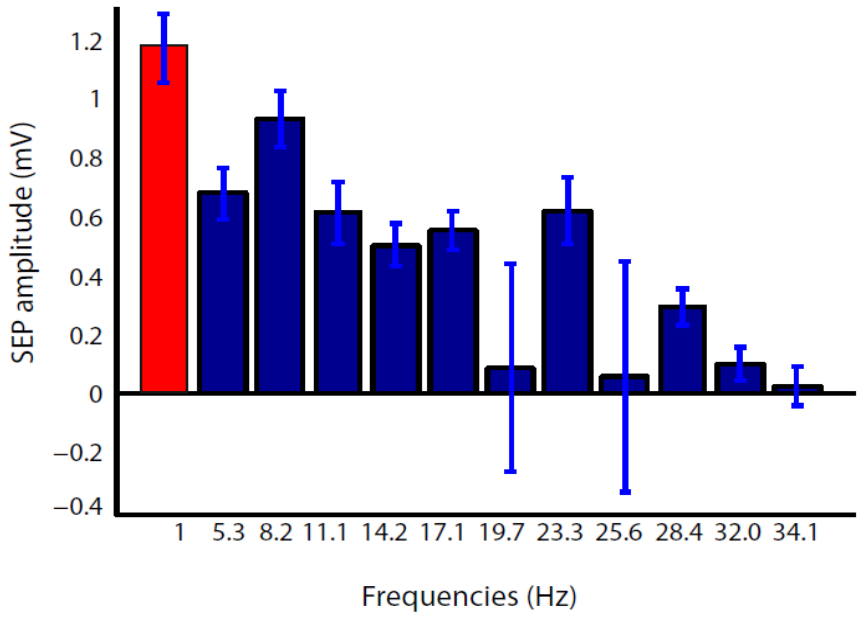

Figure 3-5 ***Figure of SSEP amplitude and frequency on standard and non-standard SSEP tagging condition.***
12 frequency bins corresponding to 12 frequencies of stimulation (1, 5.3, 8.2, 11.1, 14.2, 17.1, 19.7, 23.3, 25.6, 28.4, 32.0, 34.1 Hz). Red bar represents the standard SSEP amplitude at 1 Hz. Blue bars represent the change of SSEP amplitude at non-standard SSEP condition. Errorbars were calculated as the mean and standard deviation of SSEP amplitude divided by the square root of the number of subjects in both standard and non-standard condition

To further test whether SSEP could be frequency tagged and whether increased SSEP amplitude response at beta and alpha range frequencies could also be identified in the power spectrum, frequency analysis was carried out as shown below.

3.3.2 FREQUENCY ANALYSIS

Having established that stimulating the median nerve at different frequencies produced measurable SSEPs that had a significant primary component at some frequencies and that qualitatively were similar in terms of their scalp topography to the standard SSEPs, I next tested whether SSEPs could be frequency tagged. Here, frequency tagging was defined as successful only if there was a peak in the power spectrum of the EEG signal recorded over the contralateral sensorimotor cortex that was at the same frequency as the stimulation frequency. Therefore, frequency tagging would be present on the diagonal of the stimulation (input) frequency and the corresponding power at the same frequencies in the EEG signal (output) frequency (Figure 3-6). In other words, if the SSEP was frequency tagged, data laying on the diagonal would show greater power (dark red and red colour in Figure 3-6) than from data laying off diagonal (dark blue and blue colour in Figure 3-6). The analysis on the raw unprocessed EEG signal evidently shows high power on diagonal line providing evidence that sensory frequency tagging is possible (Figure 3-6A).

Before analysing these effects further, I first investigated the effect of a potential large confound that could have been driving these effects. When median nerve stimulation is given there are two responses present in the EEG, the neurophysiological response to the median nerve stimulation and a large electrical stimulation artefact that occurs at the time of stimulation. This is shown for a sample of data in Figure 3-6D (blue line). Therefore, any evidence of frequency tagging in the raw data (Figure 3-6A) might simply reflect the stimulus artefact rather than any neurophysiological response to the

median nerve stimulation. To address this potential confound, two separate analyses were performed. In one analyses, called artefact free, prior to frequency domain analysis the median nerve artefact was removed from the time series, in the second one only the median nerve artefact was analysed (see methods). From this analysis it was clear that the stimulation frequency had a clear linear relationship with the response frequency as a clear diagonal line was present in the both the artefact and artefact free time series. Consistency also the raw and artefact free data included the increased theta and alpha power activity in both, further is further evidence that power increases and the clear input-response frequency relationship were not driven by the median nerve stimulation artefact.

Distribution of this frequency analysis data were checked, and it was wider than expected, therefore logarithmic normalization was carried out to make distribution more symmetric.

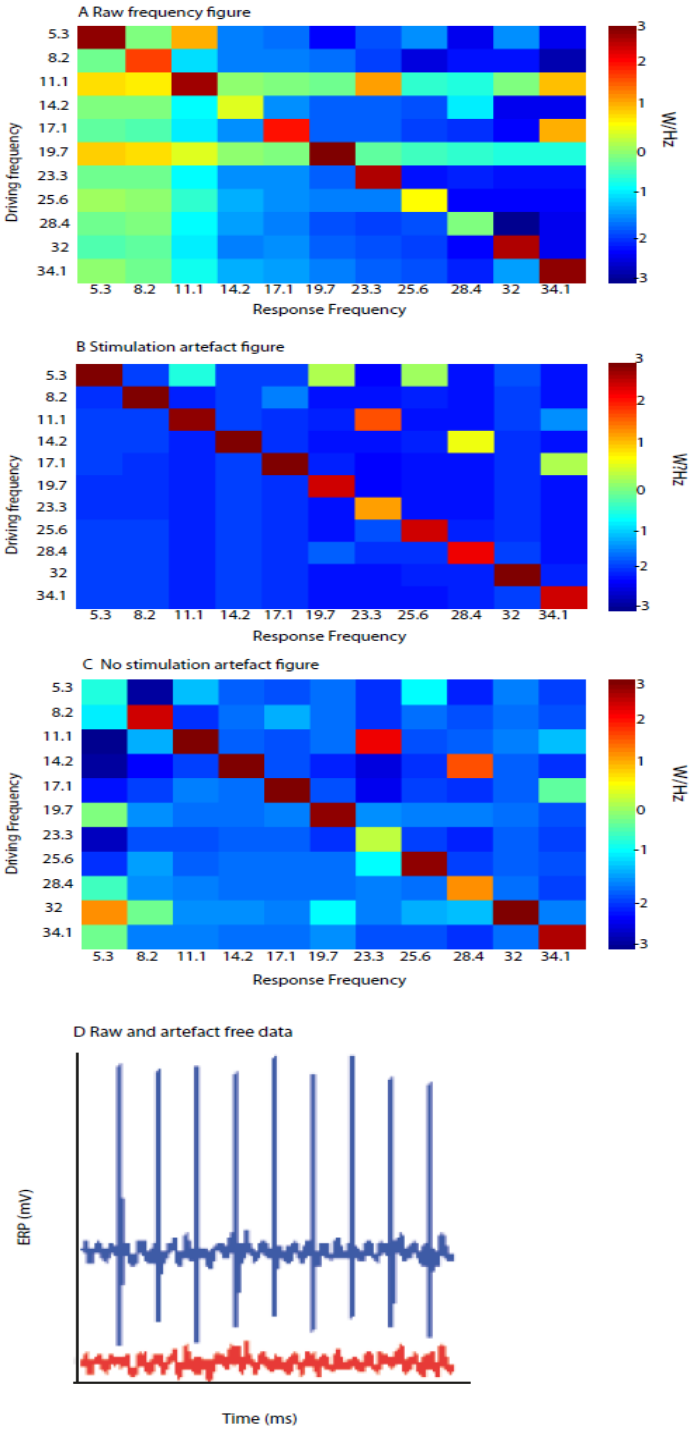

Figure 3-6 ***Figures of raw data, of stimulation artefact and of stimulation-free data. Figure of raw and when artefact is eliminated.***

A, *Average mean power raw data. Great power seen on the diagonal line as predominantly colours on the diagonal line are dark red and red. Theta activity is seen at 5.3 Hz and alpha power activity at 8.2 and 11.1 Hz.* ***B,*** *Average mean power for artefact mean data. Clear diagonal line is evident, high power on diagonal line dark red and red predominate. Increased theta and alpha power activity is seen.* ***C,*** *Average mean power for stimulation artefact only data. Clear diagonal line is presented.* ***D, Blue*** *line represents the raw data where artefact is still present.* ***Red*** *line represents the stimulation free data when artefact is removed. Both data sets are centred on zero but for clarity the red line has been displaced*

To statistically validate the relationship between the input and response frequencies on diagonal data and demonstrate that (i) SSEPs could be frequency tagged and (ii) identify whether frequency tagging amplitude is a function of the stimulation frequency, statistical tests including ANOVAs and t-tests were carried out.

To identify whether power activity is coming from on or off diagonal data and whether it is modulated by frequency of stimulation, a two-way repeated measures ANOVA was carried out with two factors, first factor contains 2 levels (ON and OFF diagonal) and the 2nd factor that contains 11 levels (i.e. 11 frequencies of stimulation). This was performed on the artefact free data only. To produce this data the ON data was the data on the diagonal for each frequency. The OFF diagonal data was the average of the power at each output frequency that was not the input frequency. This analysis showed a significant main effect of ON/OFF diagonal data ($F(1.00, 15.00) = 6.57$, $p=0.02$), a significant main effect of Frequency of stimulation ($F(2.38, 35.77) = 9.08$, $p=0.00$) and a significant interaction between the two factors ($F(3.82, 57.32) = 3.31$, $p=0.01$). The significant main effect of ON/OFF diagonal data and significant main effect off frequencies of stimulation shows that power activity is modulated by ON/OFF diagonal data but also through the frequencies used.

However, to test which frequencies of stimulation indicate preferential response at ON diagonal data from OFF diagonal, a paired t-test was carried out by testing whether the difference between ON and OFF diagonal data were significant at each input frequency. Power activity on diagonal line was significantly greater during ON than OFF at 19.7 Hz ($p=0.01$, $t_{15}=2.68$), at 23.3 Hz ($p=0.02$, $t_{15}=2.58$), at 28.4 Hz ($p=0.04$, $t_{15}=2.14$), at 32 Hz ($p=0.009$, $t_{15}=2.98$) and at 34.1 Hz ($p=0.005$, $t_{15}=3.25$). Non significance was seen for 5.3 Hz ($p=0.3$, $t_{15}=0.87$), near significance was seen at 8.2 Hz ($t_{15}=1.90$, $p=0.07$), and no significance at 11.1 Hz ($t_{15}=1.63$, $p=0.1$). Near significance was observed for 14.2 Hz ($t_{15}=2.04$, $p=0.05$) and no significance for 17.1 Hz ($t_{15}=1.68$, $p=0.2$, Figure 3-7).

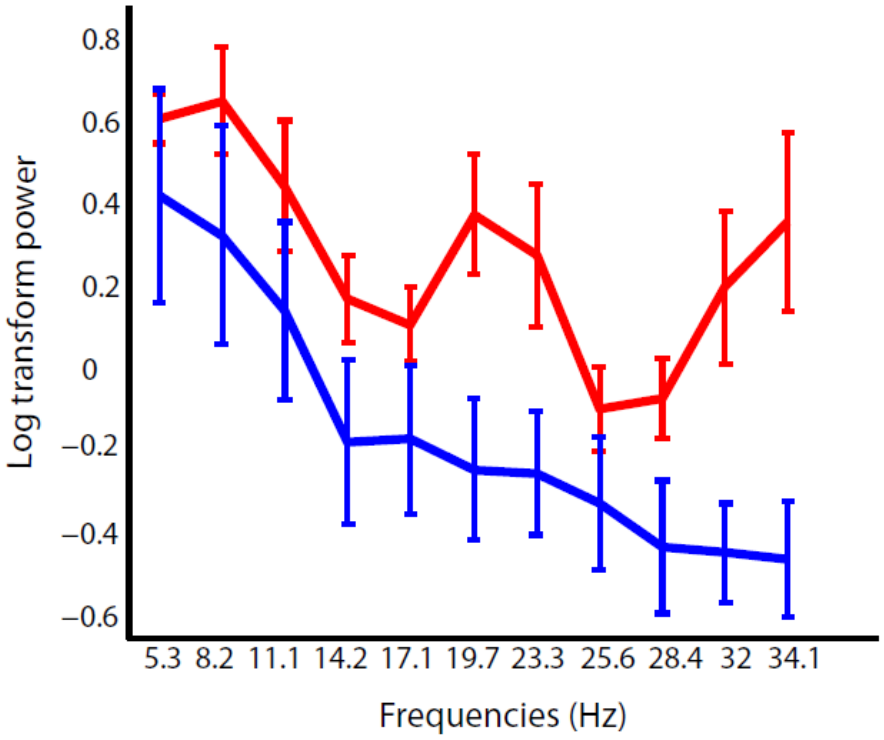

Figure 3-7 ***Figure of on and off diagonal data in relation to frequency of stimulation.***
Blue line *shows data on diagonal whereas* ***red line*** *shows data off diagonal. The significance of on diagonal data it's quite evident in relation to off diagonal data. Errorbars were calculated as the mean and the standard deviation of log power of all subjects on diagonal and all 11 frequencies and the mean and standard deviation of all subjects off diagonal and all 11 frequencies divided by the square root of the number of subjects.*

The previous analysis demonstrated significant or a trend to significance for the output frequency being greater at input frequencies close to alpha frequencies (8.2 Hz) and beta frequencies (19.7 Hz). This could either reflect a resonant frequency in the sensorimotor system or it could reflect globally greater power in the cortex at these frequencies. To test whether the response frequency peak was specific to the driving frequency for 19.7 Hz and 8.2 Hz and not based on the oscillatory activity, a two-way repeated measures ANOVA was carried out. The ANOVA had two factors, response frequency (2 levels 19.7 Hz and 8.2 Hz) and driving frequency (11 levels all input frequencies). The logic being that if the increased out power simply reflected increased

cortical power at these frequencies then this should be the same irrespective of the input frequency. The results showed a non-significant main effect of response frequency (F (1.00, 15.00) =0.002 p=0.1), a significant main effect of driving frequency (F (2.82, 25.39) =17.629 p=0.02) and a significant interaction between the two factors (F (2.10, 31.49) =19.0, p=0.01). The significant interaction shows the evidence that the beta power was driven by driving frequency and beta activity increases at 19.7 Hz. However, alpha power activity was driven irrespective of the frequency of stimulation (8.2 Hz). (Figure 3-8).

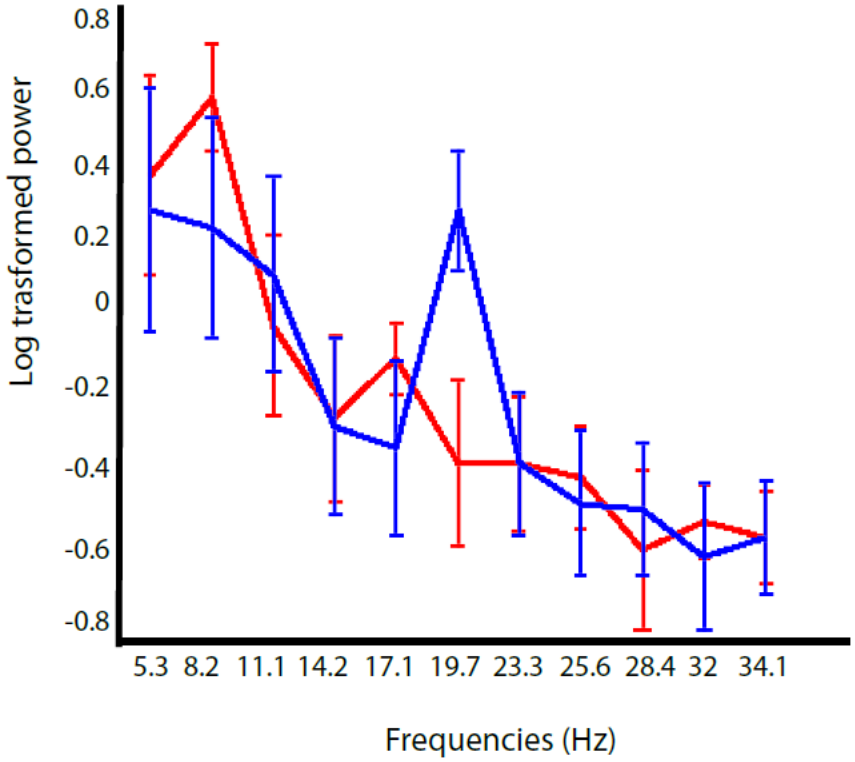

Figure 3-8 ***Figure of alpha and beta power activity modulated by frequencies of stimulation.***
Blue *line shows beta power activity. It's evident that 19.7 Hz activity is based on driving frequency and has a significant effect.* *Red* *line shows alpha power activity. It is not modulated by the frequency of stimulation (8.2 Hz). Errorbars were calculated as the mean log power of all subjects, frequency of interest and all frequencies and the standard deviation of all subjects, frequency of interest and all frequencies divided by the square root of the number of subjects.*

3.3.3 SEP AMPLITUDE AND POWER SPECTRAL ANALYSIS

Finally, after identifying SSEP frequency tagging and preferential activity at particular frequencies, a comparison between SSEP amplitude analysis and power spectral analysis was carried out to identify whether these two measures could reflect the same process. A two-way repeated measures ANOVA of two factors including data ON the diagonal the SSEP amplitude and 11 levels (all frequencies) were carried out. It showed a significant main effect of Frequency ($F(1.00, 15.00) = 37.2$, $p = 0.0$), a significant main effect of modality (amplitude/Frequency) ($F(4.08, 61.15) = 2.5$, $p = 0.03$) and a non-significant interaction ($F(4.93, 73.89) = 1.3$, $p = 0.2$) between those two factors. (Figure 10). The significant main effect of modality is not of interest as it reflects the fact that the SSEP amplitude and frequency are different measures and have different units. (Figure 3-9).

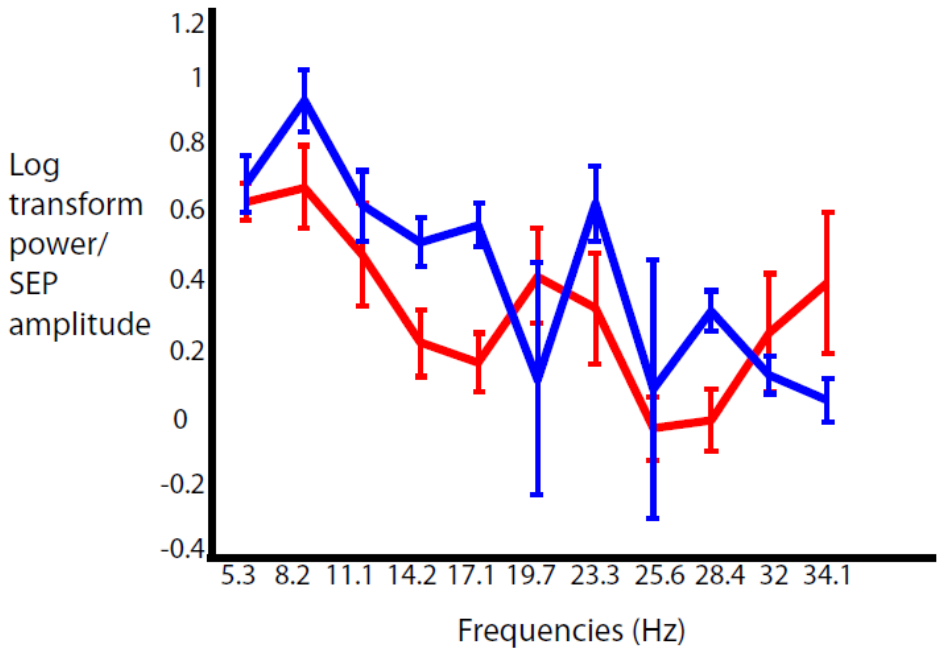

Figure 3-9 ***Figure of on diagonal and SSEP amplitude data in relation to the frequencies of stimulation.*** ***Red line*** *is the on diagonal data whereas* ***blue line*** *is the SSEP amplitude data. Interaction is not seen between those two graphs. Errorbars were calculated as the mean and standard deviation of all subjects on diagonal and all 11 frequencies, divided by 4 and mean and standard deviation of all subjects on SSEP amplitude and all 11 frequencies, divided by the square root of the number of subject*

To identify whether there is a correlation between frequency (data from the ON diagonal) and the SSEP amplitude, a Pearson's r and p-value were calculated from the correlation matrix and a correlation plot were obtained. From Table 1, it was evident that they could be somehow correlated as p value is near significance (r= 0.55, p=0.07). This is further supported by the correlation plot between these two factors (Figure 3-10).

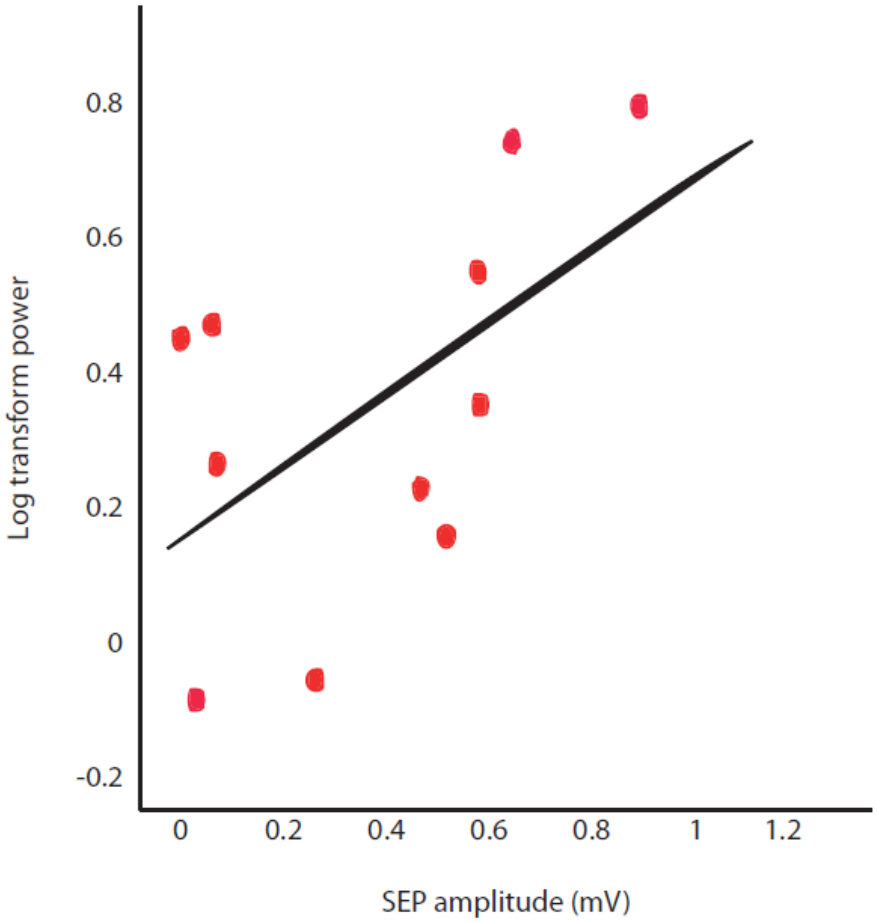

Figure 3-10 ***Shows a correlation plot between SSEP amplitude analysis and frequency analysis***

3.4 DISCUSSION

The aims of the current study were to test whether frequency tagging could be used to produce SSEPs and whether there is evidence of resonant frequencies in the sensorimotor system. Here I showed that qualitatively the SSEPs produced using high frequency median nerve stimulation are equivalent to those produced using a classic standard SSEP paradigm. Furthermore, the primary component of the SSEP showed some weak dependency upon the stimulation frequency. In addition, the results show that SSEPs can be frequency tagged and that there is a clear correspondence between the driving frequency and the output frequency. Furthermore, this relationship was modulated by frequency. Specifically, there SSEP response was greater when the input frequency was in the beta frequency range.

Similar findings have been recorded in early studies of visual field mapping (Regan and Heron, 1969; Regan and Cartwright, 1970). Eyes were stimulated through a flickering light or a chessboard and multiple repetition frequencies were presented to each eye. Preferential response of SSVEPs was noted at frequencies that occupy alpha and beta range (Regan and Milner 1978). In addition, preferential responses of steady state evoked potentials have been identified at alpha range frequencies during a binocular rivalry paradigm. Binocular rivalry is a paradigm that tests how neuronal activity changes during conscious and unconscious experiences (Tononi et al, 1998). Up to date, many studies have showed the importance of frequency tagging in recording several forms of evoked potentials, examples are the study of Hermann et al, 2001 and Kourtis et al, 2008 that has been extensively outlined in the introduction of this chapter.

This study evidently shows that SSEPs could be frequency tagged. This result was obtained by taking the data from the ON diagonal where significance was seen from those data OFF diagonal. Power on the diagonal was evidence that response was driven by the frequency of stimulation. Thus, power at the response frequencies were significantly greater at the driving frequencies than at other frequencies. These results could not simply be an artefact of median nerve stimulation. In the analysis the median nerve stimulation artefact was removed through substitution. When the median nerve stimulation artefact was removed, and artefact free data were produced there was high consistency with the raw data indicating that the results are unlikely to be artefactual. Further to this, frequency analysis showed a preferential power response on particular frequencies including around 19.7 Hz. Significance was also seen on 25.6, 28.4, 32.1, 34 Hz. Highest preferential response was seen at 19.7 Hz and as it corresponds to beta power range frequencies, it was statistically tested to identify whether the response is based on oscillatory tonic activity or on the driving frequency itself. To test this, it was compared to alpha rhythm frequency (8.2 Hz) and showed that 19.7 Hz response solely present at the driving frequency and not on tonic activity whereas 8.2 Hz response was non-significant shown to be irrespective of the driving frequency.

One question is whether the frequency measure is a measure of the SSEP amplitude or whether the two analyses capture different features of the data. To identify whether these processes are measures of different things, a correlation between ON diagonal and SSEP amplitude data was carried out. The result showed that these two processes are correlated and that they are not that different. Therefore, evidently both processes measure the primary SSEP component and they are dependent to each other. This result suggests a causal relationship between them that allowed us to proceed to the second experiment.

In this study, dominant resonant frequency for gamma oscillations was observed at 34 Hz that is in accordance to previous findings (Crone et al, 2011). Despite the study of Klimesh 2012 that found as a dominant resonant frequency of alpha to be 10 Hz in an awake human brain, in this experiment preferential response was seen at 8.2 Hz. The reason that it wasn't identifiable could be that 8.2 Hz is independent of condition (sleep/awake), it is broadly spread throughout cortical areas and peaks at different locations during different points in time whereas 10 Hz are more localized, and it is less often recorded from primary somatosensory cortex (Klimesh 2012).

To critically appraise the data, different threshold methods to select electrodes of interest were taken into consideration. The best method of choice should be algorithmic selection. However, this method in my case is problematic as different subjects can have different timepoints and show different EEG scalp topology. Therefore, the second best is to choose the electrodes based on visual inspection through an independent dataset (standard SEP condition) and through identifying the SSEP threshold for each subject.

To conclude, this study demonstrated that SSEPs could be evoked by high stimulation frequencies and that driving the system from the periphery at frequencies in the beta range produced greater cortical responses than other frequencies.

4 TIME-COURSE OF SSEP AND BETA OSCILLATIONS AT REST, MOTOR PREPARATION AND MOVEMENT. IS TIME COURSE OF SSEP CORRELATED TO THE TIME COURSE OF BETA OSCILLATIONS?

4.1 INTRODUCTION

The results of the previous chapter demonstrated that SSEPs could be driven and evoked at high frequencies and that the frequency of stimulation produced a clear response at the driving frequency. Furthermore the amplitude of the primary component of the SSEP evoked at the different driving frequencies was correlated with the overall power evoked at the driving frequency, suggesting that the two were related. In addition, I showed that the system was most sensitive to being driven at frequencies in the beta range. This suggests that there could be potential link between the oscillatory activity in the beta frequency range in the motor system and the amplitude of the primary component of the SSEP. The aim of the experiment described here was to test that hypothesis.

According to the active inference hypothesis sensory attenuation is necessary for movement and reflects the reduction of sensory precision to allow the movement to occur (Friston et al., 2011, Friston et al, 2016). One consequence of this framework is that in order to be able to move the prediction errors about the hidden states must be greater than the prediction errors about the somatosensory expectations. In other words, in order to be able to move the gain of the somatosensory prediction error signal must be reduced and this results in the observation of sensory attenuation during active movement. Of particular interest is that within the active inference framework a failure to move can be modeled by a failure to sufficiently attenuate precision on the somatosensory expectations. Indeed, it has been proposed that some

of the hypokinetic symptoms of Parkinson's disease, specifically akinesia and bradykinesia, can be recast as a result of a pathology in reducing the precision of the somatosensory expectations (Friston et al. 2012, Macerollo et al, 2016). Recent research has provided evidence that cortical oscillations in the beta-frequency range (~15-30Hz) might be functionally related to these parameters of uncertainty (Torrecillos et al. 2015, Tan et al. 2016, Palmer et al. 2016). If this is correct then there should be an observable relationship between the time course of sensory attenuation and the modulation of beta power prior to and during movement. The aim of the current study was to test this specific hypothesis.

Previous research has reliably demonstrated that sensorimotor beta power is reduced during preparation to move and during the period of movement and is transiently increased subsequent to the end of the movement (Kilner et al. 2000, Baker et al 1999, Baker et al. 1997, Pfurtscheller & Lopes Da Silva 1999, Hari & Salmelin 1997, Bhatt et al, 2016; Seeber et al, 2016). Whereas the modulation of sensorimotor beta oscillations are well studied there is by comparison much less consensus on the modulation of SSEPs during rest, passive movement, and motor preparation. The majority of studies show attenuation of the components of the SSEP prior to and during active movement (Rushton et al, 1981; Starr and Cohen 1985, Abruzesse et al, 1981). However, more subtle differences in the reporting of the modulation of the SSEP seem to depend upon which components of the SSEP are investigated. Shimazu et al. (1999) showed that P14-far fields, N20 in primary somatosensory cortex and P22 in frontal areas remained the same throughout all conditions whereas frontal N30a/N30b and N60 components seen to be attenuated during movement compared to rest and count condition. In addition, the P30 has also been demonstrated to be decreased to some extent during movement. On the other hand, Boecker et al. (1993) showed that parietal long latency components (N70-P100) showed significant SSEP amplitude decreases during movement. However, very little is known about the time course of SSEP attenuation

during motor preparation and movement. This in part is due to the experimental difficulties in recording SSEPs at multiple time points during a motor task. Here I aim to build upon the results of the previous chapter and evoke SSEPs at a rapid rate during a motor task to firstly test the hypotheses that (i) rapid median nerve stimulation (~10 Hz) can reliably evoke SSEPs and a measurable primary SSEP component (ii) to test how that SSEP component is modulate during the motor task and (iii) to test the hypothesis that any task specific modulation in the SSEP amplitude is correlated with the modulation in the power of the sensorimotor beta oscillations.

4.2 METHODS

4.2.1 DATA ACQUISITION

4.2.1.1 PARTICIPANTS

24 healthy subjects took part in the study (mean 32.5 age years, range 22-43 age years). All were right-handed, had normal or corrected-to-normal vision and were naive with respect to the purpose of the experiment. The experiment was performed with the approval of the ethics committee of University College London and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

4.2.1.2 MEDIAN NERVE STIMULATION

To elicit an SSEP response, stimulating electrodes were placed over the median nerve of the right wrist. The intensity of the electrical stimulus was at 80% of the motor threshold. The motor threshold was determined separately for each participant by

unilaterally applying discrete electrical square wave pulses (0.5 ms duration each) at the median nerve at the wrist. The lowest value that produced a twitch of the thumb (observed by the experimenter) was taken as the motor threshold. EMG was recorded using surface electrodes that were placed on the thumb and proximal to the thumb where abductor pollicis brevis of the thenar eminence was recorded.

4.2.1.3 BEHAVIOURAL TASK

The subjects performed a simple behavioural motor task. In each trial initially, a red circle was presented on a screen in front of the subject (Figure 4-1). This indicated to the subject that the trial had started and the subject was instructed not to make a response to his stimulus but just to rest. After a variable time between 1-3 seconds the red circle changed to a yellow circle. The yellow circle was a cue to the participants to prepare to move. Finally, after a variable time between 1-3 seconds the yellow circle changed to a green circle. This was the imperative signal. Participants were instructed to respond as quickly as possible to the green circle by using the thumb of their right hand to press the response button. After a variable time between 1-3 seconds the next trial began by the green circle turning red. Participants performed four blocks of 60 trials of this task, in total 240 trials. On three quarters of the trials the median nerve was stimulated at a relative rapid rate of between 10-13 Hz starting one second before the onset of the red circle and lasting until one second after the response button had been pressed. In the remaining quarter of trials no median nerve stimulation was given during the task. Stimulation and no stimulation trials were intermixed and were randomly occurring throughout each block.

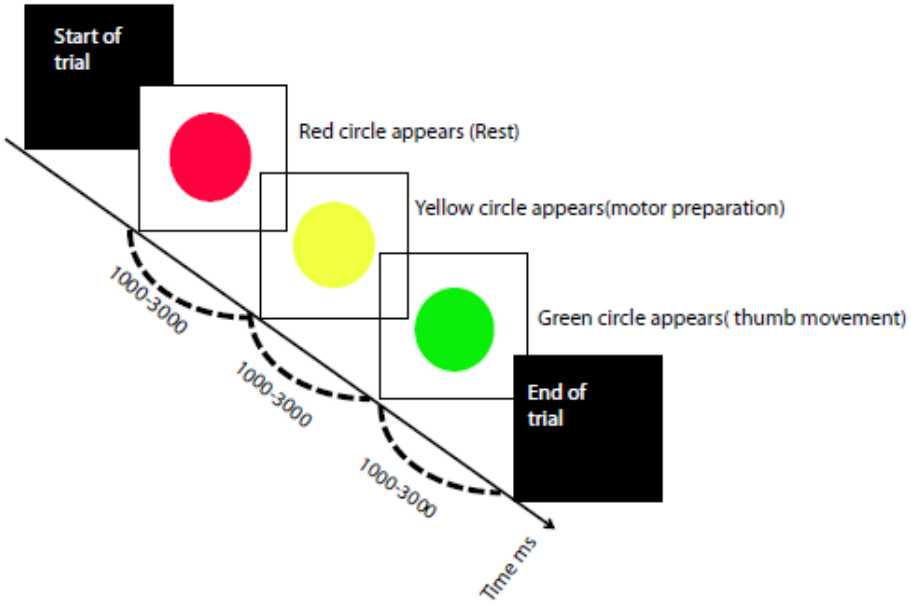

Figure 4-1 ***Behavioural task of experiment 2****.*
Every ~2000 ms each circle appears. Red circle represents rest, yellow circle motor preparation and green circle represents movement.

In all conditions the subjects sat in a comfortable chair in a darkened room, with the stimulated arm supported in a cushion.

4.2.1.4 EEG AND SSEP PROTOCOL

EEG was recorded with a Biosemi system with 128 scalp electrodes at a sampling rate of 2048 Hz. Earlobe electrodes were used as reference. All pre-processing and initial data analysis was performed within SPM12 (http://www.fil.ion.ucl.ac.uk/spm).

4.2.2 DATA ANALYSIS (SSEP)

4.2.2.1 PRE-PROCESSING, SSEP AMPLITUDE MODULATION

Of the 24 subjects there were substantial noise on all channels in 6 of the subjects and these were eliminated from the analysis before any further analysis. The remaining analysis was therefore performed on the remaining 18 subjects. Before epoching the EEG data were converted to SPM format and high band filtered at 0.1 Hz. In an initial analysis the EEG data were epoched with a 6000 ms window centred on the presentation of the different coloured circles. In this way, epochs were generated centred on the red circle, yellow circle and green circle. A 6000 ms initial window was chosen, however, it should be noted that due to the intertrial jitter in the length of stimulus presentation of 1-3 seconds only the central 2000 ms window, 1000 ms before and 1000 ms after stimulus presentation was used in all analysis reported.

The aim of the experiment was to test the hypothesis that the amplitude of primary component of the SSEP was modulated as a function of the task. To this end, to generate an estimate of the time course of SSEP amplitude modulation during the task the following analysis was performed. In an initial analysis, all median nerve stimulations that occurred in two different 2000 ms windows were selected. The two-time windows chosen were the transition from red stimulus to yellow stimulus and the transition from the yellow stimulus to the green stimulus. The 2000 ms were centred on the onset of the yellow and green stimuli taking 1000ms before the onset to 1000 ms after. For each median nerve stimulus, the EEG signals at each electrode were then epoched with a 350 ms window, 100 ms before to 250 ms after the median nerve stimulation.

4.2.2.2 PRE-PROCESSING AND BAD TRIALS REJECTION

Stimulations in each block (total of 60 trials) and for each subject that showed divergence from others due to noise, were eliminated before averaging of the data. The noise could be either physiological noise based on body movement (eye blinking, muscle contraction other than the movement of the thumb) or environmental noise as a form of fluctuations in electrical signal produced by electronic devices. Stimulations were removed when range of 20-30 mV and -20 to -30 mV was exceeded as anything above these values are not anticipated to be neurophysiological activity based on the experimental design. The threshold was decided by eye. An example is presented in Figure 4-2 for a single subject's data. (Figure 4-2). The number of stimulations in each block (containing 60 trials) for each subject within a 6000 ms time window were around 15,000 to 16,500. As a central 2000 ms time window was selected, the number of stimulations presented are around 5,000 to 5,500 as seen in Figure 4-2.

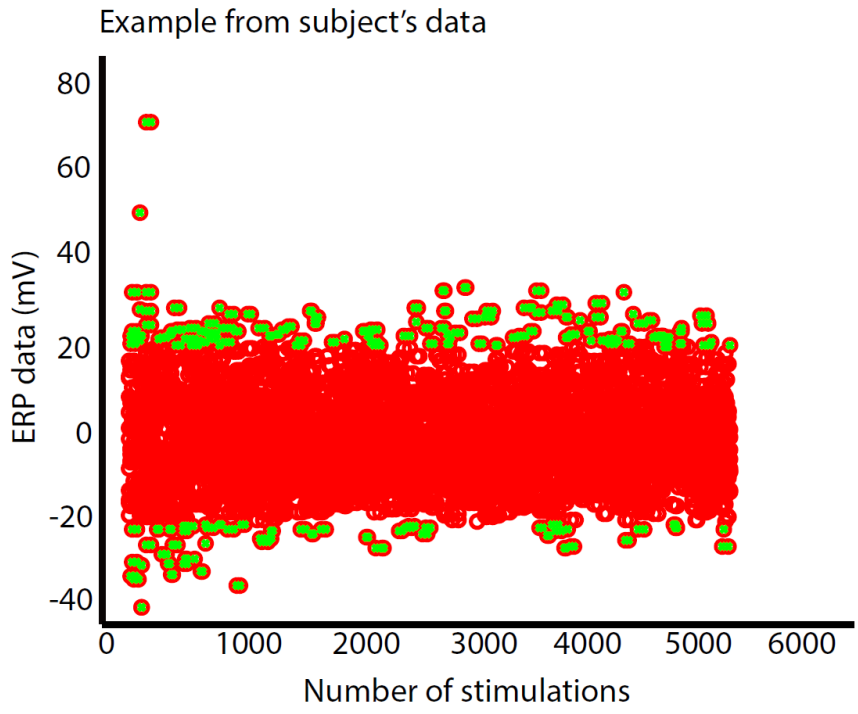

Figure 4-2 ***Shows single subject's data and how the trials are distributed.***
Red circles represent all the trials whereas green circles show the trials that need to be eliminated.

All subsequent analysis focussed on the amplitude of the primary component of the SSEP contralateral to the stimulated median nerve. To this end the SSEPs were averaged across trials, across electrodes of interest and the time points of the N20 and P25 of the primary component were chosen. For each subject to determine the electrodes of interest, the SSEPs were averaged across trials resulting in an SSEP ERP at each electrode. These SSEPs were then plotted as scalp maps and for each subject. The electrodes contralateral to the stimulated median nerve that lay approximately over the somatosensory cortex where the signal was maximally negative at ~20ms and positive at ~25 ms after stimulation were selected. Subsequently a single SSEP was produced for each subject by averaging across electrodes and across all trials. The time points of the N20 and P25 components were selected manually and the magnitude of this primary SSEP component was defined as the difference in amplitude of the SSEP at these two time points. Importantly, the electrodes and time points chosen were averaged across all trials and therefore the subsequent analyses were not confounded by condition effects. All further analyses of the SSEP used the magnitude of the primary SSEP component.

4.2.2.3 SSEP MAGNITUDE ANALYSIS BY TASK

The aim of this experiment was to test the hypothesis that the amplitude of the primary component of the SSEP was modulated during preparation and movement and that this modulation was correlated with modulations in the power of beta oscillations. The previous analysis described the process of selecting the amplitude of the primary component of the SSEP and the removal of bad trials from the SSEP. To test whether this SSEP amplitude was modulated as a function of the behavioural task the time course of the SSEP amplitude was calculated. This was carried out in the following

way. For each condition, red-to-yellow and yellow-to-green, the 2000 ms peristimulus time window was subdivided into 21 bins of 100 ms in length. For each condition and each 100 ms time window the median nerve stimulations that occurred in that window were found and the magnitude of the primary component of the SSEPs resulting from these stimulations was calculated (Figure 4-3). The magnitudes of the primary component of the SSEPs were then averaged to produce one average magnitude for each 100 ms window for each subject. In this way for each subject and each subject there were 21 SSEP magnitudes. All further analyses were performed on these values.

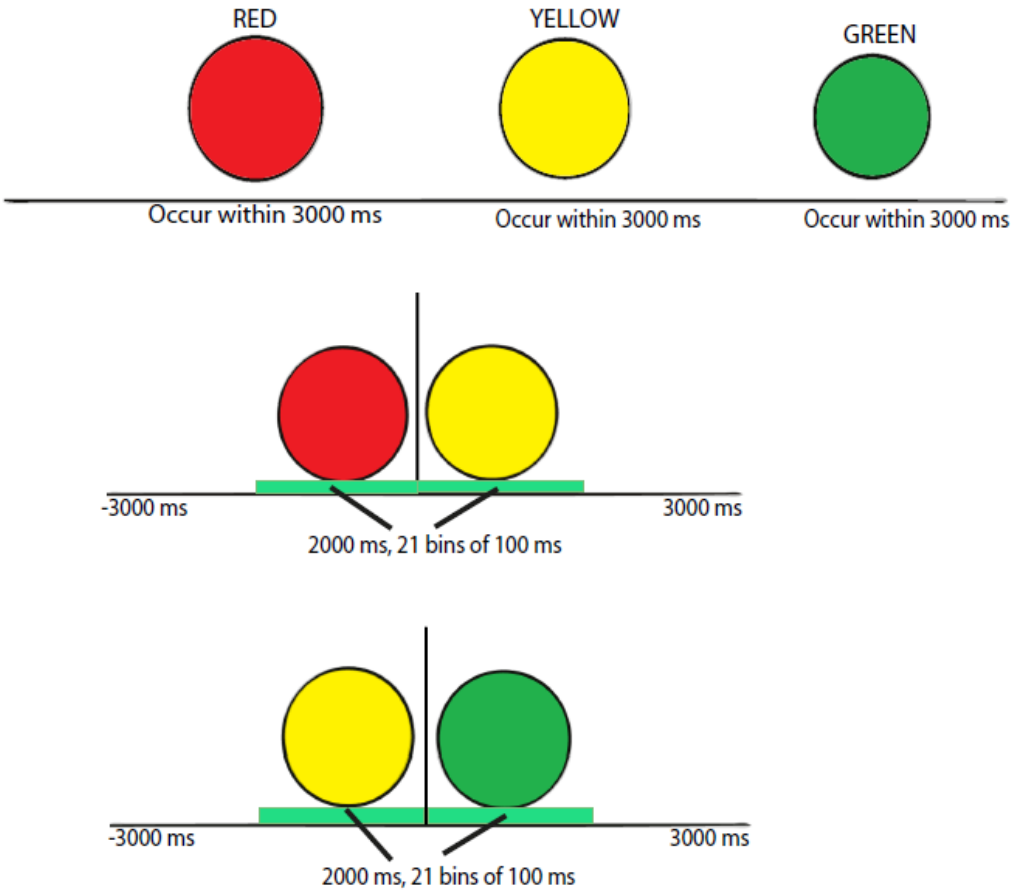

Figure 4-3 ***Figure showing how data analysis is performed for the SSEP amplitude data.***
It shows how circles (red, yellow, and green) are aligned to visual change at time 0 and how 2 100 ms time bins are concatenated into 1000 ms.

To test the hypothesis that the amplitude of the primary component of the SSEP was modulated by condition and/or time and if there was an interaction between conditions and time, a two-way repeated measures ANOVA was carried out. The ANOVA had two factors, CONDITION (three levels) and TIME (21 levels). Finally, to test whether the SSEP amplitude response was different from the average SSEP amplitude at specific time, two one sample t-tests were carried out one for the 21 values in the rest and start of motor preparation window and one for end of motor preparation and movement window.

4.2.3 DATA ANALYSIS: BETA OSCILLATIONS

4.2.3.1 PRE-PROCESSING AND BETA OSCILLATORY MODULATION

Whereas the previous analysis for the SSEP focussed on the three quarters of trials in which the median nerve was simulated the analysis of the beta power uniquely analysed the trials in which there was no median nerve stimulation. As seen in the previous chapter the EEG power is modulated by the median nerve stimulation and here the aim was to investigate the modulation of beta oscillations in the motor system in the absence of the median nerve stimulation. To this end, EEG data were converted and epoched using a time window of -3000 to -3000 ms. After epoching, all trials in which the median nerve was stimulated were removed from the analysis. The EEG data were then down sampled to 200 Hz. Time-frequency analysis was calculated in SPM using morlet wavelet analysis at all frequencies from 1-100 Hz for a time window from -3000 ms to 3000 ms centred on the time of the stimulus transition from red to yellow and from the transition from yellow to green. The time-freqeuncy data subsequently were log transformed. As with the SSEP analysis all further analysis focussed on a peri-time window of -1000 to 1000 ms. This analysis produced a time

frequency image with 100 frequency bins 1 for each frequency and 39 time bins with ~50 ms time resolution. (Figure 5-4).

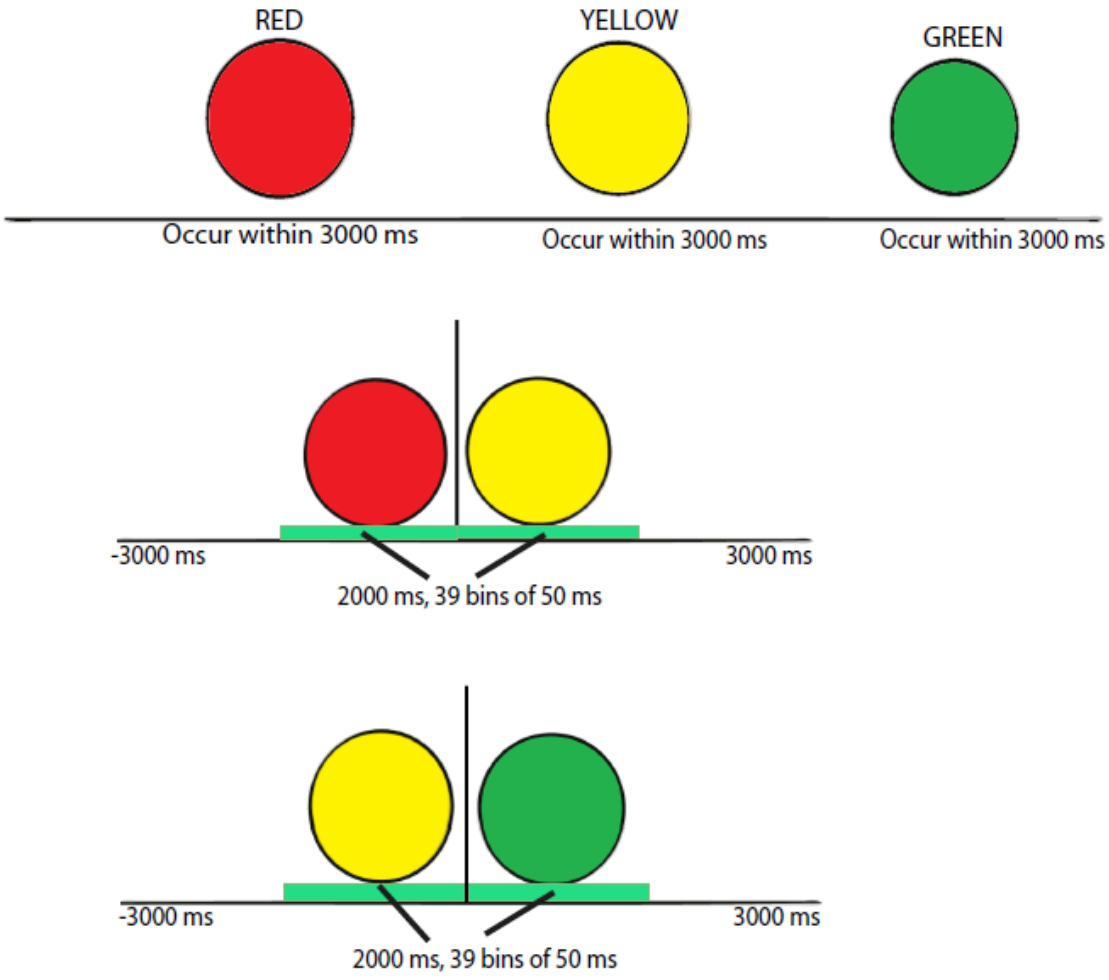

Figure 4-4 ***Figure showing how data analysis is performed for the beta oscillatory data***
Within peri-time window of -1000 to 1000 ms, 39 bins of 50 ms are presented. Beta oscillatory data are averaged, and one value is produced for each 39 time bins.

4.2.3.2 PRE-PROCESSING AND BAD TRIALS REJECTION

Before the blocks of each subject being merged and the trials of all blocks being averaged, trials that seemed to be very noisy were eliminated. Noise other than bad electrode choice, could be other physiological based on body movements or environmental noise based on fluctuations of electrical signal. The same paradigm for trial elimination was used as in SSEPs, removing anything above 20-30 and below -20 to -30 mV range. Threshold was decided by eye as for the SSEPs analysis above.

4.2.3.3 BETA OSCILLATIONS: CONDITIONS AND TIME ANALYSIS

After merging and averaging across trials, the time frequency plots were then averaged across the same electrodes as the SSEP analysis (see above). This produced one time frequency image per subject per condition. To test the hypothesis that there was a task specific modulation in the beta power, the time frequency images were averaged across the beta frequency range, 15-30 Hz. This resulted in 39 time points for the modulation of beta power centred on the time of occurrence of the yellow circle and green circle. These data were used for all statistical analyses.

A two-way repeated measures ANOVA having 2 factors, first factor having 2 levels (conditions) and the second factor having 39 levels (time bins) was carried out. As above, to test the hypothesis whether beta oscillations are modulated either by conditions or/and by time, a p value of less than 0.05 was taken and degrees of freedom of n-1.

Further to this, to identify which specific time bins modulate beta oscillatory activity more than others, two one sampled t-tests were carried out, one for first condition and

one for the second. Again, t-statistic was recorded in the results section and hypothesis tested at a p value<0.05.

4.2.3.4 CORRELATION BETWEEN SSEPS AND BETA OSCILLATIONS

To test whether SSEPs and beta oscillations are correlated, a linear regression was performed between the beta power and the SSEP amplitude. As the time resolution of the beta power analysis was twice that of the SSEP. The beta power was downsampled to be at the same time resolution as the SSEP, with both having 100 ms resolution and consisting of 20 time points. Taking each subject and all time bins, r squared value and gradient of the line were calculated. R squared values are bound between 0 and 1, closer to 1 the more the variables are correlated. This was performed for each subject and was also performed on the average time course of beta power and SSEP amplitude modulation across subjects.

In addition to the R^2 the gradient of the line of best fit between the two regressors was calculated for each subject and the consistent of the direction of this gradient, i.e. whether it was consistently positive or negative, was tested.

4.3 RESULTS

4.3.1 SSEP PRIMARY COMPLEX (N20-P25)

Prior to testing the hypothesis that any task dependent modulation in the time-course of the SSEP amplitude was correlated with corresponding modulations in the power in the beta frequency range, I first analysed the data to confirm that there was a primary component (N20-P25). To this end, the SSEPs evoked by all median nerve stimulations were averaged over all trials for each block of the task. Subsequently, I then averaged across blocks of each participant. Electrodes of interest were selected for each participant separately depending on where N20-P25 primary complex showed the highest deflection. Lastly, all blocks and participants were averaged to produce a grand average. The resultant grand average scalp maps presenting N20 and P25 are shown in Figure 4-5A&B. The scalp maps show the grand average at electrodes of choice at the time point of the N20 and P25 SSEP components (on average these occurred at ~21 and 24 ms respectively in both conditions). Figure 4-5A shows a region overlying left somatosensory cortex contralateral to the stimulated right wrist where the magnitude of the SSEP was maximal. Scalp maps of N20-P25 component are qualitatively and quantitatively consistent and this is clear evidence that an SSEP was present.

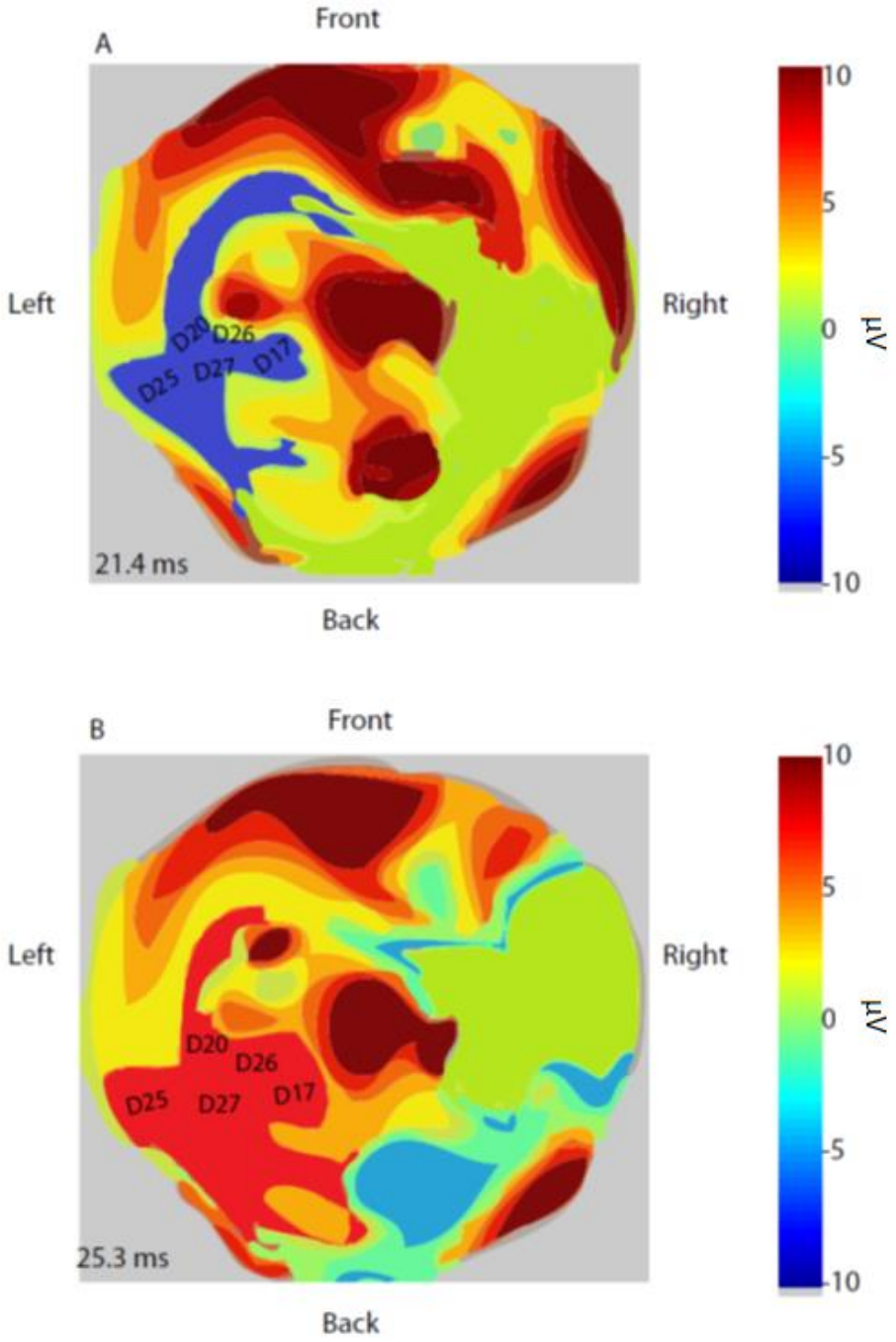

Figure 4-5 ***Grandmean scalp maps for primary (N20-P25) SSEP component.***
A. *Shows N20 SEP component as lowest activity in the scalp* ***(blue)*** *at the left. This figure also shows the hotspot of electrodes chosen.* ***B.*** *Shows P25 SEP component as the highest activity in the scalp (red) at the right.*

After grand average scalp maps were calculated, an analysis was performed to identify the electrodes of interest for each subject individually based on where the ERP showed the largest deflections relative to baseline at a post-stimulus time point and scalp position consistent with a median nerve SSEP (~20 ms after stimulation with overlying left central electrodes shown as the blue area in Figures 4-5A).

Further analysis of the SSEP focussed on the magnitude of the primary complex defined as the difference between the amplitude of the SSEP at N20 and the P25. To this end the time points of the N20 and P25 components were calculated for each subject across all trials (118 trials) in a non-biased way. For each subject the SSEPs were first averaged across the electrodes of interest (see above for methods) and then across all SSEPs evoked by the median stimulation irrespective of whether which condition they occurred. The time of the N20 and P25 components were then selected from this SSEP by eye for each subject. The magnitude of the SSEP was defined as the difference in the SSEP amplitude at these two time-points (Figure 4-6A, 4-6B). In terms of scaling, Figure 4-5 represents a map of the whole scalp that contains all brain areas as well as the area of interest, left somatosensory cortex. Figure 4-6 N20-P25 was taken within the area of interest and it is a microscale representation across all subjects or across each subject.

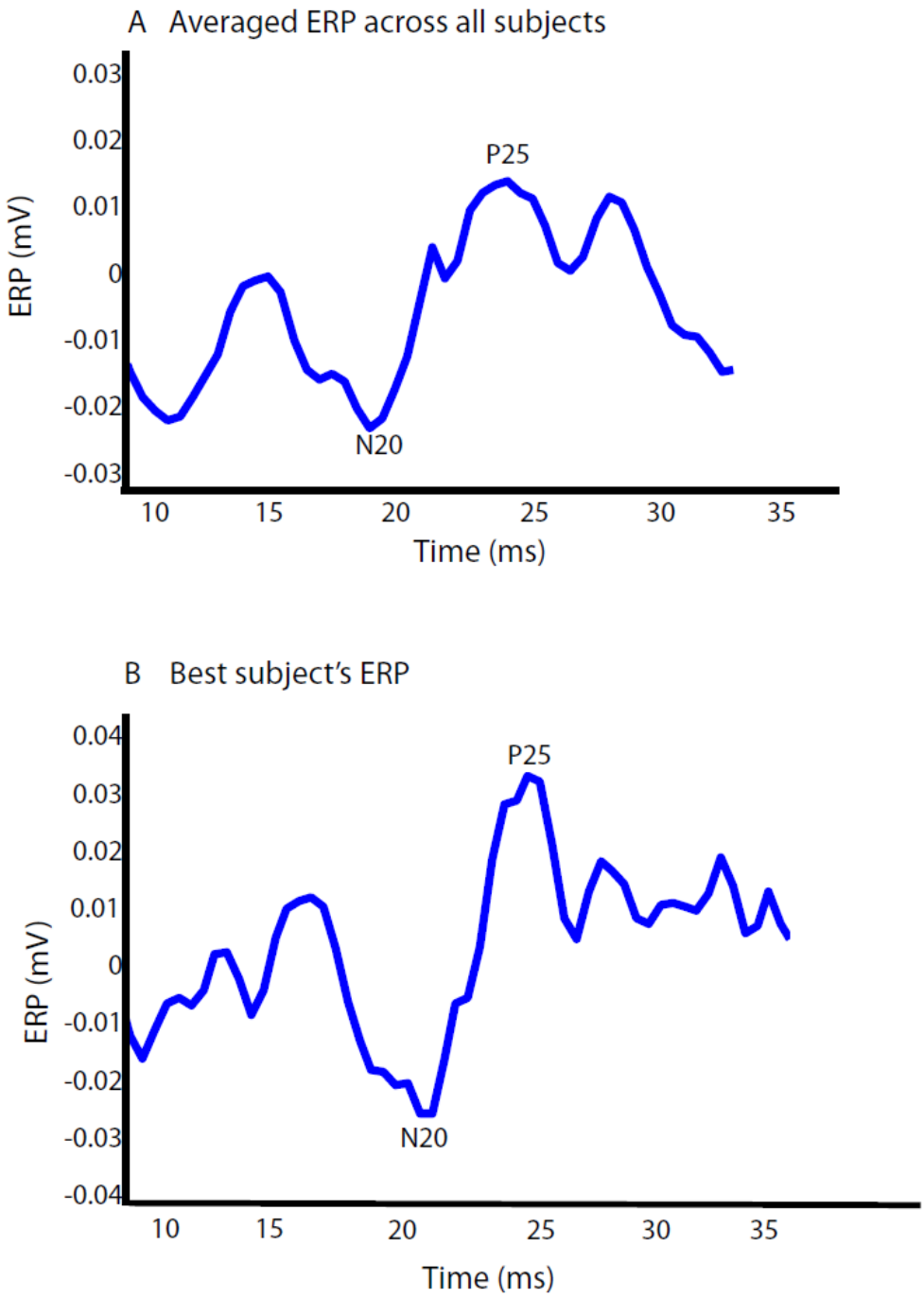

Figure 4-6 ***Averaged and single subject's ERP.***
A. *Shows the averaged ERP across all subjects and how N20 and P25 are selected.* ***B,*** *Best subject's ERP also how N20, P25 are selected at around 20 ms and around 25 ms respectively.*

The spread of N20-P25 timepoints in milliseconds for each subject seem to be variant, some subjects showed N20 and P25 component activation earlier or later than others. But that is common due to subject variability seen in neurophysiological studies (Kojovic et al, Sandnicka et al, Naatanen) (Figure 4-7).

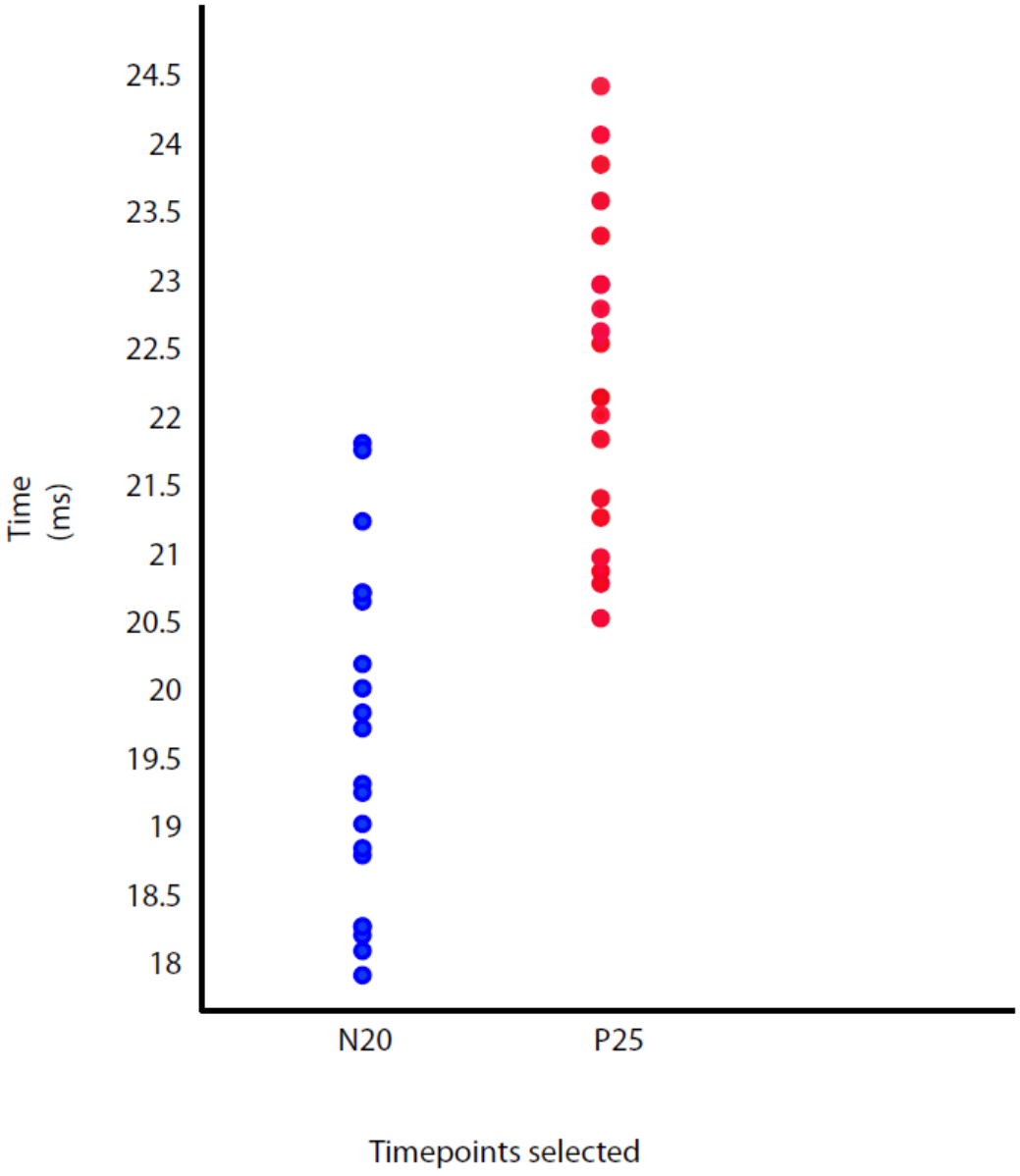

Figure 4-7 ***Shows the spread of N20-P25 timepoints across all subjects.***
Blue and red dots represent each subject N20 and P25 timepoints respectively.

One aim of this study was to investigate how the amplitude of the primary component of the SSEP was modulated between the different conditions, rest, motor preparation and movement. To test whether the SSEP amplitude was modulated before and during rest, motor preparation and movement based on task design and time, a two way repeated measures ANOVA was carried out having one factor with 2 levels (rest and start of motor preparation condition, end of motor preparation and movement) and one factor that represents time with 21 levels. The results show that there was no main effect of condition whether it was rest and start of motor preparation or end of motor preparation and movement, i.e. there was no evidence that the amplitude of the SSEP varied as a function of the motor task subjects were performing ($F(1.00, 17.00)=0.12$) ($p=0.73$). However, there was a trend towards significance with two task periods ($F(7.15, 121.49)=1.82$, ($p=0.08$). No significant interaction was seen between conditions and time ($F(7.06, 120.01) = 0.93$, $p=0.48$).

Further to this, to test whether there was evidence that the time modulation of the amplitude of the SSEP significance was more driven by the change from rest to prepare or from prepare to move, a one way repeated measures ANOVA having one factor time with 20 levels was carried out separately for each of the two conditions. No significance was seen for the rest and start of motor preparation ($F(7.16, 121.71) =1.272$ and $p=0.269$). Neither significance was noted for end of motor preparation and movement as ($F(7.06, 120.04) =1.556$, $p=0.154$).

To further test whether the SSEP amplitude was modulated during the tasks, the average amplitude of the SSEP across all time bins, irrespective of task, was calculated for each subject and subtracted from the SSEP amplitude in each time bin. These values were then tested to determine whether there was any difference from zero for rest and start of motor preparation condition based on time, using a t-tests. For the time course centred on the onset of the preparation period, the yellow circle, the only time point that was significant was 400 ms prior to the onset of the yellow circle

during the rest condtion (t_{17}=-2.15) (p=0.04). Trend towards significance was seen at the time of the onset of the yellow circle (motor preparation) at 0 ms (t_{17}=-1.82) (p=0.08). These confirm that there was little evidence that the SSEP amplitude was modulated during rest and motor preparation.

For the time series centred on the imperative stimulus, the transition from motor preparation to movement onset, there was a significant modulation in SSEP amplitude 500 ms and 300 ms prior to the imperative stimulus and (t_{17}=-2.71, p=0.01 and t_{17}=-2.49, p=0.02 respectively). Furthmore, there was a trend to significance 400 ms prior to the imperative stimulus (t_{17}=-2.09, p=0.05) and 200 ms prior to the imperative stimulus (t_{17}=2.10 and p=0.05). After the imperative stimulus, green circle, significance was seen 700 ms after the green circe (t_{17}=1.76) (p=0.09). These results suggest that there was weak evidence of a reduction in the SSEP amplitude 500-300 ms prior to the imperative stimulus during the period of motor preparation.

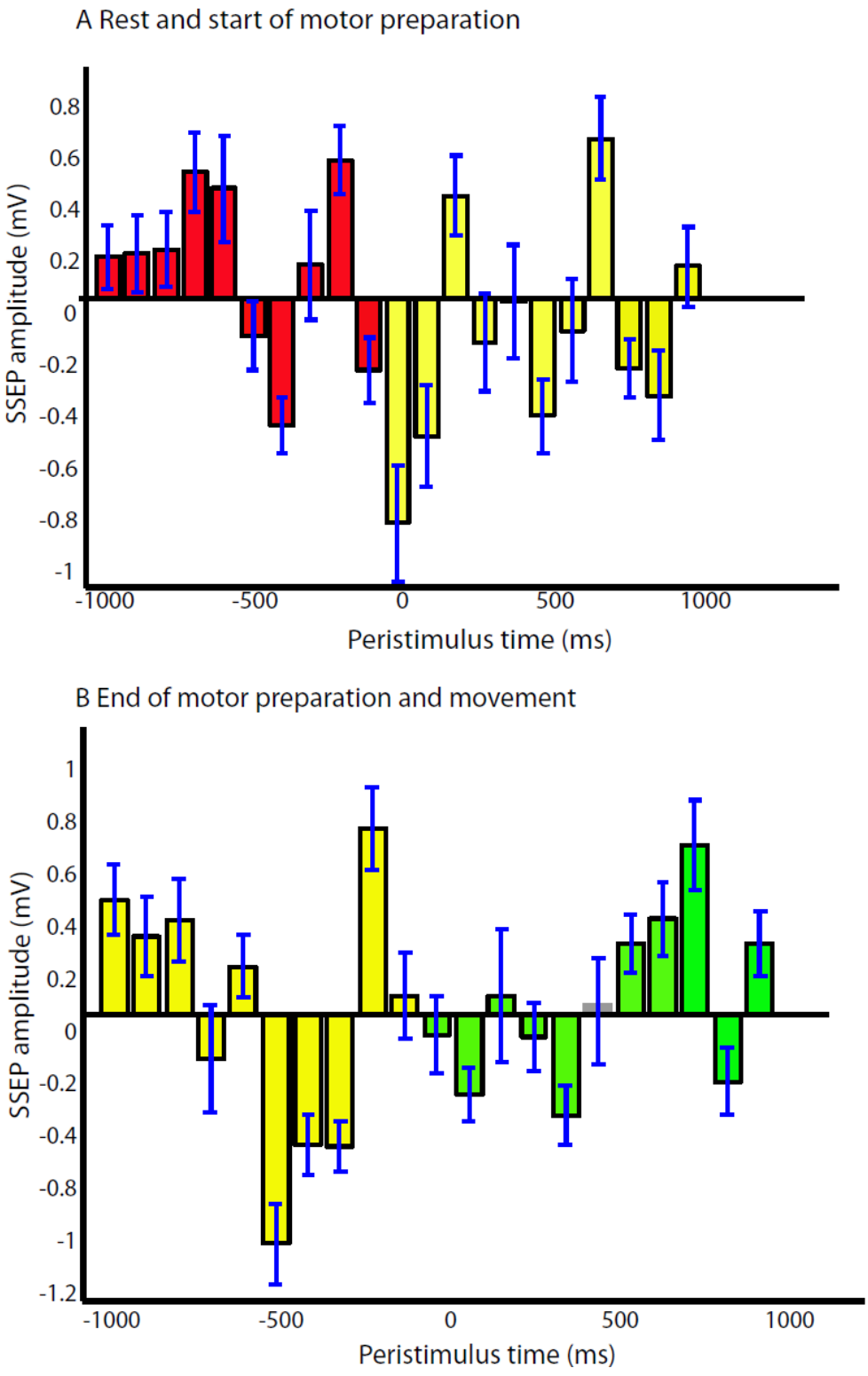

Figure 4-8 ***Figures of SSEP amplitude activity in relation to peristimulus time under two conditions.***
A. *Within time window of -1000 to 1000 milliseconds, rest and start of motor preparation is evident. At -1000 to 100 ms red circle occurs (rest) presented in red. At 0 ms yellow circle (motor preparation) is presented in yellow. It occurs from 0 to 1000 ms. It continues to Figure 5B.* ***B,*** *within time window of -1000 to 1000 ms, end of motor preparation is evident. At -1000 to -100 ms yellow circle continues presented as yellow. At 0 ms green circle (movement) is presented in green. It occurs from 0 to 1000 ms. No clear SEP attenuation (SEP amplitude decrease) noted during rest and motor preparation. It was more evident during movement. In movement, clearer rebound phase was also presented.*

4.3.2 BETA OSCILLATIONS

The second aim of this study was to investigate the modulation of sensorimotor beta power during the different phases of the task, rest (red condition), motor preparation (yellow condition) and movement (green condition).

As with the SSEP data, prior to statistical testing the average beta power over all time bins was subtracted from each bin for each subject. In other words, if there was no modulation with respect to time then there would be no statistical difference from zero. (Figure 4-8 A&B).

To test whether beta oscillatory activity is modulated based on task design and time, a two way repeated measures ANOVA was carried out having one factor with 2 levels (rest and start of motor preparation, end of motor preparation and movement) and one factor time with 39 levels. The result show that there is no main effect of condition, i.e. no evidence that beta power was different between the two conditions ($F(1.00, 17.00) = 0.115$, $p=0.738$). There was a significant main effect of time ($F(1.81, 30.84) = 12.193$, $p<0.01$) and no interaction between the factors ($F(1.80, 30.63) = 1.265$, $p=0.294$).

To further investigate whether beta oscillatory activity was modulated as a function of time each value at each time point was tested against the null hypothesis that they were equal to zero, using t-tests. For the beta power centred on the time of presentation of the yellow stimulus there was a widespread significant attenuation of beta power during the rest period when the red circle was on the screen. The t-tests showed significant attenuation from 1000-750 ms 650 ms and at 500-400 ms prior to the onset of the movement preparation cue. (1000 ms, $t_{17}=-3.19$, $p=0.005$, 950 ms, $t_{17}=-3.42$, $p=0.003$, 900 ms, $t_{17}=-2.99$, $p=0.008$, 850 ms, $t_{17}=-3.12$, $p=0.006$, 800 ms, $t_{17}=-2.72$, $p=0.01$,750 ms, $t_{17}=-2.62$, $p=0.01$, 650 ms ,$t_{17}=-2.47$, $p=0.02$, 500 ms, $t_{17}=-2.27$ and $p=0.03$, 450 ms, $t_{17}=-2.74$, $p=0.01$ 400 ms, $t_{17}=-2.37$, $p=0.02$). In addition,

there were trends to significance at 700 ms and 350 ms prior to the preparation cue (t_{17}=-2.01, p=0.05, t_{17}=-2.00, p=0.06). Significance was also seen at 400 to 1000 ms after the cue to prepare to move. (400 ms, t_{17}=2.35 p=0.03, 450 ms, t_{17}=2.22, p=0.03, 500 ms, t_{17}=2.35, p=0.03, 550 ms, t_{17}=2.68, p=0.01, 600 ms, t_{17}=3.03, p=0.007, 650 ms t_{17}=3.64, p=0.002, 700 ms, t_{17}=2.79, p=0.01, 750 ms, t_{17}=3.40, p=0.003, 800 ms, t_{17}=3.87, p=0.001, 850 ms, t_{17}=3.75, p=0.001, 900 ms, t_{17}=3.62, p=0.002, 950 ms, t_{17}=3.26, p=0.004 and 1000 ms, t_{17}=3.01, p=0.007).

For the time window centred on the time of the imperative stimulus the beta power was significantly attenuated compared with the average beta power 1000 to 200 ms prior to the imperative stimulus during motor preparation. (-1000 ms, t_{17}=-5.51, p=<0.01, -950 ms, t_{17}=-4.64, p<0.01, -900 ms, t_{17}=-4.95, p<0.01, -850 ms, t_{17}=-3.94, p=0.001, -800 ms, t_{17}=-3.80, p=0.001, -750 ms, t_{17}=-3.47, p=0.002, -700 ms, t_{17}=-3.01, p=0.007, -650 ms, t_{17}=-2.89, p=0.01, -600 ms, t_{17}=-2.91, p=0.009, -550 ms, t_{17}=-3.77, p=0.001, -500 ms, t_{17}=-3.34, p=0.003, -450 ms, t_{17}=-2.80, p=0.01, -400 ms, t_{17}=-2.80, p=0.01, -350 ms, t_{17}=-2.71, p=0.01, -300 ms, t_{17}=-2.75, p=0.01, -250 ms, t_{17}=-2.17, p=0.04 and -200 ms t_{17}=-2.31, p=0.03). In addition there was a trend to significance 150 ms prior to the imperative signal (-150 ms, t_{17}=-2.07, p=0.05).

After the imperative signal beta power was significantly augmented compared with the average beta power from 600 to 1000 ms (600 ms, t_{17}=2.21, p=0.04, 650 ms, t_{17}=2.29 and p=0.03, 700 ms t_{17}=2.43, p=0.02, 750 ms, t_{17}=2.30, p=0.03, 800 ms t_{17}=2.66 and p=0.01, 850 ms t_{17}=2.74, p=0.01, 900 ms, t_{17}=3.10 and p<0.01, 950 ms t_{17}=3.33, p=0.003 and 1000 ms, t_{17}=3.72, p=0.001) In addition a trend to significance was observed at 550 ms (t_{17}=2.07, p=0.05).

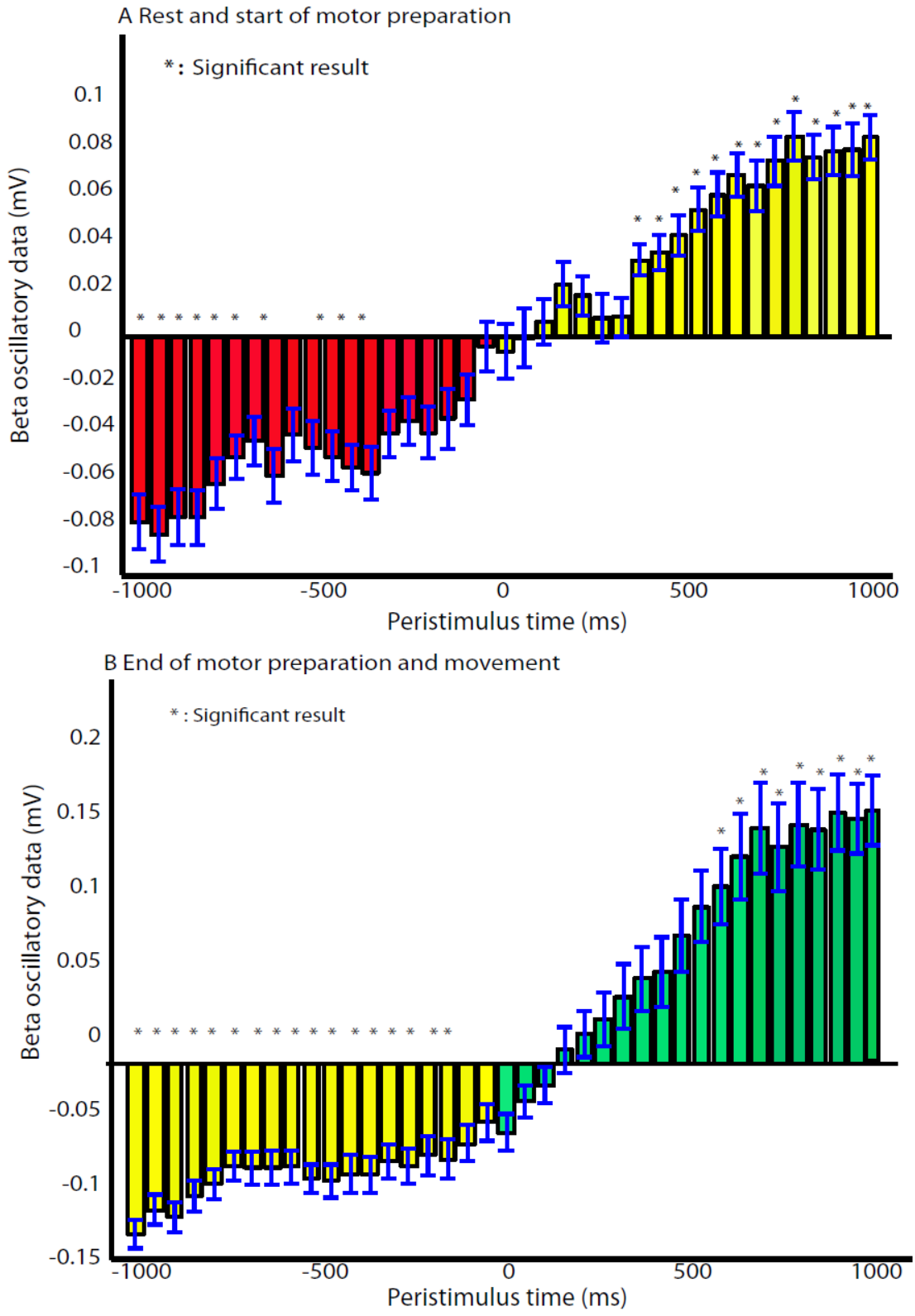

Figure 4-9 ***Figures of beta oscillatory activity in relation to time under two conditions.***
A, *This diagram shows the time window (-1000 to 1000 ms) selected for rest and start of motor preparation. A decrease is evident throughout red circle presence following by increase at the disappearance of red and appearance of yellow circle.* ***B,*** *This diagram shows the time window (-1000 to 1000 ms) selected for end of motor preparation and movement. A decrease is evident throughout yellow circle presentation following by a slight increase at the disappearance of yellow circle and appearance of green. Profound increase is evident during green circle presence (rebound phase from motor preparation)*

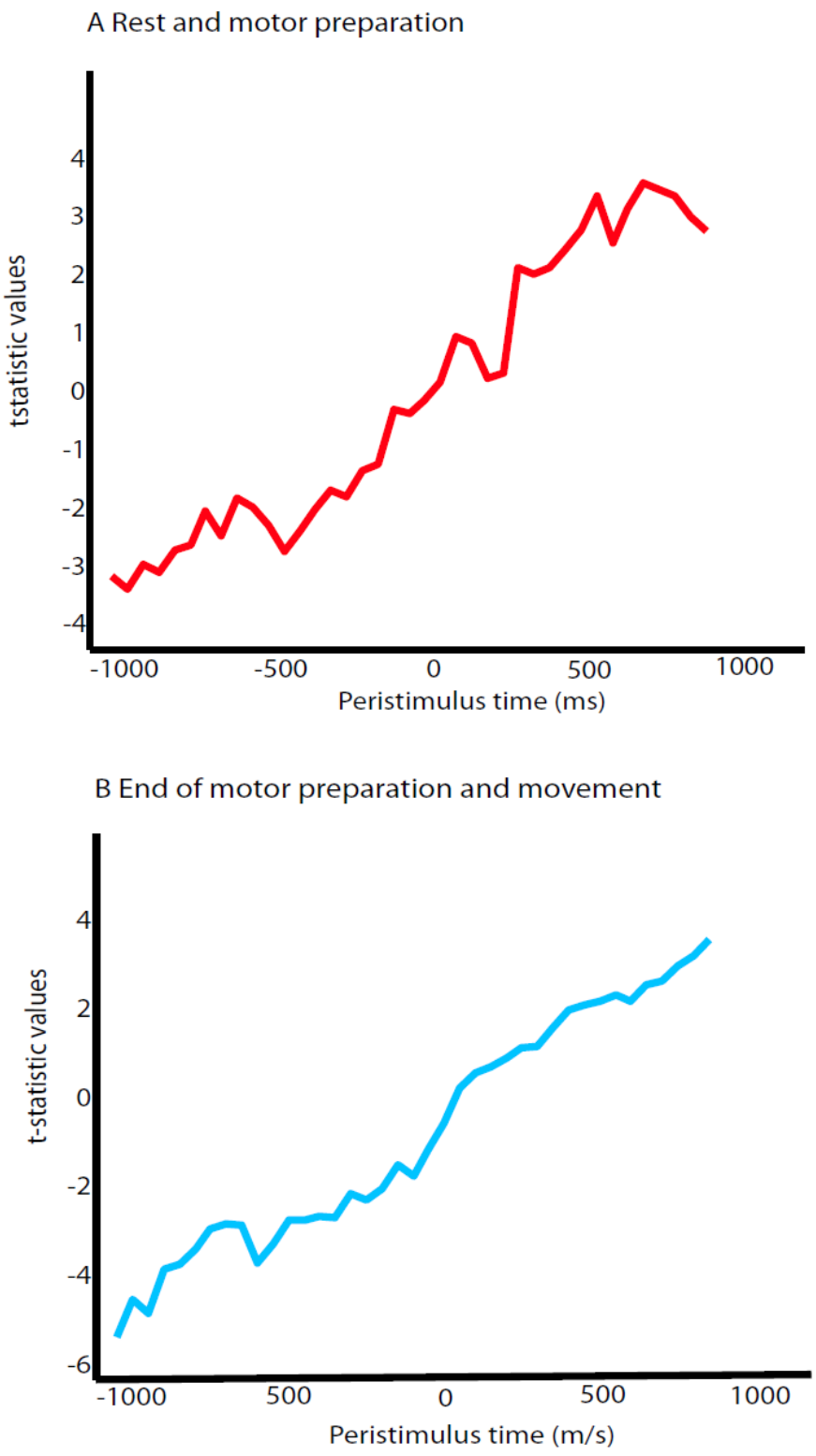

Figure 4-10 ***Shows t-statistic values versus time for the two conditions.***
A. *Diagram shows t-statistic values for rest and start of motor preparation within -1000 to 1000 ms time window selected. T-statistic values higher than 2 and lower than -2 are the most significant.* ***B.*** *Diagram shows t-statistic values for end of motor preparation and movement within -1000 to 1000 ms time window selected. As for the previous conditions, t-statistic values higher than 2 and lower than -2 are the most significant.*

To show how beta oscillations are modulated in terms of frequency within beta frequency range (15-30 Hz), the data were averaged for the time windows selected for all conditions and over all subjects. Time frequency diagrams were plotted for rest and start of motor preparation as well as end of motor preparation and movement (Figure 4-11A&B).

From the figures below, it could be seen that there was a beta oscillatory frequency modulation in beta frequency range as there was a decrease before 0 ms especially between 15-30 Hz in both figures following by an increase after 0 ms at all frequency range, but also in 15-30 Hz.

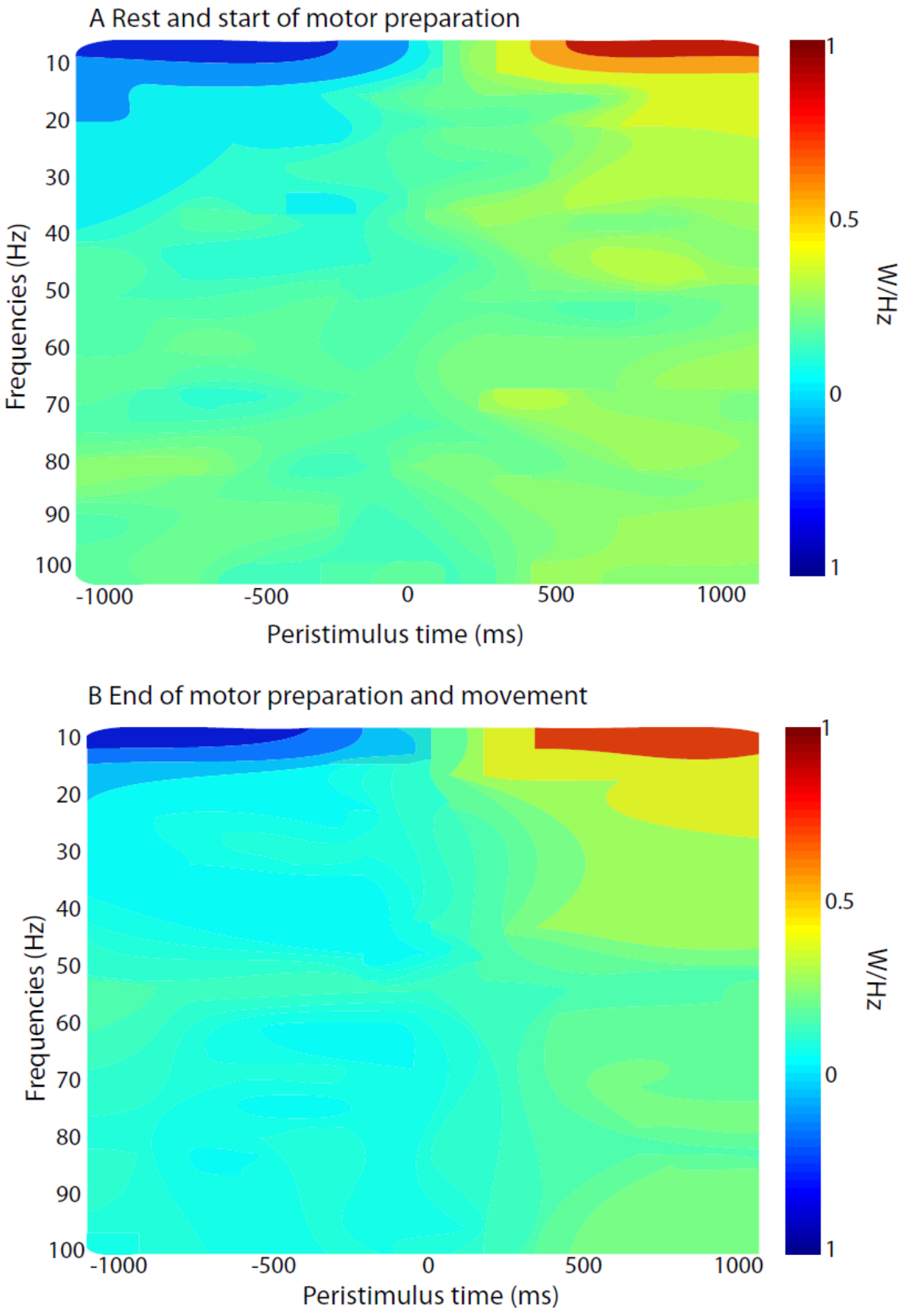

Figure 4-11 ***Figures show beta power modulation at the two conditions in relation to time-frequency analysis.*** ***A,*** *Shows how beta is modulated at frequency range 15-30 Hz by a decrease in beta oscillation during red circle presence and increase as yellow appears.* ***B,*** *Shows how beta is modulated at frequency range 15-30 Hz by decrease in beta during yellow circle presence and an increase after yellow has ceased.*

The next question that had to be answered is whether there is a correlation between time-course of the amplitude of the primary component of the SSEP amplitude and the time-course of beta oscillations. To answer this, a correlation analysis was carried out using beta time-frequency data and SSEP time data.

SEP and beta oscillatory data for rest, start of motor preparation and for end of motor preparation and movement were averaged across all subjects. These results are shown in Figure 4-12A&B.

Correlation analysis for rest and start of motor preparation showed r squared value to be insignificant as r^2=0.04, p value of the regression was also insignificant as p=0.39. F-statistic that is the test statistic of the F-test on the regression model was also insignificant as F=0.76. R squared, F-statistic and p-values were also identified for end of motor preparation and movement. Again, R squared value was insignificant (r^2=0.001). The F-statistic on the regression model was insignificant as F=0.02. The p-value of the regression model was also insignificant as p=0.88.

As averaging across all subjects, did not show any correlation, correlation analysis of SEP and beta oscillatory data per subject was carried out for the two conditions. However, r squared values for each subject at each condition were too small for the data to be correlated.

This could be seen by Figure 4-13A&B for rest and start of motor preparation, for end of motor preparation and movement. At rest and start of motor preparation r squared values for each subject are even smaller than at the end of motor preparation and movement.

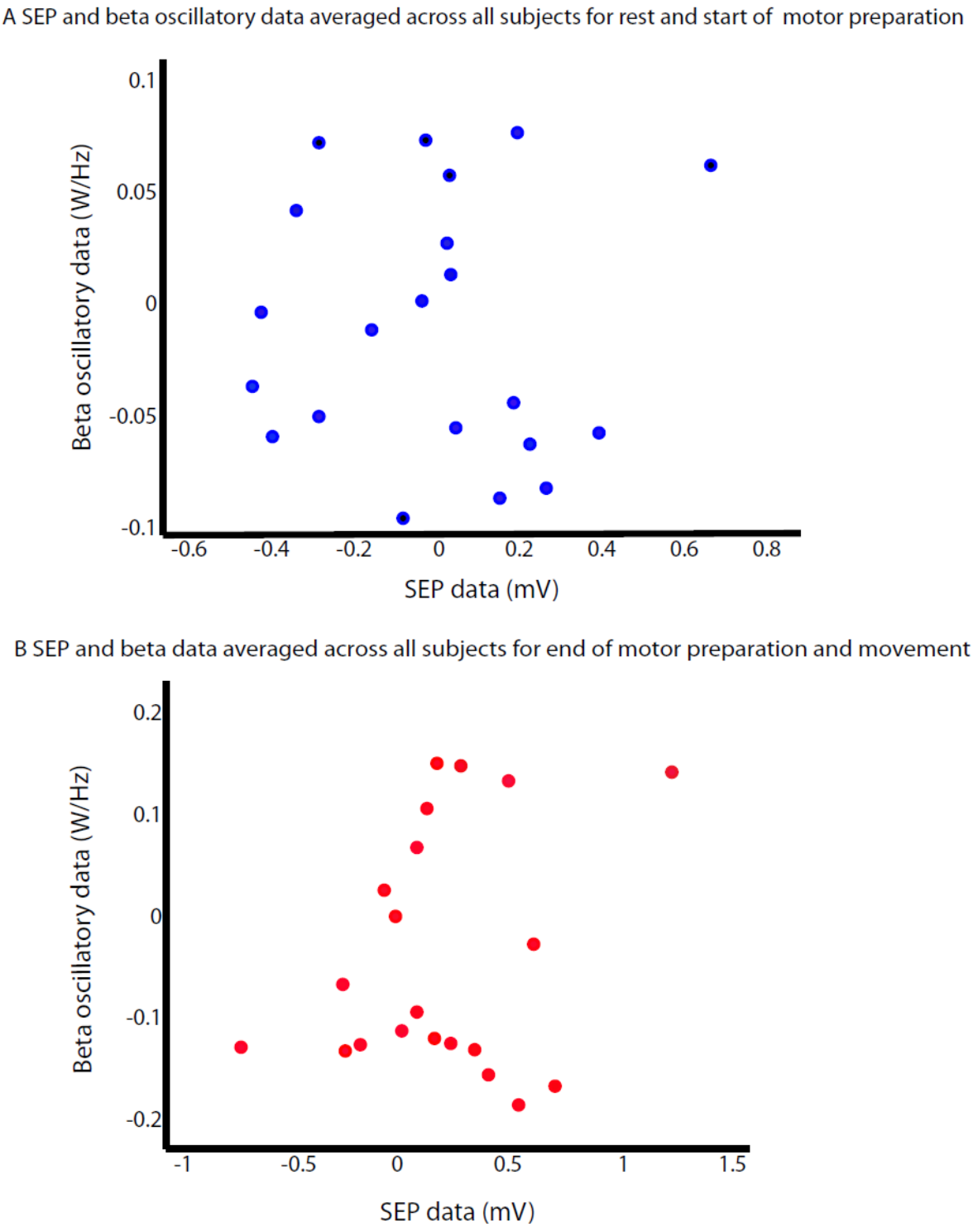

Figure 4-12 ***Correlation plots between beta oscillatory power and SSEP data across all subjects for the two conditions.***
A, *Shows SSEP and beta oscillatory data for all subjects at the first condition (rest and start of motor preparation).* ***B,*** *Shows SSEP and beta oscillatory data for all subjects at the 2nd condition (end of motor preparation and movement)*

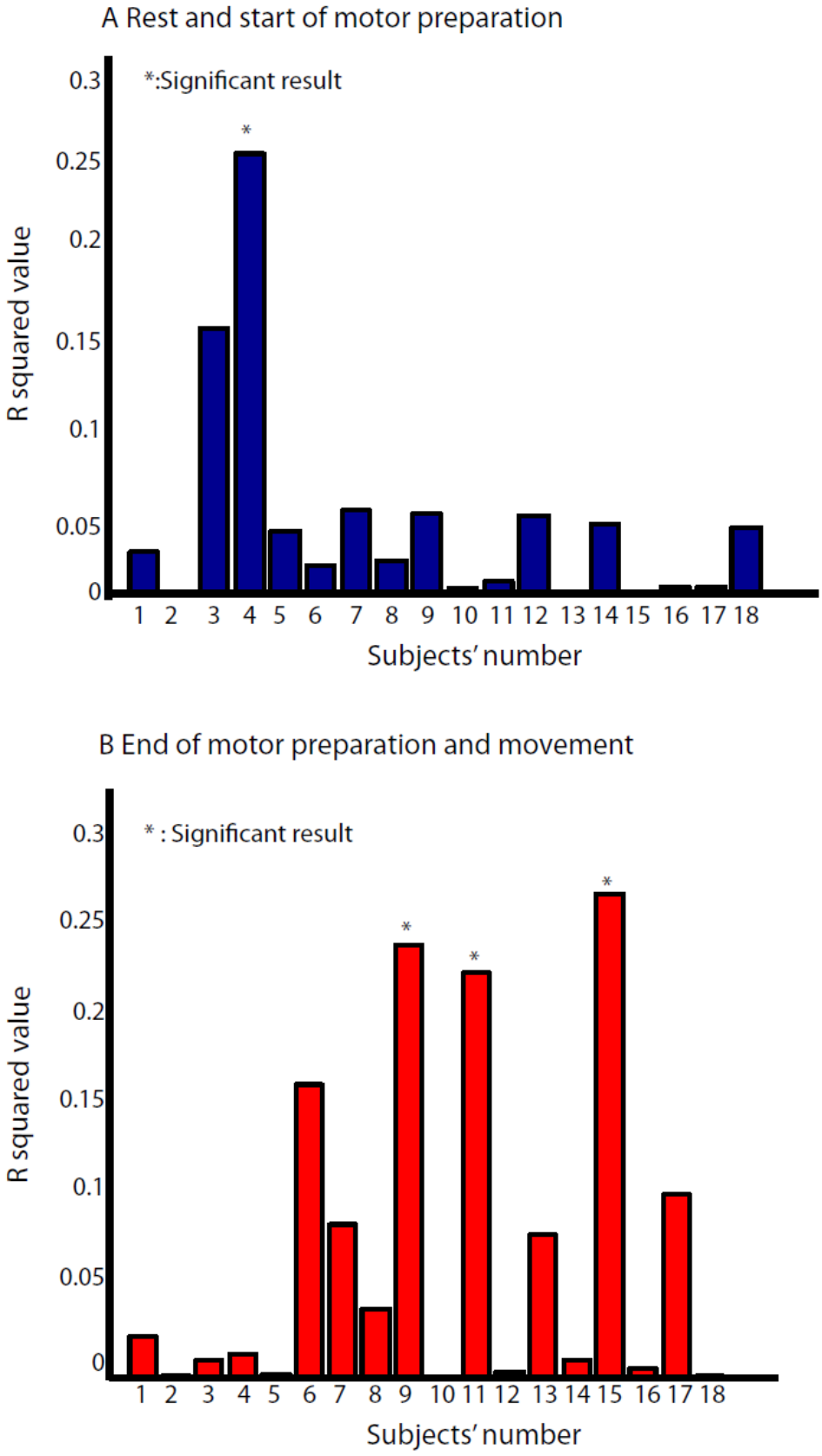

Figure 4-13 ***Figures that show r^2 squared values for each subjects at the two conditions.***
A, *It shows that r squared values for each subject at rest and start of motor preparation. The values are too small for beta frequency data and SEP time data to be correlated.* ***B,*** *The same applies as with the second diagram where r squared values of each subject are too small for paired quantitative data to be correlated*

The highest r squared value in the first condition of 0.25, was seen at subject 4. This coincide with a significant F-statistic on the regression model (1.00, 18.00) = 6.64 and p-value of 0.01. Near significance was noted at subject 3 having F-statistic (1.00, 18.00) = 3.50 and a p-value of 0.07. In the second condition highest value as well of 0.25 is seen at subject 15. This coincide with a significant F-statistic (1.00, 18.00) = 5.93 on regression model and a p-value of 0.02. Significance was also seen at subject 9 with F (1.00, 18.00) = 5.14 and a p-value of 0.03 and at the subject 11 with F (1.00, 18.00) = 4.72 and p=0.04. Near significance was noted for the subject 6 with F (1.00, 18.00) = 3.19 and p=0.08 (significance is represented with a * in Figure 4-13).

Although r squared values are too small for correlation to occur, t-tests were carried out for the first and the second condition to determine whether the slope of the regression line differs from zero. It showed no significance for both conditions. For rest and start of motor preparation, t-stat was t_{17}=1.17 and p-value was p=0.25. For end of motor preparation and movement t-statistic was t_{17}=-0.72 and p=0.47. Therefore, beta time-frequency data and SEP time data for the first and for the second condition are not correlated.

4.4 DISCUSSION

The main aims of the second experiment were to test active inference framework and SSEP attenuation in the time domain during rest, motor preparation and movement. Also, to record whether attenuation of beta oscillations was evident and if SEPs and beta oscillations could be correlated. The results evidently show the presence of N20-P25 SEP complex when all subjects trials are averaged irrespective of condition (rest, motor preparation, movement).

Although there are previous accounts that show that SSEP amplitude reduces prior and during movement (Rushton et al, 1981; Starr and Cohen, 1985; Abbruzesse et al, 1981; Seki and Fetz, 2012; Voss et al, 2006; Murase et al, 2000; Kourtis et al, 2008), in this experiment, N20-P25 SSEP amplitude attenuation cannot be identified in any condition. The repeated measures ANOVAs that carried out for rest and start of motor preparation, end of motor preparation and movement in relation to the time selected confirms that SSEP is not modulated at any condition as F-statistics and p-values are not significant. T-tests also did not show any conclusive evidence that the amplitude of SSEPs is attenuated.

On the other hand, results from beta oscillations show a differential response. A two-way ANOVA was carried out for the conditions in relation to time and showed no main effect of condition but significant effect with time. Further, t-tests were carried out for the two conditions and showed significance throughout. Although overall beta oscillatory modulation is seen throughout, astonishingly an enhancement is seen at some points in time for start of motor preparation and movement.

The reasons for these results have been thoroughly discussed in the general discussion chapter.

5 STOP SIGNAL REACTION TIME TASK (SSRT)

5.1 INTRODUCTION

The experiments described in the previous chapters were designed to investigate whether SSEPs could be frequency tagged and if so whether this technique could be employed to investigate sensory attenuation as a function of task. Although there is clear evidence that SSEPs could be frequency tagged there was no, or at best very weak evidence that this method, could be used to investigate task dependent modulations in SSEP amplitude.

Active inference states that sensory attenuation is necessary to allow movements to occur and reflects the reduction of sensory precision. This allows predictions of movement to be resolved by generating actual movements via spinal reflex arcs rather than being explained away by sensory evidence that the movement has not yet occurred (Friston et al, 2016). In active inference the reduction of the estimate of the somatosensory precision that allows movements to be realised is believed to be modulated by top-down mechanisms. Within the active inference framework the estimate of the somatosensory precision is an estimate of the noise or certainty of the somatosensory afferent signal. This means that a change in the noise of the afferent signal should lead to an updating in the estimate of the certainty of the somatosensory signal resulting in a reduction in the estimate of the precision of somatosensory signal. This allows the possibility that experimentally altering the afferent noise from the periphery could reduce the estimate of the somatosensory precision and therefore make individuals quicker to initiate and perform simple motor acts. This theory has recently been tested in a series of experiments (Macerollo et al. 2018). In these experiments ‘noise’ was added to the afferent signal through 30 s of vibration at the wrist. When vibration was applied at 80 Hz prior to the movement tasks subjects were

reliably and reproducibly faster to initiate and perform simple motor tasks than when no vibration was applied or when vibration was applied at lower frequencies, 20 Hz. Although these results are interesting they are somewhat counterintuitive. If application of vibration at high frequencies at the wrist improves motor initiation and motor task speed then why have we not adapted our sensorimotor system to be able to move quicker? One possible reason is that speed of movement initiation in most situations may not be the optimal behaviour. In the study of Macerollo et al. (2018) all tasks were simple task where the subjects knew precisely which action to perform after vibration. In other words, there was always only one action to perform and there was no competition between different or alternative actions. Therefore, it is possible that although vibration might make the time to initiate movements faster and might improve action speed on simple motor tasks it might come at the cost of impulsivity to act. The aim of the current study was to test this hypothesis. To this end, tactile stimulation in form of vibration was given to subjects instructed to perform a stop-signal-reaction-time task (SSRT). The main aim of this experiment was to test the hypothesis that subjects would be more impulsive and would find it more difficult to inhibit actions when required in conditions when vibration was given.

Response inhibition is a thought to be marker of executive control. Response inhibition allows us to supress actions that are either no longer required or that might be incorrect or inappropriate. In this way response inhibition has been proposed as a mechanism that allows our motor behaviour to adapt to our ever changing environment. The SSRT task was developed as a paradigm that provides an estimate of the time to inhibit an action and is widely employed in the study of both human and animal cognition. In the stop signal paradigm, a primary stimulus is presented and subjects are instructed to press a button depending on the direction of the arrow. In a fraction of the trials a stop signal is presented and subjects are instructed to inhibit their actions on trials in which the stop signal is presented. Logan and Cowan (1984) showed that the probability of

responding when a stop signal was presented increased with the delay between the imperative signal and the stop signal. This is known as the stop-signal delay (SSD). The probability of inhibiting an action is commonly modelled as a race between the process to GO and respond to the imperative stimulus and a faster STOP response to inhibit the GO response after the STOP signal. The stop signal reaction time can be estimated by knowing the typical reaction time to the imperative stimulus, the SSD and the probability of stopping when the stop signal is given. Based on the previous results of Macerollo et al. (2018) which demonstrated that simple reaction times were decreased following 30 s of vibration at the wrist, the aim of the current study was to test the hypothesis that high frequency vibration applied at the wrist of healthy human subjects would decrease the time for the go resulting in more impulsive actions in the SSRT task.

5.2 METHODS

5.2.1 DATA ACQUISITION

5.2.1.1 PARTICIPANTS

28 healthy subjects took part in the study (mean 32.5 age years, range 22-43 age years). All subjects had normal or corrected-to-normal vision and were naive with respect to the purpose of the experiment. The experiment was performed with the approval of the ethics committee of University College London, and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

5.2.1.2 STOP SIGNAL REACTION TIME TASK

Each trial started with a delay period where a fixation cross was presented for a random time between 1-2 seconds. After this time a white arrow was presented on the screen. The arrow either pointed to the left or the right. On half the trials the arrow pointed to the left and in the other half it pointed to the right. Subjects were instructed to press the right response button with their right index finger when the arrow pointed to the right and to respond with the left response button with their left index finger when the arrow pointed to the left. They were instructed to respond as quickly as possible to the presentation of the white arrow. In this task the white arrow was the GO signal. After 750 ms the white arrow next trial started with the presentation of the fixation cross. Subject performed an initial run of 32 trials of this task to familiarise themselves with the task and to train subjects to respond as quickly as possible to the GO signal. In the actual experiment in 25% of trials at some time after the GO signal a STOP signal was presented. The STOP signal consisted of the white arrow turning red. Subjects were instructed that they should try to inhibit the action when the white arrow turned red. The STOP signal trials occurred randomly throughout a block. The delay between the presentation of the GO signal and the STOP signal was defined as the stop signal delay (SSD) period. In the first STOP trial this was set as 200 ms. The SSD was modulated on a trial by trial basis dependent upon the subjects' performance in the previous STOP trial. If a subject had successfully inhibited the response, SSD was increased by 50 milliseconds. If the subject did not successfully inhibit the movement, then SSD was decreased by 50 milliseconds. This staircase procedure was adopted as previous research has shown that in doing so the P stop, the probability of stopping, would be close to 0.5. In other words the SSD was altered such that in half the trials subjects were able to stop the action and in the other half they would make a response. Subjects performed 15 blocks with 64 trials in each block.

Subjects performed the task in three different conditions, no vibration (Novib), 40 Hz vibration (40vib) and 80 Hz vibration (80vib). Each condition consisted of five of the 15 blocks of trials. During all trials the subjects had a vibration device (Vibrasens VB115, Technoconcept) attached to their left and right wrists. In each block prior to the first trial commencing there was a pause of 15 seconds. In this period either no vibration was applied to the vibration device, Novib Condition, or 40 Hz vibration was applied, 40vib condition, or 80 Hz vibration was applied, 80vib condition. Vibration was applied simultaneously to both wrists. After 15 s of vibration the vibration was stopped and the first trial of a block commenced. After 32 trials there was a second 15 second pause in the task and vibration was applied in the same way as at the beginning. Note that in the vibration conditions the device was not vibrating during the actual SSRT task. The vibration conditions were randomised between blocks but were the same within a block.

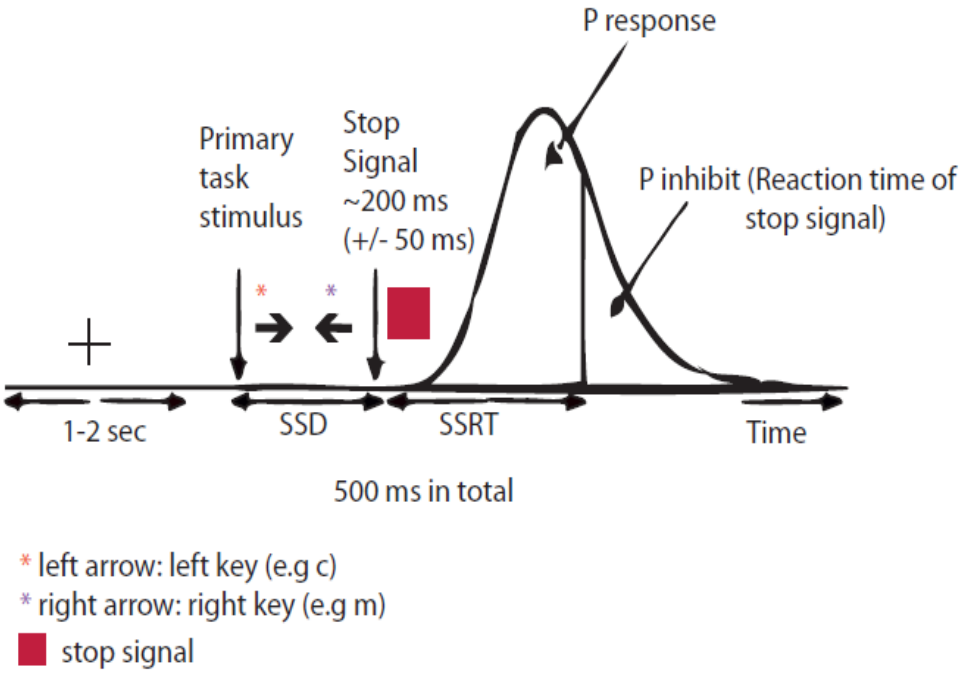

Figure 5-1. ***This figure modified by Aron et al, 2003 shows how SSRT task works.***
A delay period (fixation cross) is presented before primary task stimulus. During SSD period choice between left or right arrows would be given. At around 200 ms, stop signal would be presented, stimulus would change to red. A curve between probability of response and inhibition would be obtained. P inhibit is based on SSRT.

5.2.1.3 DATA ANALYSIS

All reaction times (go and stop signal reaction times) irrespective of condition were calculated. Reaction times of stop signal were calculated in basis of successful inhibition for the three different conditions (no vibration, 40 and 80 Hz vibration). Reaction times for go trials were calculated in the same way, in the basis that a successful response occurred. SSD was calculated by taking the mean of all SSD for go and stop trials for the three different conditions and SSRT was calculated by using two methods for the three different conditions, the median and percentile method. For the median method, mean of SSD for all trials was subtracted from the median of all reaction times. For the percentile method, averaged SSD for all trials were subtracted from all reaction times presented in a descending order for all three different conditions.

The reaction times of each subject have already been multiplied by the ratio of trials that were not inhibited. The ratio was calculated by dividing the number of trials that were uninhibited in the last 160 trials from the number of trials that were uninhibited within the first 160 trials for each subject and for the three different conditions.

The experimental design was adapted from Aron et al, 2003 and as shown in Figure 5-1, the SSD period within the diagram divides go trials into 2 probabilities: the probability of response and probability of inhibition. The probability of response is subjects' ability to respond fast and avoid inhibition. On the other hand, probability of inhibition is subjects' ability to inhibit the movement. The varying SSD from trial to trial depending on subject's performance was used so that probability of inhibition will remain at 50% or 0.5. However, for most of the subjects the Pinhibit was not fixed at 50%. Therefore, it was necessary to use the percentile method so that reaction times will be multiplied by the ratio of uninhibited trials and thus a better SSRT would be calculated (Figure 5-2B).

All subjects' data were taken into consideration, although some of the subjects had reaction times that were extremely slow.

ANOVAs were carried out for all the variables calculated to show if and how vibration could influence response or inhibition and if reaction times changes irrespective of vibration.

5.3 RESULTS

The aim of the current study was to test whether the SSRT was affected by vibration. Specifically, whether the SSRT was modulated by high frequency, 80 Hz, compared with lower frequency, 40 Hz, vibration applied at the wrist. When the SSRT was calculated using the median method, at the group level there was no significant main effect of vibration on SSRT ($F(2,54)=0.74$, $p=0.48$, mean noVib = 236.1 ms, mean

40Vib = 231.8 ms, mean 80Vib = 232.1 ms; Figure 5-2A). In Figure 5-2A, 320 trials for each condition were taken. The time presented in x-axis represent SSRT times that are found by subtracting the mean SSD times from the median reaction times. Furthermore there were no significant pairwise differences between the 3 vibration conditions (noVib – 40Vib; $t(27)=0.953$, $p=0.35$, noVib – 80vib; $t(27)=1.013$, $p=0.32$; 40Vib-80Vib; $t(27)=-0.115$, $p=0.91$). The experiment was designed so that using a staircase method the SSD would change on a trial by trial basis based on whether, in the previous instance, the participant had correctly or incorrectly withheld the action. The staircase procedure should result in participants inhibiting an action on 50% of stop trials. If this is the case the median methods of calculating the SSRT can be employed. However, it is not valid if the proportion of trials in which participants inhibited an action, Pinhibit, is not close to 50%. Indeed, in this experiment not all participants inhibited the action on 50% of the trials. In fact the Pstop was correlated with the participants mean reaction time. The slower the participant reacted the higher the proportion of Pinhibit ($r=0.9$, $p<0.001$; Figure 5-2B). In Figure 5-2B, the reaction times of all trials (960 trials in total) was presented in x-axis whereas probability of inhibition through all trials was represented in y-axis.

Therefore, the median method of estimating the SSRT was not valid. In a subsequent analysis the SSRT was re-estimated using the percentile method. This method is robust to the proportion of Pinhibit not being close to 0.5. In this method all reaction times to the imperative stimulus are ranked from in descending order. Then the reaction time that equates to the point of Pinhibit ratio is taken and the average SSD is subtracting from this to give the SSRT. This method I will refer to as the SSRTq. When the SSRTq was calculated at the group level there was no significant main effect of vibration on SSRTq ($F(2,54)=0.202$, $p=0.82$, mean noVib = 203.5 ms, mean 40Vib = 199.8 ms, mean 80Vib = 200.7 ms; Figure 5-2C). In Figure 5-2 C, SSRTq times was obtained using the percentile method where all SSD times were subtracted from all

reaction times that were multiplied by the ratio of uninhibited trials. 320 trials for each condition were taken.

Furthermore there were no significant pairwise differences between the 3 vibration conditions (noVib – 40Vib; t(27)=0.551, p=0.59, noVib – 80vib; t(27)=0.459, p=0.650; 40Vib-80Vib; t(27)=-0.17, p=0.866). These analyses do not provide any support for the hypothesis that the SSRT was modulated by high frequency vibration in the periphery.

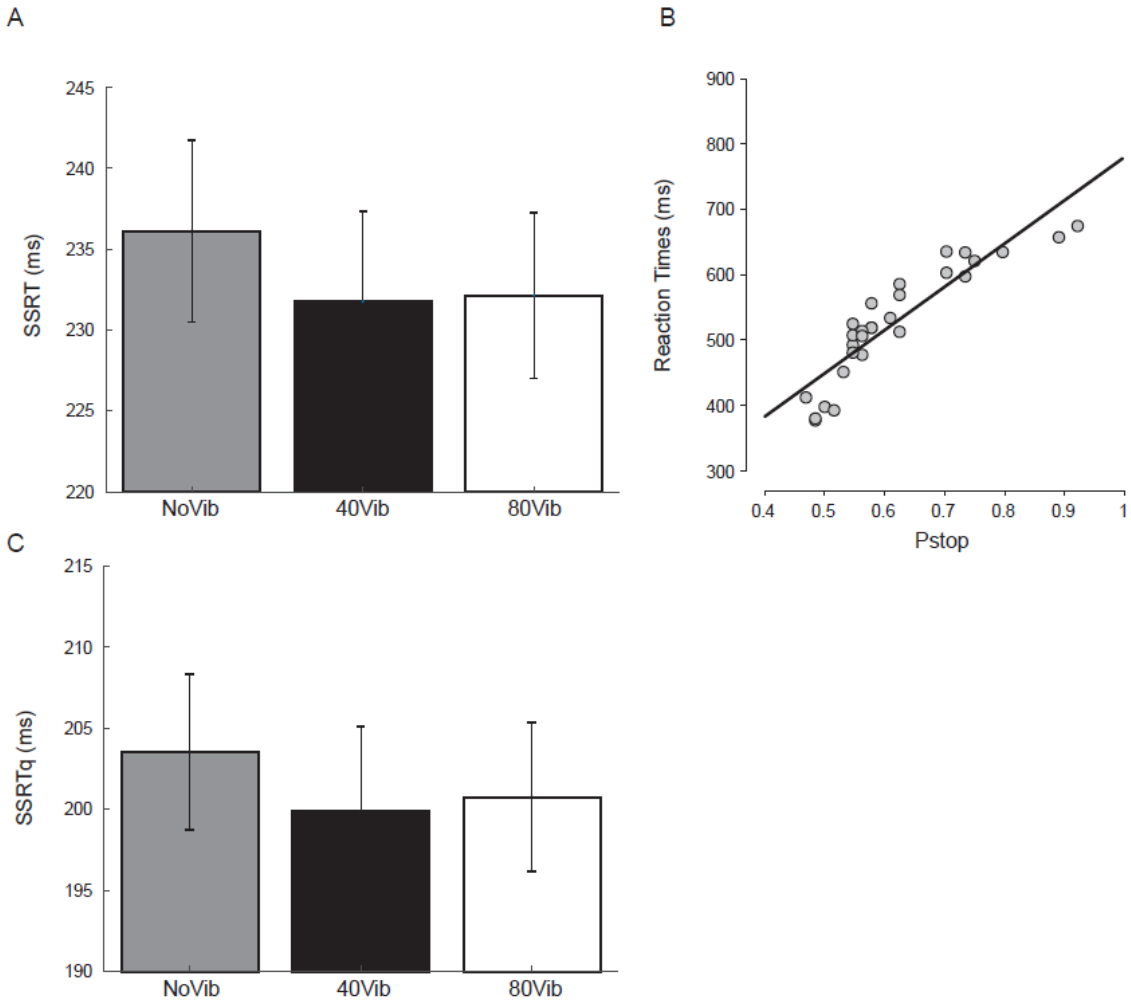

Figure 5-2. ***Figures showing SSRT modulation in the 1st and 2nd method and correlation between Pstop and RT.*** ***A.*** *Shows SSRT at a group level during the three conditions: no vibration, 40 Hz and 80 Hz vibration.* ***B.*** *Shows a positive correlation between the probability that participants stopped and their reaction times.* ***C.*** *Shows SSRTq at a group level during the three conditions: no vib, 40Vib and 80Vib*

Previous research that has employed vibration in the periphery to study its effects on motor performance has demonstrated that the reaction times were faster subsequent to 80 Hz vibration compared with no vibration and a lower 20 Hz vibration.

Here I tested whether in this task the SSD and the mean RTs were modulated by the vibration in a similar way. For the SSD at the group level there was no significant main effect of vibration ($F(2,54)=1.745$, $p=0.184$, mean noVib = 288.7 ms, mean 40Vib = 297.6 ms, mean 80Vib = 291.6 ms; Figure 5-3A). Furthermore there were no significant pairwise differences between the 3 vibration conditions (noVib – 40Vib; $t(27)=-1.54$, $p=0.136$, noVib – 80vib; $t(27)=-0.574$, $p=0.571$; 40Vib-80Vib; $t(27)=1.772$, $p=0.088$). Although there were no significant differences in the pair wise t-tests there was a trend to significance between the average SSD time after 40 Hz vibration and after the 80 Hz vibration, with the SSD being slower after 40 Hz than 80 Hz vibration (Figure 5-3A).

For the RTs to the imperative stimulus in the absence of the stop signal at the group level there was no significant main effect of vibration ($F(2,54)=1.149$, $p=0.325$, mean noVib = 526.2 ms, mean 40Vib = 530.9 ms, mean 80Vib = 525.0 ms; Figure 5-3B). Whereas there were no significant pairwise differences between the noVib and either the 40vib or 80vib conditions (noVib – 40Vib; $t(27)=-901$, $p=0.375$, noVib – 80vib; $t(27)=312$, $p=0.757$), there was a significant difference between the 40vib and 80 vib conditions (40Vib-80Vib; $t(27)=2.094$, $p=0.046$). As with the SSD, after stimulation in the periphery at 40 Hz there RTs were significantly slower than after 80 Hz vibration (Figure 5-3B).

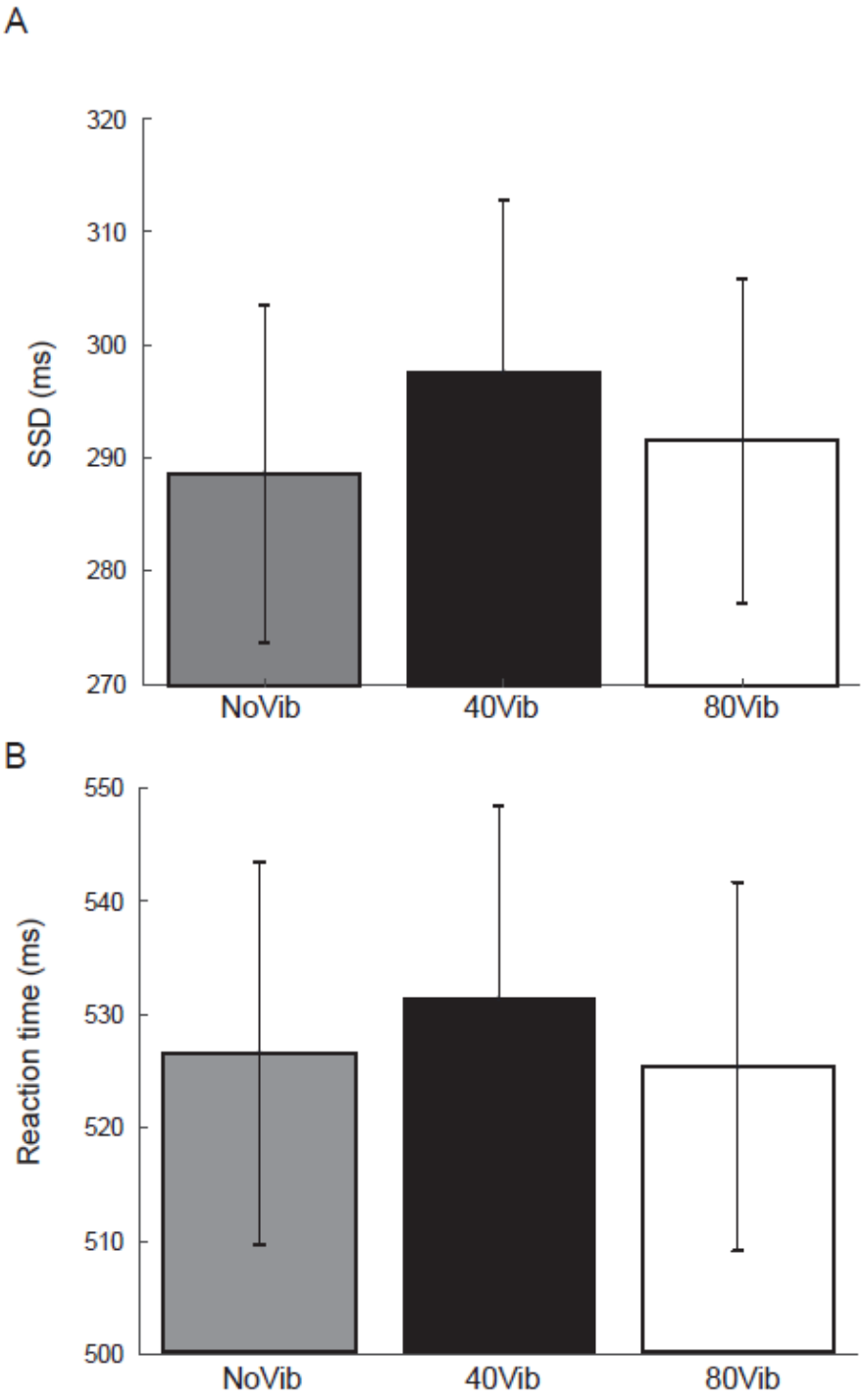

Figure 5-3. ***Figures showing how SSD and RT are modulated under the three conditions.***
A, *Shows how SSD is being modulated at the three different conditions: no vibration, 40 Hz and 80 Hz vibration.* ***B,*** *Shows how Reaction Times are being modulated at no vibration, 40 and 80 Hz vibration.*

5.4 DISCUSSION

The aim of the current study was to build on the previous results of Macerollo et al. (2018) which demonstrated that simple reaction times were decreased following 30 s of vibration at the wrist and to test the hypothesis that there is a cost to this decrease in reaction time, specifically that participants would become more impulsive. Therefore, I tested whether high frequency vibration applied at the wrist of healthy human subjects would decrease the time for the GO resulting in more impulsive actions in the SSRT task. I showed no evidence that SSRT was modulated by vibration and therefore found no evidence that participants became more impulsive with high frequency vibration.

The study was predicated on the previous work by Macerollo et al. (2018) that showed that simple movements, including a simple reaction time task, were performed more rapidly after 80 Hz stimulation compared to no vibration and 20 Hz vibration. In the SSRT task, where in the no stop conditions participants are performing a 2 AFC task, I found no evidence that participants were faster after 80 Hz vibration compared with no vibration. Here, for technical reasons, I used 40 Hz vibration as a control condition. There was some evidence that participants were slower after 40 Hz vibration compared with 80 Hz vibration. This was present both in the SSD data and more strongly in the RT data. These results are therefore clearly different to those previously found. There are a number of differences between the two tasks. In the reaction time task used previously participants were told to respond as rapidly as possible when a cue appeared on the screen. There was only one cue and one response button. Here, excluding the STOP condition, subjects had to respond correctly to either the left or right arrow with either the left or right response button. Therefore it is possible that such a simple change in the task demands might be enough to abolish the previous effect. In addition here on some trials subjects were instructed to inhibit the action when the STOP signal appeared. It would appear that this instruction had a large effect on subjects' reaction times. Many of the participants would appear to have adopted a

cognitive strategy of slowing their response and waiting to see if the STOP signal appeared. This is demonstrated by the relationship between the average reaction time and the Pstop (Figure 5-2B). Therefore, there is evidence that in this task the reaction time was not a pure reaction time but confounded with a cognitive strategy. This could account for the differences between the observed and predicted modulation in RT in the 80 Hz condition. The question remains though why did 40 Hz vibration slow both the reaction times and the SSD compared with the 80 Hz vibration?

It has previously been shown that high frequency vibration of forearm muscle tendons, which selectively activates muscle spindles (Brown et al., 1967; Burke et al., 1976; Roll et al., 1989), produces the illusion that the arm is moving or has been displaced (Goodwin et al., 1972; McCloskey, 1973; Craske, 1977). The central nervous system incorrectly interprets this increased firing rate of muscle spindles as if the affected muscle is contracting, which generates uncertainty in the actual position of the limb. This has been demonstrated in a number of position-matching and pointing tasks all of which show increased error, or reduced accuracy, following high-frequency peripheral vibration (Capaday and Cooke, 1983; Inglis and Frank, 1990; Cordo et al., 1995, 2005; Tsay et al., 2016). Previous research has shown that peripheral vibration at 80Hz impairs performance on a number of proprioceptive tasks (Inglis and Frank, 1990; Cordo et al., 1995, 2005; Tsay et al., 2016), which is thought to be driven by increasing uncertainty in the proprioceptive input. Indeed, high frequency vibration produces the illusion that the relevant muscle is contracting in the absence of any EMG activity by transmitting incorrect kinesthetic information to the brain and spinal cord such that the brain is uncertain about the relative position of the limb (Goodwin et al., 1972; McCloskey, 1973). Moreover, previous studies have demonstrated that high frequency peripheral vibration leads to sensory attenuation, as indicated by a decrease in the amplitude of SSEPs evoked by electrical stimulation of the afferent nerve. Peripheral vibration at 60Hz causes an attenuation of early components of the cortical and

cervical SSEP (Abbruzzese et al., 1980; Cohen and Starr, 1985); yet, 50 Hz cutaneous vibration between the thumb and finger and 20 Hz vibration at the wrist does not produce significant sensory attenuation (Kakigi and Jones, 1986; Legon and Staines, 2006). However, these effects were observed with frequencies typically higher that 40 Hz and are more consistent with the findings of Macerollo et al. (2018). Future studies will investigate the relationship between RT, task complexity and vibration frequency to reconcile the results shown here with those previously reported by Macerollo et al. (2018).

6 GENERAL DISCUSSION

The main aim of this thesis was to test predictions for the active inference framework relating somatosensory attenuation prior to and during movement. Specifically to investigate whether modulation of somatosensory attenuation elicited by median nerve stimulation during movement is correlated with beta oscillations in the sensorimotor cortex. Here I will briefly review the aims and results of my research and discuss the wider implications my results.

6.1 CHAPTER 2: IS FREQUENCY TAGGING A GOOD TECHNIQUE FOR SSEP RESEARCH?

Based on the general aim of this thesis, the first experiment aimed to test a prediction of active inference in relation to SSEP attenuation and frequency tagging. The aim of the first experiment was to test the hypothesis that frequency tagging is a viable technique for the study of SSEPs and whether frequency tagging was modulated by the frequency of stimulation. Here I studied the amplitude of SSEPs at rest using frequency tagging paradigm by applying square wave electrical pulses to the median nerve to elicit SSEPs and record these SSEPs through EEG. On this basis, to identify whether SSEPs could be frequency tagged, amplitude of SSEPs were calculated at different frequencies of stimulation. Further to SSEP amplitude analysis, to show evidence that SSEPs could be frequency tagged, frequency analysis was carried out. It tested whether response frequency measured through EEG was modulated by the input frequency, that is the frequency produced through median nerve stimulation. The results showed that the response frequency was modulated by the input frequency, especially in the beta power range. SSEP amplitude analysis also showed valid

evidence that particular frequencies drives the SSEP amplitude response. On this basis, it is valid to say that SSEPs could be frequency tagged.

Frequency tagging was firstly employed by Regan in visual field mapping to measure responses of different visual processes using multiple stimulation frequencies. Each eye was simultaneously stimulated by a weak flickering light or through a presentation of a chess board where white and black boxes alternated at different frequencies. This technique enabled the researchers to identify visual retinal defects by reducing ssVEPs variability and therefore ssVEPs were recorded with higher precision (Regan and Heron, 1969; Regan and Cartwright, 1970).

This technique was further developed and name as ‘frequency tagging’ by Tononi and colleagues in 1998. Here frequency tagging was employed to study binocular rivalry. Binocular rivalry is a paradigm used to identify neuronal activity that is based on conscious experiences. Subjects are presented with different stimuli in each eye but they perceive only one stimulus at any one time. Which stimulus is perceived changes every few seconds. In this study, whole head MEG recording of steady state evoked responses was carried out. Red vertical gratings and blue horizontal gratings were presented to each eye. They were flickered at a frequency range of 7-12 Hz and steady state evoked responses were observed at the frequency of flicker presentation. The results firstly showed that neural responses were observed in a number of cortical regions extending to anterior, lateral and visual areas. Secondly, neuromagnetic responses were greater in amplitude at the frequency of the flicker rate of the consciously perceived stimulus compared with the amplitude at the frequency of the non-perceived flickering stimulus. The fundamental insights in this study is that frequency tagging enables differentiation between stimulus related responses from

background activity using high temporal resolution, also in combination with whole MEG it allows investigating the distribution of stimulus related signals beyond sensory projections. Lastly and most importantly this technique can be generalized and applied to stimuli of any sensory modality as long as the frequencies selected induce stimulus related responses (Tononi et al, 1998).

Since then, there have been many studies to date that adapted the frequency tagging paradigm to study ssVEPs in visual domain (Klimesh, 2012; Herman et al, 2001; Regan and Heron, 1969; Fawcett et al, 2004; Norcia et al, 2002; Srinivasan et al, 2006). In addition this technique has been employed to study ssAEPs in the auditory domain (Buchwald et al, 1981; Cohen, 1982, Lee et al 1984). These previous studies employed frequency tagging to study the processing of visual and auditory stimuli. One assumption here is that the amplitude of the ssVEP or ssAEP is not modulated by the frequency of stimulation. This was investigated in the visual domain was by Hermann et al, 2001. In this study, ssVEPs were tested using a flickering light and repetitive stimulation at different frequencies from 1-100 Hz in 1 Hz steps (Herman et al, 2001). ssVEP amplitudes were modulated by the frequency of stimulation. Clear resonance phenomena were seen especially at 10,20,40,80 Hz that represent alpha, beta and gamma oscillations (Herman et al, 2001). This study demonstrated that the cortical response to sensory inputs was dependent upon the frequency of stimulation, suggesting that there are resonant frequencies in the visual cortex for the processing of visual sensory inputs. Here I showed that SSEPs driven by median nerve stimulation show a similar pattern of modulation with input frequency. I showed that the sensorimotor system is particularly sensitive to being driven at frequencies in the beta range. This is consistent with the only previous study using frequency tagging of SSEPs. In this study by Kourtis et al, 2008 used stimulation at 22.2 Hz to investigate the modulation of SSEPs during movement (Kourtis et al, 2008). This study demonstrated frequency tagging at this frequency but did not compare this frequency

to other simulating frequencies. Here I confirm the results of Kourtis et al. (2008) but critically I extend their findings to show that the sensorimotor system is particularly sensitive to being stimulated in the beta frequency range.

From the above it is clear that frequency tagging is a useful method for studying visual auditory and, as I have shown, somatosensory stimuli. However, frequency tagging also has limitations. One of the limitations is inter-subject variability where each individual shows preferential responses at different frequencies. Another limitation is that it has low noise robustness. If there is noise at a specific frequency range that coincides with stimulation frequency range, then entire signal could be covered by noise and it is very difficult to detect the stimulus that is focused on this frequency range. Lastly, oscillatory phenomena that coincide with a particular frequency range could disable detection of frequency tags in the stimuli (Norcia et al, 2015). For example, here I showed that although there was a clear peak in the response frequency to stimulation around 10 Hz this was not specific to the input frequency and power at ~10 Hz was observed irrespective of the input frequency.

Overall, from previous studies in the visual and auditory domains and from my findings in the somatosensory field it could be concluded that frequency tagging is evidently a good technique for SSEP research and it should be more readily used to describe SSEPs in both research and clinical settings.

6.2 CHAPTER 3: Is SSEP modulated during movement?

One of the original aims of this research was to use the frequency tagging technique for SSEPs, which I developed to study the modulation of response frequency as a function of the input frequency, to study SSEP modulation during a motor task. The aim

was to stimulate the median nerve at different frequencies during a simple motor task and track the modulation in power at this frequency during the task. However, this original aim was not possible due to a technical failure of the timing of the median nerve stimulations that meant that the median nerve was not stimulated precisely at the frequencies intended. However, it was still possible to investigate whether the amplitude of the SSEP was modulated as a function of the task and to test the hypothesis that SSEP attenuation in the time domain during rest, motor preparation and movement was correlated with modulations in the power of beta oscillations.

The results showed no evidence that SSEPs were attenuated in any of the phases of the motor task. Although it was clear that SSEPs were elicited by median nerve stimulation, there was no clear evidence that the amplitude of the primary component of the SSEP was modulated during the different phases of the motor task. This was unexpected given that previous studies have shown an attenuation of the SSEP amplitude prior to and during movement (Starr and Cohen, 1985; Abbruzzese et al. 1981; Voss et al, 2006; Boecker et al, 2013).

There are many potential reasons that here I did not demonstrate movement related SSEP attenuation. One potential reason is the component of the SSEP studied. Here I exclusively studied the primary component of the SSEP elicited by median nerve stimulation. However, it could be that early primary somatosensory components are less modulated during movement than the later secondary and tertiary components. This would be consistent with the results of Shimazu et al. (1999) where no SSEP attenuation was evident for the N20-P25 primary complex throughout all conditions (Shimazu et al, 1999). In addition previous studies have shown that the later components of the SSEP show greater attenuation than the primary component and have suggested that this is due to central signals arriving from motor cortices (Voss et al, 2006; Boecker et al, 2003). Therefore, although sensory attenuation could have

been observed in my experiment for the later components the design of the study was optimised for the primary component and was motivated by the previous studies that had shown attenuation of this component (Starr and Cohen, 1985). Indeed, it was not possible with my design to investigate the modulation of the later components as the rapid delivery of the median nerve stimulations meant that I could only study components in the first 50 ms after median nerve stimulation.

Another plausible reason is subject variability that could play an important role in decreasing the sensitivity of any effects at the group level. Subject variability is divided into intra-subject and inter-subject variability. Previous studies have highlighted a potential role for inter-subject variability. A good example was identified in studies investigating short-latency intracortical inhibition in primary and secondary dystonias. Controversy in experimental findings for patients with primary dystonia has been identified. Intra-cortical inhibition has been shown to be normal in some patients and significantly reduced reduced in others (Kojovic et al, 2013). In addition, there is evidence that subjects vary in their cortical responses to rapid sensory stimulation. In previous a study employed to study frequency tagging the authors demonstrated that each subject showed a differential response to the frequency of simulation (Norcia et al, 2015). Such inter-subject variance could be due to differences in cortical architecture as well as caused by behavioural and/or physical traits, age and sex. For example, in my studies there was a difference in how subjects reacted to and perceived the median nerve stimulus with some participants finding it slightly ‘unpleasant’ and inducing some anxiety. Therefore inter-subject variability in SSEP attenuation in my experiment would reduce the sensitivity to being able to detect this affect statistically.

Another reason why my results were not able to replicate the previous findings on sensory attenuation of the primary SSEP component during movement (Starr and Cohen, 1985; Abbruzzese et al. 1981; Voss et al, 2006; Boecker et al, 2013) could be

due to bimodal stimulation. In contrast to the previous studies, here I used a bimodal stimulation paradigm, where the SSEP was delivered at the same time as a modulation in the visual stimulus. In a previous study, ERPs elicited by tactile stimulation at the index finger were modulated by the presence of task relevant visual stimulus (Staines et al., 2014). The authors demonstrated that task relevant visual stimulation increased the response on the ERPs from the tactile stimulation and argued that this likely reflected a top-down attentional effect. In the task design I employed, the motor task was cued by a change in the visual stimulus and although this was not a cue for the median nerve stimulation it could have modulated the subjects attention to the somatosensory signal potentially leading to an increase in response amplitude which would have countered any possible attenuation of that signal.

The other major difference between previous experiments that have studied the modulation of the primary component of the SSEP during movement and the experimental design I employed here is the rate of median nerve stimulation. Previous studies have stimulated the median nerve at frequencies greater than 1 Hz whereas here the median nerve was simulated at ~10 Hz. The reason for the fast stimulation was to avoid the difficult time constraints of stimulating at the slower frequencies. When stimulating at slower frequencies previous studies could only deliver median nerve stimulation and a few time points of the motor task (e.g. before movement baseline, at movement onset, and during movement). Even then the experiments were typically performed on few individuals (often the authors) and took many hours to complete (e.g. 6 hours. Starr and Cohen, 1985). However, although it was possible to detect and measure the amplitude of the SSEP with rapid median nerve stimulation it is possible that the rapid presentation itself attenuated the amplitude of the SSEP. Such an attenuation of the SSEP amplitude, even in the rest condition, would have a large impact on the sensitivity to detect further attenuation that was related to the motor task.

Overall, based on the findings and the limitations discussed above it could be concluded that rapid delivery of median nerve stimulation to elicit SSEPs is not a very good approach to investigate the time-course of SSEP attenuation.

6.3 CHAPTER 3: BETA OSCILLATIONS AND SENSORIMOTOR SYSTEM. WHAT ARE THEY IMPORTANT FOR?

Despite the fact that the primary component of the SSEP showed no attenuation, beta oscillatory attenuation was also tested. Beta oscillations and its functions have been widely studied for over 50 years but their functional role is still controversial. Its controversy arises as to whether beta oscillations are a by-product of brain activity or whether they are central to brain functioning. Beta oscillations have been widely recorded from several brain areas including somatosensory, primary, parietal, visual and extrastriate cortices. Research has shown that they could maintain existing motor task and compromise new movements (Engel et al, 2010). To show that beta oscillations but also alpha and gamma power are not just a by-product of brain activity, studies to understand the ascending and descending pathways of cortical microcircuits have been carried out. To evaluate cortical microcircuits, intrinsic connectivity within a cortical column and extrinsic connectivity between different cortical columns need to be investigated (Bastos et al, 2012).

One of the first to study cortical microcircuits in relation to oscillatory phenomena in monkeys was Livingstone in 1996. Looking at the L2/L3 layers of V1, he showed that half of the cell population showed increased gamma power where gamma power

activity was less prone in cells of L4C and infragranular cells. Although alpha and beta power activity was not recorded, it could be concluded that superficial and deep layers are functionally distinctive and thus oscillations show functional distinctive roles in these layers (Livingstone, 1996). To this end, Roopun et al, 2006 also showed gamma oscillations to be prominent in L2/L3 of somatomotor cortex of the rat. In L5 layer of somatomotor cortex, gamma and beta oscillations co-exist. In addition, if L4 is disconnected from the circuit, beta and gamma oscillations disappear. Therefore, it is safe to say that oscillations arise from these layers when they are intact (Roopun et al, 2006). Another study that also showed this segregation of oscillatory power between supragranular , infragranular and granular layers was Maier et al. (2010). They showed that high gamma power was observed in supragranular layers whereas conversely high alpha and beta power was observed in infragranular and granular layers (Maier et al, 2010).

The studies described before, were highly influential for studies that aimed to connect these cortical microcircuits with the neuronal computations of predictive coding. Bastos et al. (2012) showed directed interactions between different visual areas and showed the same spectral asymmetry as identified previously. They showed evidence that top-down expectations and bottom up prediction errors give rise to frequency asymmetry. Deep layer activity that was influenced by top-down expectations showed predominance of alpha and beta oscillations whereas superficial layer activity that was influenced by bottom up prediction error showed predominance in theta and gamma oscillations (Bastos et al, 2012). It has also been shown by Bastos et al. (2015) that frequency asymmetry is correlated with the anatomy in primate visual cortex (Bastos et al, 2015). Top down beta oscillations have been observed to be linked with processing in lower levels of a hierarchy, which fits with predictive coding. Predictive coding states that top down signals are sent in slower rates than bottom up prediction errors that are

sent in faster rates. Therefore, this is consistent with the observation that as top down signals are based on lower frequencies (beta) whereas bottom up signals are based on higher frequencies of stimulation induced by gamma (Richter et al, 2015).

From all the results gathered, it could be concluded that beta oscillations, but also alpha and gamma oscillations, are not just epiphenomena but play an important role in brain processing. This could also be justified from my results from my second experiment. Beta oscillations are induced from proprioceptive input (median nerve on the wrist) through the periphery where beta power range frequencies seems to dominate time-frequency spectrum throughout rest, motor preparation and movement. Although beta oscillations are not epiphenomena, their functional role throughout the conditions is still not fully understood.

In addition to the studies above, frequency asymmetry, as well as different gamma and beta responses, have seen in the auditory cortex. Studies have shown that omission of sound is an isochronous activity where during its presentation gamma oscillations are enhanced and then suppressed. In comparison, beta is suppressed or desynchronized and then re-synchronized (known as beta rebound) (Arnal and Giraud, 2012). However, beta desynchronization and re-synchronization is not only evident during the presentation of a sound. It has been observed to be prominent in movement as well. Beta oscillations have been seen to decrease before and during motor execution and increase when movement has ceased. In addition, there are several studies showing that that beta power seems to be attenuated during not only movement but also during motor preparation (Kilner et al. 2000, Baker et al 1999, Baker et al. 1997, Pfurtscheller & Lopes Da Silva 1999, Hari & Salmelin 1997).

The notion that beta oscillations are not epiphenomena of brain activity is also supported by beta oscillatory function in the basal ganglia-cortical motor loop. As levels of beta oscillations are used to measure voluntary action, in turn dopamine levels inside the basal ganglia-cortical motor loop modulate beta oscillatory activity. In motor pathologies especially in patients with Parkinson's disease, decrease in dopamine within the loop changes beta oscillatory function as beta oscillations are exaggerated and beta power attenuation is not prevalent anymore. In turn, it is believed that this functional change may cause the characteristic parkisonian symptoms including bradykinesia and rigidity (Jenkinson et al, 2011; Brown, 2007). This beta oscillatory increase is reversed when levodopa is administered to boost dopamine levels. This effect is also prominent when deep brain stimulation (DBS) is applied by electrically stimulating motor areas of PD patients. In addition to the restoration of beta oscillations, both agents seemed to ameliorate PD symptoms (Moran et al, 2011; Eusebio et al, 2012). Whether beta oscillations cause the motor symptoms linked to PD is still controversial. However, it could be concluded that as beta oscillations are central to normal brain functioning, they are also centrally impaired in motor pathologies.

In my second experiment I tested the hypothesis that there would be a tight correlation between the time course of sensory attenuation and beta power in the sensorimotor system. This hypothesis was generated from a similarity in the known modulation of beta power during movement and in PD pathology and a parameter of the active inference framework that has been proposed to drive sensory attenuation, namely the precision of the estimate of the somatosensory input (Friston 2015, Palmer et al. 2017).

Accoring to Friston (2015) predictive coding theory states that prediction errors, which in this case would be the difference of the sensory input and the predictions of that sensory input, are minimized to update expectations in the higher hierarchical layers. Critically the prediction error is weighted by the precision (Friston 2015). To this end, Palmer et al. 2017, predicted that predictive coding and sensory precision could be

tightly linked to beta oscillations and beta power desynchronization/resynchronization. The logic of this hypothesis stems from the observation that according to active inference, precision is reduced in order to allow movement and is increased when inhibiting and action. Previous studies have shown that beta power is attenuated prior to and during movement and increased when inhibiting an action. Therefore, Palmer et al. (2017) proposed the beta oscillations could be either a neurophysiological biomarker of precision or possible related to the mechanism by which precision is implemented in the brain.

However, the hypothesis that there is a tight link between beta oscillations and SSEP attenuation (a consequence of attenuated precision) was not supported by the results of my second experiment as there was no significant correlation between the time course of the SSEP and beta power modulations. This is perhaps unsurprising given that the SSEP amplitude was not modulated as a function of the motor task as predicted (see above). However, in addition the modulation of the beta power was also not a predicted. It was expected that beta power desychronization and re-sychronization would be evident, with beta power attenuation prior to and during movement. However, beta power was significantly increased after the change in the visual stimulus for both the change from rest to motor preparation and from motor preparation to motor execution. This is at odds with the previous literature on the modulation of beta power during motor tasks but is similar to previous studies that have observed modulations of beta power during visual tasks. Studies have demonstrated that beta power enhancement is prominent in humans during perception of visual patterned stimuli and during visual attentional tasks. For example, when visual patterned stimuli are presented after a delay period beta activity has been shown the increase (Tallon-Baundry and Bertrand, 1999). Similar findings were found in studies where visual attention of participants was modulated. Attending to visual stimuli

throughout a behavioral task was shown to be related to increased beta activity. When participant's visual attention decreases, no change in beta activity was observed (Gola et al, 2013). Visual stimulus expectation has also been shown to lead to beta power enhancement (Basille et al, 2007). Therefore, in my study described in Chapter 4 experiment, the unexpected observed beta enhancement after the visual cues could have been related to the change in the visual stimuli presented on the screen and to visual attention to the colour change as opposed to the predicted modulations in the sensorimotor system related to movements.

6.4 FUTURE DIRECTIONS

In this section I will discuss possible future directions that I could take to better understand my research questions both in terms of experimental design as well as different analysis tools or methods one could use.

6.4.1 Visual or Auditory cued movements?

Overall, there are quite a few limitations in experimental design and analysis that could have compromised my results. As a future directions to study SSEP attenuation and beta oscillatory attenuation, I would suggest a different experimental design to the one used here and described in Chapter 4. In this experiment subjects were cued to the different phases of a motor task by the presentation of large coloured circles on a screen in front of them and subjects were instructed to respond with their thumb. Previous studies that have found SSEP attenuation at movement onset have cued the movement using an auditory tone (e.g Starr and Cohen, 1985). Median nerve stimulation was also presented at different points in time. The results of this study

showed SSEP attenuation of primary components before and after thumb abduction. However, this study has a great statistical limitation as only 3 healthy subjects were tested, thus power and sample size were low. Another great limitation this study had wass that it required 6 hours to finish recording of each subject so it was highly time consuming. Simple thumb movement was also recorded in the study of Abbruzzese et al, 1981 during passive and active movement. SSEPs were recorded by applying stimulation on the median nerve. A marked reduction of primary components of SSEPs including N20, P25 was observed in both passive and active movements (Abbruzzese et al, 1981). Similarly, presentation of two auditory tones followed by a delayed auditory tone, TMS and cutaneous stimulation of the right finger showed SSEP attenuation that was still evident when right finger extension occurred (Voss et al, 2006). However, that was not evident in all the studies that used simpler tasks to study movement. A good example was the study by Shimazu et al, 1999 where participants carried out a simple movement after presentation of an auditory tone and median nerve stimulation. Attenuation of short latency SSEP components was not evident. Similar findings were seen in the study by Boecker et al, 1993 where three simple tasks were carried out including motor preparation, movement and rest after movement execution (Boecker et al, 1993). To date, there are not many studies that use complex tasks to evaluate SSEP attenuation and use visual instead of auditory stimulation. In my study I used visual stimuli to cue the movement and did not find evidence for SSEP attenuation. In addition, though I also used a rapid stimulation of the median nerve to elicit the SSEPs. Therefore, it is unclear whether my null results are driven by a change in the cue, visual

compared to auditory, or a change in the median nerve stimulation, rapid compared to slow, or both. One piece of evidence suggesting the cue type might have had a larger effect than I anticipated is that the modulation of the beta oscillations are also not as predicted and seem to be dominated by a modulation that is more consistent with the anticipation and presentation of the visual cues and not the movements. One study that used a complex task to study movement in monkeys was by Seki and Fetz, 2012. This study relied on task training and computer presentation of targets either on the right or left for extension or flexion respectively as well as go signal presentation to move the cursor on the target followed by an active hold period and a second motor execution. Then the wrist was passively returned to rest. The results showed SSEP attenuation throughout all tasks (Seki and Fetz, 2012). Visual representations of targets on a computer screen was evident, however the paradigm used was slightly different to human experiments as monkeys need to be trained to do extension-flexion torques whereas in my experiment, training was not necessary. Also, another difference between this study and my experiment that makes them dissimilar is that temporary synchrony was not affected as targets did not change colours. Studies in humans that use visual and electrical/cutaneous/tactile stimulation investigate usually somatosensory processing and event related potentials that show increased response. To conclude, based on the results collected from studies using simple and complex tasks, I believe a way to study movement is through a simple task and through auditory stimulation. However, complex movement tasks are closer to the movements we do

every day. At this end, it would be good to see how complex movements could be utilized experimentally in an effective way by minimizing other factors

6.4.2 EEG OR MEG OR BOTH?

Could MEG potentially be better to use than EEG? The first successful attempt to record neural magnetic fields was carried out by David Cohen in 1968. The Superconducting Quantum Interference Device (SQUID) detector enabled construction of better recorders. They worked by converting magnetic field into electrical current that passed through the pickup coils and through the input coils of SQUID. The most important part of an MEG system, is its sensitivity that depends on the design of the pickup coils. There are different types of coil system including magnetometer based systems that optimize signal strength and gradiometer based systems that optimize signal to noise ratio (Hamalainen et al, 1993). Gradiometer based MEG systems are not as sensitive as EEG to physiological noise (muscle activity) and they are not affected by volume currents. However, MEG has lowered sensitivity to the activity in deep brain structures. To improve further signal-to-noise ratio in MEG systems, a collection of magnetometers and gradiometers are used as reference channels and are placed away from the head. Another important difference between EEG and MEG is that MEG detects one component of magnetic field and thus unipolar absolute values are measured. In turn, EEG measures the relative values of electrical potential by taking the difference between electrical potentials against reference/references electrodes (Hashimoto et al, 2003; Ioannides et al, 2004a; Ioannides and Fenwick, 2005). Another profound limitation of EEG is that electrical potentials are affected highly by inhomogeneities in tissue conductivities. This has as a result a wider field map produced in the EEG system and thus source localization is better with MEG. However, EEG has better estimates for orientation in relation to MEG. Therefore, in

conclusion MEG measurements are simpler to analyse and interpret than EEG (Lopes da Silva and Van Rotterdam, 1999). Overall, it is difficult to say definitely if MEG is better than EEG because they are used for different purposes but they are not as independent between each other as it is thought to be. However, the fact that EEG is not free of physiological artefacts poses a great limitation and it is less likely to be readily used. Combination of MEG and EEG should yield most accurate localization as their sensitivities are complemented and yield much better results than using either of these systems. Therefore, combination of MEG and EEG data is important as both temporal and spatial resolution is highly improved. Complementing the properties of both systems allowed to determine early evoked potentials produced by median nerve stimulation and allowed to show the tangential source in somatosensory cortex rather than radial pairs of somatosensory and motor cortices (Sharon et al, 2007). Therefore, the best way to measure and evaluate evoked potentials and in this case SSEPs is through combining those two systems.

6.4.3 COULD THE RESULTS HAVE BEEN DIFFERENT IF REST AS A BASELINE WAS USED INSTEAD WHOLE TIME SERIES?

Moreover, I would suggest that a different experimental analysis could be used. Rather comparing a baseline period taken from a period of time within the motor task, I could have employed a rest condition where subjects did not perform a motor task and used this as my baseline. A characteristic study that used this principle to identify if alpha/beta/gamma desynchronization through spectral power analysis is still prominent in patients' populations including PD, primary dystonia and essential tremors was carried out by Crowell et al, 2012. In this study, patients underwent deep brain stimulation and subdural electrodes were placed into subthalamic nucleus or

ventrolateral thalamus for those having essential tremors. Local field potentials (LFP) were recorded from sensorimotor cortex at rest, at extension-flexion of five different body parts and during relaxation known as the ‘stop phase’. Baseline period was defined during each rest epoch. Peri-movement spectral power was compared to baseline period whereas movement-related differences between frequencies was separately statistically tested at each disease state and on each frequency. The results showed increased gamma power band at primary motor cortex in PD compared with other conditions. High beta power in PD was observed at the stop phase task probably driven by akinesia. Alpha-beta band were observed at higher frequencies in PD and patients with primary dystonia had characteristic impaired beta band desynchronization in movement at primary motor and sensory cortices (Crowell et al, 2012).

Another good example that used the principle of taking rest condition as a baseline to study SSEP gating in controls and patients with writer’s cramp was by Murase et al, 2000. Particularly, two sets of experiments were carried out for controls and patients to test premovement and midmovement gating. In premovement gating, subjects remained at rest throughout. Median nerve stimulation was applied when a warning sound was given and SSEPs were recorded. In midmovement condition, median nerve stimulation was applied and SSEPs were recorded during rest, passive and active movement. Median nerve was applied for 0.2 ms duration at a rate of 20% above the motor threshold. Premovement and midmovement data were analysed separately. Three-way repeated measures ANOVA were carried out for each group, task and SSEP component. Then a two-way ANOVA was carried out for each SSEP component where group and task were analysed further. Another two-way ANOVA was carried out to analyse SSEP amplitude at rest taking group and SSEP component. In relation to previous findings, the results did not show impairment of SSEP components in midmovement gating neither for controls or patients. On the other hand, impairment of N30 SSEP gating was identified for controls and impairment of P22 gating for patients

in premovement gating. At this end, taking rest as a baseline gives us evidence that SSEP gating in healthy subjects is possible and impairment in disease is evident. The fact that during active and passive movement, SSEP attenuation was evident and not abnormal could be as peripheral and efferent gating mechanisms were not impaired. Therefore, if severely affected patients that cannot move properly were tested, then impairment of SSEP components could have been seen. Overall, this principle shows satisfactory results when attenuation of beta or of SSEPs are tested. Potentially it could have been used to test SSEP attenuation. However, it was not followed as the aim was to characterize SSEPs throughout all conditions in a continuously manner (Murase et al, 2000).

6.4.4 Modelling data or testing predictions?

The work in this thesis tested different hypotheses relating to active inference and Bayesian models of normal brain function. For example, I hypothesised that SSEP attenuation would ne correlated with modulations in beta power. However, although all these hypotheses were based on the active inference model I did not explicitly use a build a model to fit to my data. From the active inference framework it could be derived that brain operates through Bayesian statistics allow the belief in the hypothesis to be shifted as upcoming evidence is collected. The new evidence could change the certainty of a belief as new evidence is realised. The most common concept that is discussed in addition to active inference, is the uncertainty. Bayesian models of brain function aim to calculate and estimate the uncertainty. Most of our senses are noisy and only perceive some parts of the world at any given time. One problem in studying the estimates of uncertainty in such models is that there is rarely a one-to-one mapping of the certainty to either a particular behaviour, e.g. faster reaction times, or a specific neurophysiological measure, e.g. an ERP component. For example in the experiment

using the SSRT in Chapter 5 I used vibration as an intervention that I argue should change somatosensory uncertainty, however, I have no explicit evidence that this parameter was modulated as predicted. One approach to access these hidden parameters is either to simulate models and see how any given parameter changes the output or to explicitly fit some data with a model with these parameters are free variables. This could be done by using Bayesian modelling. Bayesian models estimate relevant variables of the world that are based on observations that our senses make. Bayesian models have been used to explain many brain phenomena including perception, action, neural coding etc. Although Bayesian models have different forms, all of them share the same principle that all parts of information need to be combined to estimate the variables (Vilares and Kording, 2011). A very good example that shows pre-shaping and evolution of motor cortical neurons based on prior beliefs during motor preparation was the study by Bastian et al, 2003. They trained monkeys in a multi-directional pointing task where preparatory signal provided information of all possible targets. Then a response signal after 1s delay were presented and movement was performed. Distributions of populations activation was constructed. It was identified that the distributions were pre-shaped by prior information and showed continuous evolution during preparatory phase. Therefore, this study follows the concept of Bayesian statistics and Bayes rule which shows graphically using probability distributions that previous information shapes movement directionality and evolution occurs so that the movement is performed accurately (Bastian et al, 2003). Another study that tried to map uncertainty and confidence using Bayesian models was by Tan et al, 2016. The aim of this study was to test post-movement beta synchronization (PMBS), how and if PMBS indexed confidence using feedforward estimations of sensory feedback. Higher amplitudes showed high confidence and thus more accurate motor output. On the other hand, low PMBS showed lower confidence that required adaptive changes driven by sensory feedback and changes of behaviour to understand alterations in sensorimotor relationships. It was also identified that PMBS was

negatively correlated with uncertainty in feedforward estimations. Therefore, high confidence shows low uncertainty and low confidence high uncertainty. Uncertainty due to biased prior knowledge has been also investigated in decision making and action selection (Tan et al, 2016). A study by Hsu et al, 2005 has shown that the level of uncertainty in decision making during action selection positively correlates with amygdala and orbitofrontal cortex activation (Hsu et al, 2005). Furthermore, electrophysiological experiments have relieved that neuronal firing of single neurons of orbitofrontal cortex in mice index confidence in decisions (Keepecs et al, 2008). Although the studies outlined here show promising results between mathematical modelling and experimental data, few studies to date have tested Bayesian theories and Bayesian statistics in neurophysiological data of movement. This poses a great challenge for neuroscientists and it is difficult to determine how motor or sensory neurons code information about sensory uncertainty (Knill et al, 2014).

6.4.5 CAN MARKOV CHAIN MONTE CARLO APPROACH NEUROPHYSIOLOGICAL DATA?

In addition to Bayesian framework that could have been used to identify the neurophysiological mechanism behind the recorded electrode potentials, as dicussed above, another neural fitting model that could have been used is Markov Chain Monte Carlo (MCMC) approach. The recorded electrode potential, it is a summation of extracellular current flow of sources and of oriented large scale neuronal population that its parameters could be estimated by the MCMC approach. Use of Bayesian estimation helps evaluating the posterior distribution. However, as drawing samples from a posterior distribution is not easy, a proposal distribution is designed. Therefore, this approach provides high dimensional values calculating by using Markov principle (Hettiarachchi et al, 2012). Andrey Markov was a Russian mathematician that he is best known about his stochastic model known as Markov chain. Markov chain is

defined as a series of random variables that are conditionally independent and they are represented as a graph in a form of a chain. Markov chain is specified by giving the probability distribution of the initial variable and the conditional distribution of subsequent variables in the form of transition probabilities. At this basis, MCMC approach allows sampling of proposal distribution and dimensionality of the sample space. In this case, current state is maintained, and the proposal distribution depends on the current state where series of samples form a Markov chain. There are many algorithms that can be used with MCMC, the one mostly used, is the Metropolis-Hasting algorithm (MH) that states that proposal distribution is symmetric. Multiple copies of samples are included but some of them are accepted and others rejected (Bishop, 2006).

Going back to understand the electrical potential of EEG, in the study by Hettiarachchi et al, 2012 they used MH algorithm but also jointly particle filter (PF) to estimate the state of EEG model by breaking down hidden states and static parameters. EEG signal consists of two parts, the stimulus evoked response and background activity. They were linearly separated so that simulation of only EEG stimulus evoked response was carried out. The results were satisfactory and showed a great potential of using MH MCMC algorithm and PF to simulate and understand EEG signal evoked response. However, using only stimulus evoked response of EEG does not allow to compare the performance of the algorithm to experimental data as no ground truth values are present. Also, simulation was carried out on a single cortical region, so the results are not sufficient to evaluate simulation of a complex activity (Hettiarachchi et al, 2012). To date, only few studies have tried to use models such as MCMC to explain neurophysiological data from EEG. Some studies used other neural mass models (NMM) to explain alpha rhythmic activity, also other frequency band oscillations, olfaction, the coupling of MEG/EEG, connectivity of EEG rhythms and event related

potentials (Lopes Da Silva et al, 1974; Freeman, 1987; David and Friston, 2003; Wendling et al, 2002; Zavaglia et al, 2008; David et al, 2005). However, there is not much evidence and cross-correlation between neural computational models and experimental data and thus more research is needed to associate mathematical models with various experimental data.

6.4.6 WHAT ABOUT INDEPENDENT COMPONENT ANALYSIS?

In the SSEP analysis presented in this paper any effects observed were small and could be particularly susceptible to different artefacts. Although here I removed contaminated trails using a threshold approach there are other approaches that could have improved the data quality. One way to remove artefacts but also to decompose a multi-channel time series into linearly separated spatial modes is through Independent Component Analysis (ICA). When separated spatial modes are added together then original observations are retrieved. The separated spatial modes dynamics make them independent and uncorrelated. ICA has been attracted particularly in the analysis of MEG or EEG time series (Friston et al, 1998). To deeper understand the role of ICA, let's consider that two people are talking at the same time and we record them through two microphones, the signals will be given by linear combination of the amplitude of the two voices. The coefficient remains the same, so we could infer its value from the data and by inverting the mixing process. Then two clean signals can be obtained where each one contains the voice of each person. This is known as blind separation as only mixed data are known and not the original data or the mixing coefficients (Cardoso, 1998). In this case, a generative model is considered where two variables are the unobserved speech signal amplitudes that follow a joint distribution and the other two are the signals observed through the microphones and are given by linear combination. There is no need to add a noise distribution as number of latent variables is the same as observed variables. Therefore, marginal distribution of the observed variables is not

singular and observed variables are purely deterministic, linear combinations of latent variables. The success of ICA lies in the fact that these latent variables need to be non-Gaussian (Bishop, 2006). That is the most beautiful motivation behind ICA as non-Gaussian or sparse distributions are more interesting than Gaussian. Biological systems receive contributions for many sources and usually observations are roughly linear mixture of interesting things (Friston, 1998).

ICA can also be used to remove artefacts from EEG. Artefacts can be noise due to muscle activity recorded by EMG, due to heart activity that can be recorded with ECG and noise derived from eye movements that are obtained through EOG. In the study of Turnip et al, 2014, EEG signals were recorded under normal conditions, when subjects closed their eyes or blinked, and the aim was to remove artefacts due to eye movements. For all these conditions, the dominant frequency of EEG is in the alpha-beta range. The way to perform ICA to remove artefacts it is the same as discussed before through blind separation. The figures in Turnip et al. (2014) the results clearly showed the presence of artefact during eye movements. Bandpass filtering and processing of raw data was also included. In the result section, brain maps to show the signal separation using ICA method were constructed. It could be identified that separation of mixed signals on each channel occurred and it can be seen from the active brain regions that are separated. Overall, in this study it was demonstrated the success of using ICA and when ICA is used, signal amplitudes are smaller and represent closer resemblance to the original signal (Turnip et al, 2014). However, there are some limitations of using ICA for artefact removal. One limitation is that if there are not enough number of electrodes, it becomes an overcomplete problem. Another limitation is that distributions of biosignals are usually closer to Gaussian than to non-Gaussian where ICA success relies on non-Gaussian distributions. It has been also identified that ICA can separate only artefact component when artefact is predominant. For ICA to estimate independent sources, the sources need to be

independent, the number of mixtures need to be at least the same as the number of independent components. The mixtures need to be linear and there should not be, or it should be very little delay during recordings. However, if the limitations outlined above are all avoided, and the statements made are true, then it could be concluded that ICA is very successful method for artefact removal (Djuwari et al, 2005).

6.5 ACTIVE INFERENCE. IS IT A FRAMEWORK WE NEED TO REVISIT?

The concept of the “Predictive brain” is currently much researched and discussed topic in neuroscience. A novel view about the brain and prediction is that prediction is characterized as an ‘’intrinsic built-in principle’’ identified throughout cortical and sub-cortical processing (Clark, 2013). This novel view traces its roots to Helmhotzian theory. Helmhotz proposed *the unconscious inference theory* where perception is based on unconscious processes that interpret stimulus presentation based on prior experiences. He believed that sensory report was made before one’s subjective experience. He was one of the first to propose that brain uses an internal probablistic generative model to describe the causes of sensory inputs and how these sensory stimuli are perceived (Helmholtz, 1860-1962). Since then, there has been extensive research carried out to theoretically explain predictive signals, for example motor control theory (Wolpert, 2007) and active inference or predictive coding (Friston, 2005a). Predictive coding and active inference allows the brain to alleviate surprise by minimising prediction errors, and therefore to make estimates about one’s body states and also the external states. To explain this in more detail, in predictive coding it is proposed that the prediction travels top-down to probabilistically weight excitation in downstream areas. In turn, downstream areas sends prediction errors to higher cortical areas to update the prediction of the sensory causes. Therefore, this is not a one-off propagation of signal but rather an exchange of signals between cortical layer representation neurons and error neurons to keep the nervous system prepared and

updated about internal and external representations (Schubotz, 2015). This signal exchange occurs constantly until prediction error is minimized and precision of sensory causes is maximized (Friston 2002).

Although in my thesis I have focussed on models of predictive coding and active inference in relation to movements, many researchers have employed these models to study perceptual prediction. Perceptual prediction is frequently applied to understand the present states of the human body and the external environment. A good example that satisfies this notion is object perception. In this case, object information that travels up the ventral stream is influenced by two distinctive top- down prediction signals. The first prediction signal arrives from the visual areas to oribitofrontal cortex to provide an initial prediction about the stimulus and a second prediction signal that arrives to parahippocampal areas to provide object recognition (Bar, 2003; Bar, 2004). Other examples which are in line with an initial prediction and cannot strictly rely on bottom-up information are repetition suppression (Summerfield et al, 2008), expectation suppression (Todoriv and de Lange, 2012) and MMN effect (Friston, 2005a, 2005b, Garrido et al, 2009).

One limitation of predictive coding (and related theories) is that they cannot easily dissociate mechanisms of attention from those of perceptual prediction. Both promote perceptual recognition and detection but in different ways. In attention, processing is prioritized based on stimuli that motivates somebody's attention, in this way attended stimuli will increase perceptual responses. For example, it has been demonstrated that frequently occurring targets elicit large ERPs, whereas infrequent distractors do not (Bowman, Filetti, Wyble, & Olivers, 2013). On the other hand, in perceptual prediction if a stimuli can be predicted then the response to that stimuli will be decreased as seen in

MMN effect (Garrido et al, 2009). The key to this finding is that is really difficult to dissociate attention from mechanisms of predictive coding. In relation to my work it is likely that with repetitive median nerve stimulation both of these factors could have played a role in SSEP amplitude modulation. Possibly, attention as mentioned before for the ERPs, could have induced a micro scale SSEP amplitude enhancement every time median nerve stimulation was presented. If it is true, then it goes against predictive coding theory where prediction error is used to decrease surprise and enhance prediction signals (Friston 2002, 2003, 2005; Wolpert & Ghahramani 2000).

Although it is hard to dissociate attention from predictive perception Friston has proposed a theoretical mechanism that can explain both the influence of attention and perecpetual prediction. This is precision weighting. Precision weighting considers attention as a means to weight prediction errors to increase their influence. In this way, the precision weighting allows the system to modulate prediction errors at different levels of the hierarchy (Feldman and Friston, 2010). Although there is some evidence that attention is considered to promote prediction errors in attended stimuli, more studies need to be carried out to evaluate whether precision weighting of attention occurs (Schubotz, 2015).

There is a large and growing body of research that has used predictive models to explain motor behaviour and motor learning (Wolpert et al, 1998; Wolpert et al, 2001). However, these studies focus on simple motor tasks where it is easier to relate the data to simple theoretical models. For example, in my work I have focussed on sensory attenuation. Here sensory attenuation can be reduced to two nodes, one sensory node and one predictive node, where the predictive node predicts the activity in the sensory node. This approach can be considered as modelling local networks and their

parameters. However, such an approach is at best a simplification of the neuronal networks involved in even the simplest of tasks. In reality, the brain is a vast nested network of interconnected areas with parallel as well as local processing. This is reflected in the fact that our behaviours and actions are complex, multimodal and multidimensional events and are more than simply motor control. Although predictive models of motor control have been successful, they have employed simple tasks in a controlled environment and context. This is far from the reality of our everyday actions and behaviours (Rohlfing et al, 2003). In this way action predictions need more than dynamic forward models, and at the very least the models need to include parameters of all different memories including semantic, episodic, normative and social that are known to modulate actions (Hrkac et al, 2013; Schubotz et al, 2012). Therefore, it could be concluded that predictive coding and active inference is far from complete as different memory sources need to be applied on those models to predict complex actions.

In addition to difficulties with the scale of predictive models the mode of estimation could be either probabilistic or dynamic. Probabilistic estimation of future states is typically employed in reinforcement learning (Garrison et al, 2013; Glimscher 2011, Schultz, 2013) and reward experiments (Lucantonio et al, 2012; Schoenbaum et al, 2009). Probabilistic estimation is stochastic and is based on certain probabilities that do not change. In contrast, dynamic prediction is based on constant observable changes in the system and is a more plausible model of neuronal networks. Active inference makes dynamic predictions (Schubotz, 2015). However, we are far away from high performance predictions as predictions should be estimated not only on statistical knowledge but also in correlation with semantic and episodic memories (O'Reilly et al, 2013).

In relation to the problem of scale, discussed above, the majority of theoretical and practical research into the utility of predictive models in the sensorimotor system, whether these are forward models (Wolpert et al, 1995) or active inference (Friston et al, 2009), have focussed on uni-sensory outcomes of actions. In reality our actions result in multi-sensory inputs. For example, when I knock on a door, I hear the sound of the knocking, I feel the proprioceptive input of my arm moving, I feel the tactile sensation of the knock as my knuckles hit the door and I see my hand doing the movement. Therefore, to predict all these actions I will need multiple simultaneously predictions at different time scales rather than prediction of unisensory outcomes. Investigating multisensory action outcomes will give better predictions about actions in a more natural environmental context (van Kemenade et al, 2016).

A very important insight from these findings is that the models required to explain brain and action are more complex than what it has been predicted from predictive coding and active inference and as discussed before, predictions needs to be based in multi-sensory rather than unisensory consequences and thus in multi-sensory outcomes (Kemenade et al, 2016). There are more determinants and causes other than the ones tested. For example, attention, learning and memories are some of those determinants. The most important one that is highly discussed in this chapter, is attention. Unfortunately, attention has to be experimentally and theoretical predicted so that it does not limit experimental findings. For decades, several studies have focused in several forms of attention, visual attention, lexical attention, auditory attention and so on. A big break-through have seen of how all these forms of attention could affect perception, task performance, motor control and even motor functions. However, there is not a clear solution of how to alleviate completely attentional limitations experimentally and theoretically. Therefore, more studies need to be carried out to alleviate this limitation.

Lastly, the most interesting challenge that active inference framework faces is the dark room dilemma. Based on predictive coding, if brain tries to minimize prediction errors, then to make things easier we would have to stay in a dark room and remain in this stable state that is perfectly predictable. However, we don't choose to do that but we rather like exploring existing and new environments. A solution to this problem, has been set by Little et al, 2013 that theoretical information needs to be enriched by mutual information where sharing of internal models and sensations occurs (Mumford, 1992; Little et al, 2013; Clark, 2013).

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