The functional neuroanatomy of auditory sensory gating and its behavioural implications

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Doctor of Philosophy

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Auditory sensory gating (ASG) is the ability in individuals to suppress incoming irrelevant sensory input, indexed by evoked response to paired auditory stimuli. ASG is impaired in psychopathology such as schizophrenia, in which it has been proposed as putative endophenotype. This study aims to characterise electrophysiological properties of the phenomenon using MEG in time and frequency domains as well as to localise putative networks involved in the process at both sensor and source level. We also investigated the relationship between ASG measures and personality profiles in healthy participants in the light of its candidate endophenotype role in psychiatric disorders. Auditory evoked magnetic fields were recorded in twenty seven healthy participants by P50 'paired-click' paradigm presented in pairs (conditioning stimulus S1- testing stimulus S2) at 80dB, separated by 250msec with inter trial interval of 7-10 seconds. Gating ratio in healthy adults ranged from 0.5 to 0.8 suggesting dimensional nature of P50 ASG. The brain regions active during this process were bilateral superior temporal gyrus (STG) and bilateral inferior frontal gyrus (IFG); activation was significantly stronger in IFG during S2 as compared to S1 (at $p<0.05$). Measures of effective connectivity between these regions using DCM modelling revealed the role of frontal cortex in modulating ASG as suggested by intracranial studies, indicating major role of inhibitory interneuron connections. Findings from this study identified a unique event-related oscillatory pattern for P50 ASG with alpha (STG)-beta (IFG) desynchronization and increase in cortical oscillatory gamma power (IFG) during S2 condition as compared to S1. These findings show that the main generator for P50 response is within temporal lobe and that inhibitory interneurons and gamma oscillations in the frontal cortex contributes substantially towards sensory gating. Our findings also show that ASG is a predictor of personality profiles (introvert vs extrovert dimension).

Keywords: P50 ERP, sensory gating, Magnetoencephalography, connectivity, neural oscillations

Dedication:

“I dedicate my thesis to the loving memories of my dad S. Kulbir Singh Virk, without his love, support and blessings I wouldn’t have reached this far..”

Acknowledgments

With the blessing of Almighty, I have accomplished this piece of work. I would like to express my special appreciation and thanks to my supervisor Professor Stefano Seri, for his tremendous support and guidance throughout the course of my studies. I am very fortunate to have had the opportunity to witness his way of work and leadership.

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Contents

List of abbreviations

AEP- Auditory Evoked Potential

AER- Auditory Evoked Response

ASEBA- Achenbach Empirically Based Assessment

ASG- Auditory Sensory Gating

ASP- Adolescent/Adult Sensory Profile

CAEP- Cortical Auditory Evoked Potential

DCM- Dynamic Casual Modelling

EEG- Electroencephalography

EP – Evoked Potential

ERP- Evoked Response Potential

GFP- Global Field Power

IFG- Inferior Frontal Gyrus

ISI- Inter Stimulus Interval

MEG – Magnetoencephalography

MRI- Magnetic Resonance Imaging

SIAS – Social Interaction Anxiety Scale

SNR- Signal-noise-ratio

SPM- Statistical Parametric Mapping

SQUID - superconducting quantum interferences devices

STG- Superior Temporal Gyrus

tSSS- Temporal Signal Space Separation

VEP- Visual Evoked Potential

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Chapter 1: Introduction

1.1 Event Related Brain Potentials (ERP)

Event-related potentials (ERPs) are a series of very small voltage changes in brain electrical activity generated in the brain structures in response to specific events or stimuli (Blackwood & Muir, 1990). These phenomena are thought to reflect the summed activity of postsynaptic potentials produced when a large number of similarly oriented cortical pyramidal neurons (in the order of thousands or millions) fire in synchrony while processing information (Peterson et al., 1995). Physiologically ERPs can be defined as the post-synaptic neuronal activity occurring synchronously in active group of neurons. The ERP waveforms can be recorded when an individual is exposed to a range of sensory and cognitive stimuli or performs motor tasks and reflect the response of brain structures to experimental manipulations (Bartholow & Amodio, 2009). ERPs have traditionally been recorded using Electroencephalography (EEG), where EEG signal consists of a superposition of phasic signals on background noise, and signal is time locked to the event. Relative to background brain activity, evoked potentials are of lower amplitude, making the identification of single trial EPs technically challenging. To overcome this problem of low signal to noise ratio, a series of identical stimuli are presented to the participant and consecutive responses are averaged; this procedure progressively reduces random background activity and increases signal- to- noise ratio (de Bruin et al., 2003). This averaging technique is applied based on the assumption that ERP waveform is phase-locked, maintaining the same polarity each time the event is repeated. Recently, generative models of EPs have been proposed, amongst these the two competing models, the additive model and phase-reset model are discussed below.

According to the classical evoked model, ERPs reflect transitory time and phase-locked responses to a stimulus or event (Luck, 2005). This model is based on the additive voltage theory, which suggests that cortical neurons become excited post stimulus presentation. As a result, cortical cells respond to external stimulation by increasing or decreasing their firing rates producing as output the evoked potential (Brosch and Schreiner, 1997, 2000). Based on Lopes de Siva's and Katznelson's work, it has been suggested that EP characteristics and variability can be explained by to the non-linearity of the neural networks processing the sensory input and that these networks receive both sensory and non-sensory related input simultaneously (Jansen et al., 1993). This hypothesis was further confirmed in a visual evoked potential (VEP) study by Jansen et al., (1995), who suggested that VEPs occurred as result of gradual activation of excitatory intra-cortical connections rather than due to direct thalamic input. These findings were consistent with those of previous studies conducted on cats (Douglas et al., 1989) and humans (Jansen et al., 1993). However, Sayers, Beagley & Henshall (see Burgess, 2012 for review) challenged the evoked model as it fails to provide a reasonable explanation on the characteristic shape of ERPs and argued that if ERPs are generated by evoked signals superimposed on the continuous EEG, then the power during post stimulus period should be higher than in pre stimulus time window. After testing this hypothesis, it was suggested that there was no increase in post stimulus period as predicted based on additive model and this led to the proposal that ERP responses emerge from phase reorganisation of the ongoing activity (Sayers et al., 1998).

The phase reset model suggests that on-going brain activity (oscillations) undergoes a phase reset and that this in turn generates the evoked response to a given stimulus (Sayers et al., 1974; Basar 1999; Penny et al., 2002; Jansen et al., 2003; David et al., 2005). Due to the random distribution of phase in the on-going EEG activity, the summations of its signal will tend to zero, as positive and negative peaks will cancel out. In the phase alignment model, external stimulus are thought to cause oscillations and shifts in phase in a way that positive and negative peaks will tend to align. Under these conditions, these peaks will be summed up to form ERP response. Studies supporting this model have found a link between magnitude of ERP components and the power in EEG pre stimulus window (Burgess, 2012). However, Makinen et al., (2005) conducted a study to understand the relationship between auditory ERPs and continuous brain activity using MEG; and concluded that ERP generation is independent of ongoing brain activity. This supposition can be supported after considering limitations of phase reset model, which suggests that

instead of a localised source, peaks and troughs of ERP response occur due to phase alignment of neural oscillations occurring across large area of the cortex, and are mere artefacts of this phase-reorganisation. On the contrary, the evoked model proposes that it is the increase in the activity of a localised area that generates ERP response; this is supported by ERP source localisation findings in literature. It is possible that both the evoked and phase reset models contribute to EP generation, and these are solely different aspects of a single process (Burgess, 2012). Presently, there is no unique model which explains the ERP generation although several studies have consistently reported that phase reset of neural oscillations play a critical role in ERP generation (Basar, 1999a, Makeig et el., 2002, Barry et al., 2003; Yeung et al., 2004).

Based on the properties of the generative stimulus, ERPs can be divided in two categories: Exogenous and Endogenous. The early waves (components) peaking within the first 100 milliseconds (ms) after stimulus presentation are termed ‘sensory’ or ‘exogenous’ as they depend largely on the physical properties of the stimulus. In contrast, ERPs generated at longer latency after stimulus presentation reflect how the subject evaluates the stimulus and are referred to as ‘cognitive’ or ‘endogenous’, as they indicate later stages of information processing (Burkard et al., 2007). Depending on the modality of stimulus presentation ERPs can be also categorised as visual, auditory or somatosensory. In this thesis focus is laid upon auditory evoked potentials (AEPs), i.e. responses produced after the exposure to auditory stimuli. An auditory evoked response (AER) is an activity (a response) within the auditory system (which encompasses the ear, the auditory nerve and auditory processing regions of brain) that is generated in response to the presentation of sounds. Stimuli may range from clicks to tones or speech sounds. The sounds are normally presented to a person via some type of acoustic transducer (device to convert electrical energy into sound /acoustic energy) such as earphones (Hall, 1992).

Early studies of Auditory Evoked Responses have delineated the activation of ascending pathways shown in Figure 1.1 . Presentation of an auditory stimulus to the external ear passes through the middle ear that transforms air-borne sounds into pressure waves in the fluid compartments of the cochlea. The structural and functional properties of the middle ear cavity can influence the way the signal reaches the cochlea both in terms of energy and frequency (spectral) content. The signal then travels to the primary afferent neuron innervated in the cochlear inner hair cells of the cochlea that transmits the information to the central auditory system. The

role of cochlea is to transduce complex sound waves into neural activity in the auditory nerve (Raph & Altschuler, 2003). Signal is then transmitted to the VIII (auditory) cranial nerve, and then to auditory brain stem followed by thalamus and auditory cortex (Calhoun, 2008; Musiek & Oxholm, 2000). This anatomo-functional pathway and its putative neural generators are summarised in Table 1.1.

Figure 1.1 Represents Central Auditory Pathway in human beings. With permission from Hill, M.A. (2014) Embryology Hearing - Neural Pathway.

Fifteen distinct components have been identified in the scalp recorded averaged evoked potentials following the presentation of an auditory stimulus. There are different brain structures (generators) involved in the process of EP production. These will be discussed below with each referring to the latency and type of AEP. As seen in Figure1.1 while a sound travels through different regions from ear to brain, it produces different evoked responses during this pathway. This complex waveform with the associated components is presented in Table 1.1

Types of ERP	Components	Latency	Generators
Early latency	I - VI	1-8 ms	Cochlea and auditory brain stem
Middle latency	N_o, P_o, N_a ,P_a, N_b	8-50 ms	Thalamus, auditory cortex
Long latency	P_1, N_1, P_2, N_2	50 -300 ms	Primary Auditory cortex, and frontal cortex

Table 1.1 Identifies different ERP characteristics and their source generators.

Figure 1.2 ERP components as a waveform showing different amplitude values for each ERP response recorded. Adapted from "The Senses" by H.B. Barlow and J.D. Mollon, Cambridge University Press (1982).

Compared to measures, ERPs reflect the direct neural output of a given process and are therefore less prone to interpretational bias. This property also allows investigating processes that do not require conscious elaboration; this is particularly valuable in participants who are either unwilling or unable to provide overt report of their perceptual or cognitive experience. Their exquisite temporal resolution is also critical to deconvolve the behaviour of complex neural networks in response to external stimuli.

In the auditory domain the most frequently investigated ERP components include the P1/P50, the N1/N100, P2/P200 and the P300. One of the common ERP measures P50 has already been studied extensively in literature yet it is not well understood and is investigated further as part of this thesis.

1.2 P50/M50 as a measure of auditory sensory gating

1.2.1 Sensory Gating: definition

Sensory gating is the neural process of filtering out irrelevant sensory input at central nervous system level, preventing unnecessary sensory information from reaching higher level brain processing and ensures normal information processing (Braff & Geyer, 1990). It has been considered as central to the nervous system's ability to modulate responses to incoming stimuli (Adler et al., 1998). Two known aspects of sensory gating are: gating out and gating in. Gating out refers to the brain's ability to terminate response or to significantly reduce the magnitude of an

individual response to incoming irrelevant stimuli. Gating in, is described as the re-respond to the novel stimulus or an alteration in ongoing stimuli (Boutros, Zouridakis & Overall, 1991). There are at least two stages essential for sensory input: a stimulus identification stage followed by a stimulus evaluation stage (Freedman et al., 1991). It has been proposed that a neural memory trace is produced by the first incoming stimulus and that this has a persistent effect in higher neural circuits. When a subsequent stimulus is presented at a relatively short time interval from the first, it is compared with that memory trace and if it contains no new information the response is inhibited (Cromwell et al., 2008). Sensory gating can be observed in most sensory modality including visual, somatosensory and auditory. As mentioned earlier for this study emphasis is laid upon gating within auditory system which is discussed below in detail.

Auditory Sensory gating stimuli considered as irrelevant are “filtered out” in the early stages of auditory neural processing. The middle latency AEP obtained around 50 ms post stimulus presentation known as P50 and referred to as M50 when magnetic field responses are recorded, is the most frequently used response to measure of auditory sensory gating (both P50/M50 are used interchangeably throughout the thesis). The most widely used experimental paradigm is the traditional “paired-click” in which the presentation of a brief broad-band sound (conditioning click ‘C’ or S1) elicits a reduction in amplitude of the response to a second stimulus (test click ‘T’ or S2) if the latter presented within a few hundred milliseconds of the former (Wehr & Zador, 2005). This phenomenon occurs at cortical level (Miller et al., 2002) and has been hypothesized to act as protective mechanism for the restricted capacities of higher-order stages of auditory information processing (Korzyukov et al., 2007). Suppression of the P50 response in a paired click paradigm is usually measured by a ratio obtained by dividing peak–to-peak amplitude of the P50 component of second click by that of first click. This ratio is referred to as the T/C ratio (Freedman et al., 1987). Lower T/C ratio reflects stronger attenuation of irrelevant input and thus more efficient gating. Auditory sensory gating is used as a probe to investigate neural processes in healthy and pathological conditions. Impaired sensory gating would reflect failure to inhibit influx of irrelevant or distracting information. This could lead to perceptual or attention deficits due to processing inappropriate stimuli (Davies et al., 2009). Previous studies have reported, about 60% -80 % suppression for the P50 amplitude to second click as compared to the amplitude of the first one (Clementz et al, 1998).

1.2.2 Functional neuroanatomy

P50 ASG has been traditionally measured brain electrical activity with the EEG, and the initial findings largely emerged from single-trial analysis (Clementz et al., 1997; Edwards et al., 2009; Trautner et al., 2006). Single-trial analysis is a technique that considers variance only within subjects (Pernet et al., 2011). More recently, contribution to the delineation of potential sources involved in P50 ASG has been obtained from intracranial recordings in patients with drug-resistant epilepsy evaluated for surgical restive treatment (Wilson et al., 1984; Korzyukov et al, 2009; Trautner et al., 2006) and from studies of the animal analogue of the human P50 (Adler et al, 1998; Luntz-Lebyman et al, 1992). Intracranial studies have significant advantages related to the proximity of the recording electrodes to the putative neural structures responsible for ASG, but suffer from reduced spatial sampling. Little is known about the functional neuroanatomy of ASG at whole-brain level; in this endeavour, non-invasive neuroimaging techniques are ideally placed to characterise the complexity of neural networks involved. In the Table 1.2 below a brief synopsis of the sources that have been suggested to be involved in P50 ASG is presented.

Authors, yrs	Brain Regions
Reite et al., 1988	Bilateral temporal sources (Primary auditory cortex, Heschl's gyrus)
Thoma et al., 2003	Both temporal (superior temporal gyrus) and frontal regions.
Knott et al., 2009	Both temporal (superior temporal gyus) and frontal regions (pre central and post central)
Oranje et al., 2006	Bilateral temporal lobe source and frontal source
Korzyukov et al., 2007	Bilateral temporal sources and frontal cortical regions
Bak et al., 2011	Hippocampus, primary somatosensory cortex, insula and medial frontal gyrus

Table 1.2 Studies describing source localisation during P50 suppression phenomenon.

From the table above, it is evident that the temporal lobe (superior temporal gyrus) plays a prominent role in the generation of the P50 response; the findings on role of frontal cortex or hippocampus are not consistent and have only emerged more recently. The role of hippocampus as suggested by animal studies has been questioned in few recent studies (Boutros et al., 2008 & Rosburg et al., 2008) and it is not yet clear if hippocampus plays a significant role in the suppression phenomena. Undoubtedly, intracranial studies are well suited to measure task related neuronal activity and can provide substantial information about source localization. However, these studies are performed in the context of pre-surgical evaluation of patients with drug-resistant epilepsy predominantly from the temporal lobe, thus raising concerns as to what extent these findings can be generalized to the healthy population. Since it is unethical to perform such studies in healthy subjects, non-invasive techniques such as MEG and EEG have the ideal temporal resolution to understand functional neuroanatomy of P50 ASG. Most MEG studies so far based their conclusions from sensor space analysis (Edgar et al., 2003; Huotilaine et al., 1998; Makela et al., 1994) rather than investigating at source (brain) level. In this

thesis, the initial focus is laid upon source (brain) level analysis to understand P50 ASG network in healthy population.

1.2.3 Neurobiology of ASG

In-vitro studies have suggested the cholinergic drive inhibits afferent input to CA3 region of hippocampus and is responsible at molecular level of the gating process. Researchers have tried to explain this phenomenon drawing inferences from animal models (Leybman et al., 1992). It has been found that in animals, suppression of evoked response is lost after lesion to the pathway from the septal nuclei to the hippocampus (fimbria-fornix) which - amongst other tracts - also contains the cholinergic afferents to the hippocampus (refer to Leybman et al., 1992). Following this initial evidence, evoked responses in rats were examined after administering α-bungarotoxin (Cholinergic antagonist) that blocks lower-affinity nicotine receptors. It was found that this chemically blocked inhibitory gating of the early evoked response P20-N40 (in rats), produces deficits similar to those observed in schizophrenia patients (Luntz-Leybman et al., 1992). Miller and Freedman (1993) suggested from these findings that cholinergic afferents might excite inhibitory neurons resulting in the inhibition of the response of pyramidal neurons. It has been postulated that patients with schizophrenia have decreased density of non-pyramidal cells (GABAergic interneuron, which are considered to be inhibitory in nature) particularly in anterior cingulate and pre frontal cortex. Post-synaptic GABAergic inhibition has been hypothesized to play a role in the suppression of the sond response (Leonard et al., 1996). However, due to the short-lasting nature of GABAergic inhibition, which has been measured in animal studies and range between 50 and 100 ms (Wehr & Zador, 2005), it is unlikely to fully explain the long lasting suppression necessary to explain sensory gating when auditory stimuli are presented with 500 ms ISI.

Another hypothesis which was formulated to understand mechanism of sensory gating was tested using cholinergic α-7 nicotinic receptor (Adler et al., 1998; Brinkmeyer et al., 2011). Studies suggest that nicotine binding receptors increase level of dopamine in CNS, either by attaching nicotinic receptors on dopamine neurons, releasing dopamine or by inhibiting monoamine oxidase which leads to dopamine excitation in CNS (Cooper, Bloom & Roth, 1996). It was revealed in rodent studies that nicotine agonists improve ASG by either reducing S2 response amplitude or by increasing S1 amplitude (Stevens & Wear, 1997; Radeck et al., 2006). This

notion was then tested in healthy participants (smokers), as well as in schizophrenia group (Adler et al., 1993, 1998; Leonard et al., 2007; Brinkmeyer et al., 2011). It was seen that P50 ASG in heavy smokers (healthy) diminished abnormally, while in schizophrenia patients ASG improved significantly after heavy smoking however, the effect only lasts for about thirty minutes. Therefore, it is significant to control for smoking when recruiting participants for sensory gating studies as it can modulate the response leading to erroneous inferences.

Evidence from studies in patients with schizophrenia demonstrated that P50 suppression deficits were mitigated by treatment with atypical antipsychotics as compared to typical antipsychotics (Nagamoto et al., 1999; Adler et al., 2004). This difference is likely to occur due to varied neurochemical composition of typical and atypical antipsychotics. Clozapine, an atypical antipsychotic and agonist for serotonin and dopamine has been classified as most effective in achieving normal level of P50 suppression in clinical population (Nagamoto et al., 1996, 1999). To gain better understanding of pharmacological effects on neurophysiology more studies were conducted to understand the role of neurochemicals such as noradrenaline and serotonin during P50 ASG particularly in healthy participants. Hammer et al (2007), studied the effect of Imipramine (which is a selective agent for both serotonin and noradrenaline, 50gm administered orally, in healthy non-smoker males) and observed P50 suppression disruption in healthy volunteers, supplying evidence for involvement of both neurochemicals in ASG. Due to the lack of selectivity of the agent it wasn't clear if the disruption was due to noradrenergic or serotonin. Therefore, to understand further which neurochemical had an effect or not another study was conducted to look at effects of serotonin individually using escitalopram (10mg dose given to healthy male participants), since it is a Selective Serotonin Reuptake Inhibitor (SSRI) with most selective mode of action with no or little Dopamine or noradrenaline binding and surprisingly it was observed that there was no effect towards P50 ASG (Jensen et al., 2008). It was suggested that the dose might have been too low to observe any significant effects, so two years later same study was performed on healthy males, this time 15mg escitalopram was administered in twenty healthy male participants. It was found that with higher escitalopram dose P50 suppression reduced, suggesting that P50 sensory gating is sensitive to rise in serotonergic activity (Oranje et al., 2010). This proposes the possible reasons for P50 ASG modulation in depression and anxiety patients, particularly one's on high dose of anti-depressant drugs.

In most P50 suppression studies, participants were asked to abstain from exposure to caffeine prior to recording (Adler et al., 1994 ; Ghisolfi et al., 2006) due

to its CNS effects that include adenosine block and increase in serotonin and acetylcholine levels. The effect of this non-selective adenosine-receptor antagonist on P50 gating in healthy adults was studied by Ghisolfi et al (2006). It was suggested that high dose of caffeine (200gm-400gm) modulated P50 ASG in healthy participants. Above mentioned pharmacological studies suggest that different neurochemical pathways could modulate P50 suppression response, that could be a potential biomarker for pharmaco-MEG studies.

1.2.4 Age dependency of P50 ASG

Infants

There is sparse evidence in the literature on P50 sensory gating in infancy. A recent study investigating P50 ASG in infants and children up to four years of age during active sleep (REM cycle) using paired click stimulus with 500 ms ISI (Ross et al, 2013) determined that P50 sensory gating from in infancy. These findings indicate that a follow up longitudinal study, might provide insight into association of P50 sensory gating to later psychiatric illness.

Young children and adolescents

According to Myles-Worsley et al (1996), P50 gating ratio remains stable over childhood (7-9 years), early adolescence (10-14 years), late adolescence (15-19 years) and adulthood (20-29 and 30-39 years). Contrary to this, a more recent study found that children in the age group 5-7 years show lower amplitude to the first click and that this could be responsible for the reduced sensory gating when compared to older children (Brinkman & Stauder, 2007). Findings from this study concluded that sensory gating matures around age 8 years and it does vary in younger children (below 8 years). Further studies investigated if alteration in physical properties of stimulus would modulate gating response. The effect of ISI (250 ms, 500 ms and 1000 ms) was studies by Rasco et al. (2000). It was found that P50 gating was lower in normal adolescents for ISI 250 ms, and not for 500 or 1000 ms compared to adults, suggesting that age as well as stimulus properties could at least in part account for the sensory gating differences seen between adults and children/adolescents.

Adults and older adults

It has been acknowledged that physiological aging affects the peripheral auditory system which could influence auditory processing and make it challenging to detect, localise or differentiate sounds. It is believed that these changes might affect inhibitory neurotransmission of subcortical and cortical neurons altering sensory and cognitive processing (Gmehlin et al., 2011). Quantitative MRI studies identified that ageing is associated with cortical atrophy specifically in prefrontal cortex followed by temporal lobe regions (Allen et al., 2005; Gonoi et al., 2010 & Ouda et al., 2014). A comparative study between young (mean age 26 ± 5years) and older adults (mean age 72±5 years) investigating P50 ASG (using click paradigm), failed to identify significant differences in the amplitude suppression of P50 response due to age differences (Gmehlin et al., 2011). It is not yet clear whether sensory gating is preserved during physiological aging or not due to the paucity of specific studies addressing this issue.

1.2.5 Effects of behavioural states on P50 ASG (wakefulness, NREM & REM)

The literature on the effect of wakefulness or sleep (REM or N-REM) on ASG is limited. Nonetheless, it is essential to determine influence of state on ASG particularly in infants, who are mostly recorded while they are asleep as they get stressed with minor disturbances such as application of electrodes etc. As described earlier stress can increase adrenergic tone which can modulate ASG response in infants (Ross et al., 2013). In a comparative study, P50 ASG was measured in infants and young children (4 years old) during REM and NREM sleep cycle; it was observed that sensory gating was stable and well developed during REM sleep, while it was poor during NREM, which is supported by similar evidence from adult NREM studies (Hunter et al., 2015). It was concluded that during NREM mechanisms involved in ASG are functioning differently as there gating ratio is close to 1 indicating lack of suppression to second stimulus. This could possibly be a result of existence of adrenergic tone that persists during this stage as indicated by animal studies, which also state that norepinephrine neurons of the locus coeruleus are tonically active during NREM sleep, but become inactive during REM sleep (Kisley et al., 2001; Siegel & Rogawski, 1988). These findings are supported by another study which measured ASG during REM and NREM in infants three months old and later in same participants at age 4 years. It was established that during REM sleep this measure is stable and unaffected by age across early childhood; thus characterizing P50 ASG as sleep-state dependent measure (Hunter et al., 2015).

Freedman & Kisley (2001) failed to identify in adult participants significant differences in the P50 ASG between REM and NREM sleep. Kisley et al (2003) extended this line of investigation to compare P50 ASG in healthy controls and patients with Schizophrenia during wakefulness and REM sleep. As predicted there were significant differences between two groups during both states. From these results it can be stated that P50 ASG is likely to be determined by trait as it doesn't seem to depend on particular brain state.

1.2.6 P50 ASG in healthy population

Most P50 ASG studies in the literature have been conducted in small samples and have a reduced power to detect minor effects and therefore to formulate definitive

conclusions. To overcome this issue, Patterson et al (2008) conducted a meta-analysis of studies available at the time. As can be seen in,

Table 1.3 the selection of studies for this review used different characteristics of the stimulus (click intensity, click duration etc) which can allow to investigate the consistency of these effects on the response within healthy cohort.


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Table 1.3 P50 sensory gating studies in control groups as cited in review paper (Patterson et al., 2008) (*nr-not reported, dB-decibels, SPL-Sound pressure level, HL-hearing level, SL- Sound level)

There is significant heterogeneity among these studies due to variability in acquisition parameters and stimulus properties. Table 1.3 indicates that P50 ASG ratio can have a wide variability in typically developing individuals. These differences could be due to the variability in the physical properties of the stimuli used or the technique applied to extract these responses; these two factors are discussed in more detail in Chapter 2 and Chapter 3 respectively. For a dimensional measure such as P50 ASG, it is important to know its reliability and heritability before considering it as potential biomarker in neuropsychiatric research. To determine this Lu et al (2007) conducted a test-retest reliability analysis of the P50 paired-click auditory gating and found minimal within subject variability of S1 and S2 amplitudes and gating ratio. Heritability of the indices of sensory gating were explored in twin studies. Worsley et al. (1994) recorded both monozygotic and dizygotic twins to identify genetic effects in ASG, and found significantly higher intra-class correlation in monozygotic than in dizygotic twins, confirming the hypothesis of a genetic influence on P50 ASG. Another twin study estimated heritability of the S1-S2 amplitudes and gating ratio and reported substantial heritability for the amplitude of P50 response to S1 while only modest heritability for gating ratio (Anokhin et al., 2007).

1.2.7 Perturbation in Sensory gating: Clinical Applications

Schizophrenia

"*If he isn't hallucinating, his hearing is different when he's ill. One of the first things we notice when he's deteriorating is his heightened sense of hearing. He cannot filter out anything. He hears the sound from the street, in the yard and in the house, and they are all much louder than normal*."[Anonymous 1985, p.1 (quoted in Freedman et al, 1987)].

The P50 ASG to paired click stimuli has been extensively investigated in schizophrenia and has been proposed as a candidate endophenotype (Hall et al., 2006). Clementz et al. (1998) performed one of the first studies to measure differences in the P50 suppression between 36 patients with schizophrenia and healthy age-matched controls. Paired stimuli (double click) were presented with a 500 ms interval. The study found that patients with schizophrenia showed significantly higher amplitude of the P50 component in response to the second stimulus compared to healthy adults. This finding was widely replicated (Alder et al., 1999; Freedman et al., 2000; Bramon et al., 2004) and the focus then shifted to identifying if unaffected first degree relatives of patients with schizophrenia presented similar features, in the quest for a candidate endophenotype. Clementz et al., (1998) showed that patients with schizophrenia and their unaffected relatives present larger responses to the second click compared to healthy controls, confirming the suitability of this measure as a candidate endophenotype. However a review (Patterson et al., 2008) highlighted that the due to large individual differences in P50 ASG measure (i.e. Smith et al., 1994 & Boutros et al., 1991 b), stability specificity and consistency of this measure needs to be further established before it can be proposed as endophenotype. Yet, there is a still a significant gap in understanding of underlying neural mechanism of P50 ASG and other unidentified variables some of which have been addressed in this thesis.

Autism

The literature on P50 suppression in autism is controversial. One of the earlier studies conducted on children aged 3- 8 years indicated that children with high functioning autism show normal P50 suppression (Orekhova et al., 2008). This study also suggested that sensory gating improved with age in typical and atypically developing children. Following this, Davies et al. (2009) performed a study comparing click paradigm outcome in three groups: healthy adults, typical children (5-12 years) and children with sensory processing deficit (SPD). Adults showed significantly higher gating than participants of the younger groups. SPD children group demonstrated significantly less gating compared to typical children. Such findings support the age-dependency of sensory gating maturation in typical children in contradiction with evidence from other studies (Worsley et al., 1994 & Rasco et al., 2000). It also indicates that if there is a maturational trajectory in children with SPD, it

appears to be different than that of typically developing children (Davies et al., 2009). P50 measure has been found impaired in as ASD patients, who have shown atypical latencies in the early peaks that refer to generally less than 150 ms. Finally, the controversy in classification of ASD reflects the challenge of a categorical representation of this wide spectrum of behavioural repertoires.

ASG in other disorders

Following the established role of P50 suppression as a candidate biomarker for schizophrenia, the double click paradigm was used to investigate if patients with bipolar disorder presented similar deficits (Carbranes et al., 2012). Abnormalities in auditory sensory gating were found in this patient group who present deficits in inhibitory processes. A further study was performed in a group of patients with treatment-resistant depression, and showed significant difference in ASG ratio (S2/S1) and higher S2 amplitude compared to healthy controls (Wang et al., 2009). P50 suppression deficits were also investigated in patients with Alzheimer's disease, prefrontal damage and with idiopathic epilepsies (Cancelli et al., 2006; Becker et al., 2011). Zatorre et al. (2007) suggested that responses in the auditory cortex might be influenced by sensory, or cognitive systems, and that the deficits should be considered as an epiphenomenon of dysfunction of the connectivity in the gating network.

Clinical studies have shown qualitative and quantitative differences in the impairment in ASG across different conditions. For example, Grootens et al., (2008) explored the SG ratio in borderline personality disorder (BPD), and found that BPD group had intact sensory gating. Nonetheless, this group had stronger S1 response that means higher response tendency, suggesting a different modulation than seen in other clinical groups. Other studies (Fein et al., 1996; Thoma et al., 2006; Boutros et al., 2002) have reported impaired ASG in subjects with alcohol abuse, substance abuse, impulsivity. Nonetheless, there are no studies investigating the relationship between P50 ASG and personality/behavioural measures such as avoidant personality, aggressive behaviour, attention, withdrawal etc. within healthy population (details in Chapter 5).

1.2.8 Neuropsychological factors and SG

Since sensory gating impairment has been shown to have a negative effect on cognitive functioning due to overload of sensory information (Venables, 1964), it is

essential to understand how P50 ASG might affect varied domains of neuropsychological performance in clinical population. The association between P50 suppression and neurocognitive profiles in patients with schizophrenia was subject of a meta-analysis (Potter et al., 2006). Cognitive tasks examined were: attention/information processing, reasoning and problem solving, social cognition, processing speed, verbal learning and memory, visual learning and memory and working memory. It was identified that there is a significant correlation between P50 gating and measures of attention as well as working memory in schizophrenia population. Studies investigating relationship between attention mechanisms and P50 ASG, suggest pre-attentive properties of this phenomenon. However, there were no studies performed to address relationship between P50 ASG and measures of social cognition, thereby suggesting a gap in the literature. Furthermore there are no studies so far looking at relationship between processing stimuli with emotional valence and sensory gating.

Emotion processing is found to be impaired in clinical population discussed above particularly in schizophrenia and autism spectrum disorder. In a recent study, Thompson et al. (2012) examined differences in three groups of participants: First Episode Psychosis (FEP), Ultra High Risk (UHR) for psychosis, and healthy controls on three different tasks theory of mind, facial- vocal emotion recognition, and social perception. Both FEP and UHR, performed worse as compared to controls. However, there were no significant differences between UHR and FEP patient's performance on any of the tasks (Thompson et al., 2012). In a comparative fMRI study with ASD (Ashwin et al., 2007), participants were asked to perform a button-press and identify the affective valence of the presented stimuli (faces with high fear, low fear and neutral faces). Brain activity in left amygdala and orbitofrontal cortex was higher in healthy controls as compared to ASD patients, irrespective of IQ levels, suggesting that the difficulty in social interaction (Kenndy & Adolphs, 2012) accounted for most of the effect. There is very limited literature scrutinizing any association between above-mentioned measures.

There is no clear evidence to explain the clinical applicability of sensory gating. In patients with schizophrenia it has been suggested that ASG impairment might be one of the factors contributing towards auditory hallucinations (Alder et al., 1998 & Hirano et al., 2010). In terms of poor auditory gating in healthy adults, Kisley et al. (2004) proposed that this could be explained by their different sensory processing ability in their environment. In the light of evidence of frontal lobe contribution to ASG, it has been proposed that impaired gating ability could be due to possible deficits in these structures. Nevertheless a better understanding of

connectivity patterns between the auditory sensory brain and frontal lobe structures might provide insight into functional significance of ASG.

1.3 Aims of the project

(1). To understand the electrophysiological indices of sensory gating (source localization, neural oscillatory pattern and connectivity measures) using Magneto-encephalography (MEG) in healthy adults

(2). To determine correlation between behavioural measures such as personality types and ASG in healthy cohort

(3). To investigate whether emotional face processing could modulate ASG.

Brief summary of Chapters:

Chapter 1 – Introduced the framework for investigating P50 ASG and outlined aims of the present study

Chapter 2 –Describes overview about participants, stimuli design, data collection and data analysis.

Chapter 3 – Looks into electrophysiological indices of P50 ASG including source localization and neural oscillatory patterns.

Chapter 4 – Identifies functional connectivity networks of ASG

Chapter 5- Investigates association between behavioural measures and ASG

Chapter 6 – Examines the effect of emotional processing on ASG

Chapter 7 - Summarizes main findings, their implications and discusses future work motivated by this study, and concluding remarks.

Chapter 2: General Methods

2.1 Ethical Considerations

The study was started after approval by Aston University Ethics Committee (Ethics number 0412) was granted. The study adheres to the ethical principles for medical research involving human subjects. The main ethically sensitive issues included appropriate risk management, methods to obtain consent and data protection. The Institutional Ethics Committee application first addressed risk control and elimination issues related to MEG and MRI recordings. For this, an excel document which outlined the total risk (calculated from frequency, probability and severity of event) involved under abnormal conditions and emergency conditions for both MEG and MRI separately were submitted. It was suggested that as long as outlined procedures were followed use of these techniques should remain a low risk activity. Specific screening forms, information sheet, consent form and an advertisement letter were part of the submitted material as well.

On the day of the recording participants were further briefed on the procedures and given opportunity to raise any questions or concerns. Following this, written consent was sought prior to testing. Participants were informed of their right to withdraw from the study at any point in the study and were reassured that their withdrawal would not affect them in any way. They were also informed that according to the Data Protection Act, information would be kept sure and confidential. The participants' screening forms for MEG and MRI and behavioural data were kept in separate lockers in a room in the Aston Brain Centre that can be accessed only by authorized person. Unlike screening forms, behavioural data did not contain any personal information for participant. These forms were identified with the participant number to ensure confidentiality. Once collected, MEG and MRI data was transferred to sure computers in the MEG analysis lab and access was possible only to the researcher. Filenames were coded using participant number to ensure confidentiality. Oral and written debriefing was given after each session and procedure.

2.2 Participants

Between January 2013 and October 2014, thirty-four healthy volunteers (17 males and 17 females) aged 18 - 59 years were recruited for the study. The study investigated P50 ASG in healthy adults aged between 18 and 59 years. This

particular age interval was chosen due to the restrictive age criteria set by the behavioural assessment Achenbach System of Empirically Based Assessment (ASEBA), for which standardised scales are available. Participants included students under the Aston University Psychology Programme Experiment Credit Scheme, staff members and individuals who had signed-up to the Aston Research Centre for Healthy Ageing volunteer database (ARCHA) and agreed to be contacted. Although members in ARCHA database are individuals above 80 years of age, it was specified in the letter that any interested family members or friends in the required age group (18-59) were welcome to contact the researcher. The recruitment took place through three different networks: advertisement in in the University newsletter “Aston Aspects”, intranet notification on SONA (Research Participation System) and invite letters to members of ARCHA database.

Inclusion Criteria

- Age range between 18 and 59 years
- Normal hearing (assessed prior to the MEG study with tonal audiometry at 1 KHz)
- Scores based on Web Screening Questionnaire for common mental disorders (WSQ){See Appendix 1, WSQ cut-off scores: Depression: Q1≥ 5 & Q2=1; GAD: Q3≥2; Panic: Q4 ≥1; Panic with Ago Q4 ≥1 & Q5=1; Ago:Q5=1; Specific phobia: Q6 or Q7=1; Social phobia: Q8=1 & Q9=1; PTSD: Q10=1 or Q11=1; OCD: Q12≥1;Alcohol Abuse/Dependence : Q13≥2 & Q14≥3 ; Suicide : Q15=3 (exclusion)}

Exclusion Criteria

- Personal or history of psychiatric or neurological disorders identified using a screening questionnaire presented to all participants prior to the recruitment.
- History of abuse of alcohol or other substances including smoking: this information was obtained by web screening form and validated using the Achenbach system of empirically based assessment
- Being unfit to have MRI or MEG examination. These conditions included the presence of metallic implants, or any other foreign metallic object in their body; this was validated using MRI and MEG screening form

Furthermore, participants were asked to abstain from caffeinated drinks for 24 hours prior to the recording day, as caffeine has been reported to have an effect on ASG (Alder et al., 1998). After the screening procedure 4 participants were excluded from the study (one was on anti-depressants, one had a diagnosis of dyslexia, two had impaired hearing threshold on tonal audiogram).

2.3 Behavioural measures

Behavioural profiles were assessed using three questionnaire-based scales. The Achenbach system of empirically based assessment (ASEBA) (Achenbach & Rescorla, 2003) and the social interaction anxiety scale (SIAS) (Mattick & Clarke, 1998) were used to evaluate personality profiles. The adult sensory processing profile (ASP) questionnaire (Brown & Dunn, 2002) was used to identify whether atypical sensory processing patterns were present and their potential effects on functional performance. The psychometric properties of these measures are discussed in detail below.

2.3.1 Achenbach system of empirically based assessment

ASEBA is a powerful tool to assess competencies, strengths, adaptive functioning, and behavioural, emotional, and social problems in children, adults and older adults. The adult self-report (ASR) questionnaire, which forms part of the ASEBA assessment has been designed to measure adaptive functioning, empirically based syndromes (aggressive behaviour, rule-breaking behaviour, anxiety, depression, attention problem), substance use, internalizing and externalizing in age group 18-59 years (See Appendix 3) (Achenbach & Rescorla, 2003). The scales vary based on age and gender differences (there are four scales used when interpreting scores: women in age group 18-35 and 35-59 and men in the age group 18-35 and 35 -59) with healthy individuals presenting standardized t scores <60, scores between 60-80 representing the borderline range and scores higher than 80 identifying the clinical pathological range (See Appendix 4) (Achenbach & Rescorla, 2003). Data acquired from ASEBA forms was entered in the ADM automatic scoring

software that computed raw as well as t-scores. These were then exported into an Excel spread sheet to allow statistical analysis. Reliability and validity of the tool was assessed in a national survey (Achenbach & Rescorla, 2003) that showed one week test–retest reliability between 0.8 and 0.9. Internal consistency for ASR was high as well with high alpha coefficient of 0.83 for empirically based problems and 0.78 for DSM oriented scale.

2.3.2 Social interaction anxiety scale

Designed by Mattick & Clarke (1998), SIAS is an easy to administer instrument to assess the anxiety experienced by people in social interaction situations. The scale consists of 20 statements and responses are scored between 0 and 4, where 0 suggests not at all characteristic or true and 4 indicate extremely true or characteristic of the participant (See Appendix 2). Mattick & Clarke (1998), assessed internal consistency and reliability of their scale, and found that SIAS showed high Cronbach's alpha for internal consistency (ranging between 0.88to 0.94). Test-retest reliability was reported to be significantly high as well 0.92. Due to its high proficiency, this scale it has been translated and used in other languages as well; for example, Spanish population (community based) (Olivares et al., 2002) and Dutch population including both healthy as well as clinical cohort (Beurs et al., 2014).

2.3.3 Adolescent/Adult sensory profile

ASP is designed to measure any association between sensory processing patterns and its effects in daily functional performance. Unlike other assessments, this test asks questions regarding how a person generally responds to sensations (trait), as opposed to how he or she responds at any given time (state). This enables the instrument to capture the more stable and enduring sensory processing preferences of an individual, providing greater understanding about why individuals engage in particular behaviours and why they prefer certain environments more than others (Brown & Dunn, 2002). The assessment consists of 60 statements; with responses '1' being never and '5'almost always (See Appendix, 5). The questionnaire

is divided in sections based on whether questions relate to taste/smell, movement, visual, touch, activity level and auditory domain. Scoring is based on Dunn's model of Sensory Processing (1997a): sensation avoiding, sensation seeking, low registration and sensory sensitivity. The first one refers to individuals who are usually bothered by sensory stimuli so they tend to engage in sensation avoiding behaviour. Second quadrant is opposite in the sense this refers to people who create additional stimuli or look for surroundings that provide sensory stimuli in order to meet their neurological thresholds. Low registration as the term suggests indicates population, which either misses or takes longer to respond to stimuli. Low neurological thresholds that cause people to respond readily to sensory stimuli are categorized under sensory sensitivity. The possible scores are classified into five categories: much less than most people, less than most people, similar to most people, more than most people and much more than most people. The test has been standardized on English population and includes age-specific cut-off scores (11-17 years, 18-64 years & 65+). The cut-off scores do not indicate at which point a particular pattern becomes problematic instead they show how a particular person compares with a larger group of individuals without disabilities in the same age group. Following this one can identify when there is a mismatch between what individual wants or needs to do and his or her performance. For internal consistency the coefficient alpha ranged between 0.639 and 0.775 for various groups and quadrant scores (Brown & Dunn, 2002).

2.4 Paradigm Design

2.4.1 Auditory task

In line with prevalent literature, we used a paired click paradigm (Adler et al., 1998; Freedman et al., 1987) to measure auditory sensory gating. Click pairs of the same physical properties are presented binaurally through ear inserts with a short inter-stimulus interval. This paradigm has shown high test-retest reliability (Lu et al., 2007). Previous studies have reported hemispheric lateralisation of P50 response, therefore the stimulus was presented binaurally rather than monaurally (Thoma et al., 2003). While this is the most widely used protocol, recently the use of tonal stimuli has also been explored (Ninomiya et al., 2001). It was suggested that the frequency of the tonal stimulus doesn't have any influence on P50 ASG index or on the

absolute amplitude of the response. Sousla et al. (2012) confirmed that temporal acuity thresholds obtained after tones or clicks are essentially equivalent. Stimuli chosen to measure ASG in our study are of 3ms duration. White and Yee (2006) investigated the effect of stimulus duration on gating ratio and P50 amplitude and found that click stimulus duration of 1, 3, and 5 ms did not result in significant differences in these parameters. As far as stimulus intensity, Ninomiya et al. (2001) suggested that P50 amplitude increased with increase in stimulus intensity but only until 85dB, as reverse effect was observed at 100 dB. Most studies have reported intensity of clicks around 70-85dB (Freedman et al., 1987; Clementz et al., 1998; Brinkman & Stauder, 2007). Click intensity (30 dB or 50 dB) could possibly modulate P50 response however 70 dB and above resulted in no difference in gating ratio. Consequently, stimulus intensity for this study was set to 80 dB SPL presented binaurally.

A typically used inter stimulus interval (ISI) for gating paradigm which tends to produce robust suppression is 500 ms (Dolu, Süer, & Özesmi, 2001). Previous studies have reported the use of ISIs of 250 ms, 500 ms to 1s (Freedman et al., 1987; Clementz et al., 1998; Brinkman & Stauder, 2007; Rasco et al., 2000). It is often advisable to introduce a random element into the Inter Trial Interval (ITI) in event-related paradigms. This is particularly significant because anticipating upcoming stimulus is known to alter brain activity while random interval reduces this effect of expectancy (Clementz et al., 2002). Along with this too short ITIs may lead to superposition of evoked responses from consecutive trials, which are desirable only when investigating steady-state responses (though again, random jitter can allow such overlap to be deconvolved); conversely, unnecessarily long ITIs reduce the total number of trials. For this study, inter stimulus interval was 250±10 ms and random ITI between 7-10s was chosen. From a meta- analysis review, it has been reported that ASG is not affected by type of stimulus delivery either via headphones, ear inserts or ear transducers (Patterson et al, 2008).

Sound waves for paired clicks were synthesized using Adobe Audition. Since click is a square wave no noise clipping was required. The stimulus presentation script under Presentation® (NeurobehaviouralSystems Inc.) was written for the study by Dr. Caroline Witton at Aston University. The auditory file was generated which was incorporated into the Presentation script. However, the sound generated was too low and not audible. To increase the intensity an amplifier was attached to the computer to increase the sound intensity. Signal intensity was calibrated using an artificial ear to ensure consistency in sound intensity across participants. Following

flowchart helps to understand the route of the stimuli as delivered binaurally to the participants.

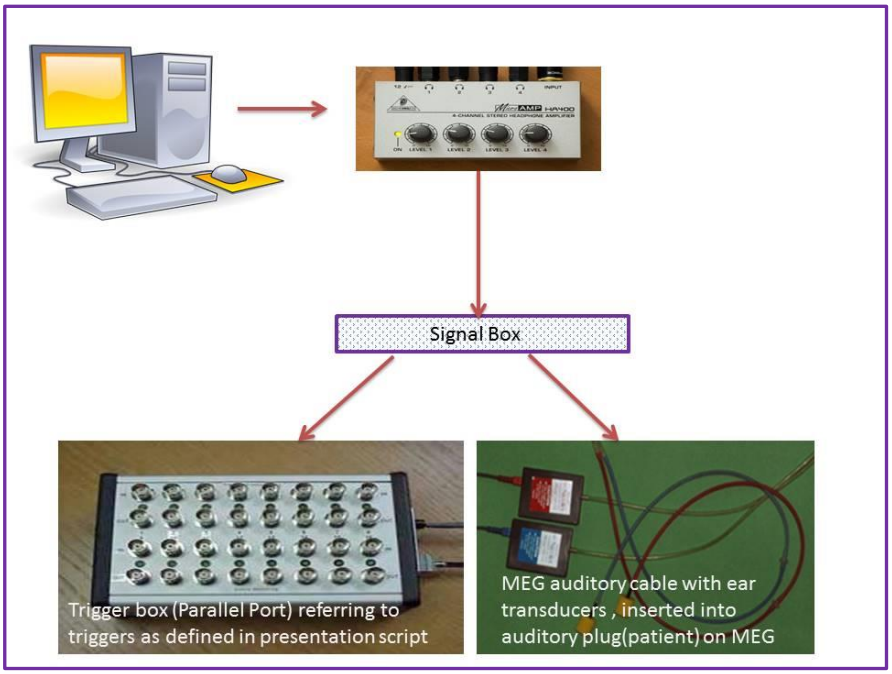


Figure 2.1 Flowchart displaying auditory stimulus delivery to MEG room.

2.4.1.1 Auditory threshold testing

Given that ERP amplitude is dependent on the intensity of the stimulus (Wunderlich & Wesson, 2006), hearing threshold at 1KHz was assessed performing a tonal audiogram prior to MEG recording. Given the technical difficulty in delivering clicks at a set HL intensity with the available equipment in the MEG room, we decided to proceed with the MEG measurements only in subjects with hearing levels between -10 and 10 dB (HL). In a sound proof room participants were presented with monaural 1 kHz tone starting with 100dB (HL) (Telephonics model TDH 39-P). Participants were given a push-button and were instructed to press it when they heard the sound and not to press it if they didn't hear the stimulus any more. Tone intensity was decreased in 10dB (HL) steps until about 40 dB (HL), and in 5 dB (HL) steps thereafter. To ensure consistency and reliability of the hearing threshold, the final stimulus intensity step was repeated three times. If the participant responded all three times, than that was assumed as the threshold or else the intensity was increased by five steps and same procedure was performed. Threshold for both right and left ear were recorded on the audiogram. Threshold values between -10 and 10 dB were considered acceptable and differences about 5dB between left and right ear

were considered as physiological variations. Apart from two participants, no one had deficits in hearing threshold measurements; the average was between -10 and 10 dB (HL) None of the participants reported having hearing deficits on the demographic questionnaire.

2.4.2 Affective modulation of P50 ASG

In order to investigate if processing stimuli with emotional valence modulated sensory gating, we designed a task in which emotionally salient stimuli were presented before the auditory click pairs. The faces presented were acquired from NimStim set of stimuli (http://www.macbrain.org/resource.htm), designed by Dr. Nim Tottenham. The stimulus set includes 672 images of facial expressions, displayed by 43 male and female actors, each producing 16 different facial poses (Tottenham et al., 2009). Some of these poses include classical expressions such as happy, sad, neutral, angry, fearful, disgusted, and surprised. Since previous literature had shown effect of race and ethnicity on behavioural measures, the chosen stimulus set addressed this problem by including racially diverse actors. The stimulus set had high validity (0.79) i.e. accuracy of participants in identifying each emotional expression and test-retest reliability i.e. the ability to recognise emotional expression at two consecutive measurements (0.80) (Tottenham, 2009). Adolphs & Alpers (2010) examined the arousal and valence using the Nim Stim set and compared it to another set of less intense expressions (Karolinska Directed Emotional Faces, 1998). They found that NimStim expressions elicited stronger emotional arousal, and were more accurately identified. For this study, permission to use NimStim has been granted by the author, who provided access to the data set that also includes a manual with instructions on using the stimulus for research purpose. To find details about parameters of this stimulus see Chapter 6.

2.5 MEG recording of P50 response

MEG was chosen for this study due to its unique capability in deconvolving the temporal and spatial properties of the P50 suppression and in characterising its time-frequency profile. At the Aston Brain Centre, we have access to a whole head Elekta Neuromag MEG system as well as high field Siemens 3T TIM Trio MRI for co-

registration of the data in source space onto the MRI of individual participants.

What is MEG?

MEG is a non-invasive neuroimaging technique, which measure magnetic fields of the brain; these signals were first measured by David Cohen in 1968. MEG measures small (in the order of femtoTesla) magnetic fields generated by neural activity with excellent temporal resolution and allows the study of neural oscillatory processes over a wide frequency range (1-600 Hz and above). To measure electromagnetic signal a magnetically shielded room (MSR) and highly sensitive detectors called superconducting quantum interferences devices (SQUIDs) are essential. SQUIDs are an array of sensors placed in the helmet, where participant's head is positioned. These are extremely sensitive magnetic flux detectors based on superconductivity and operate at cryogenic temperatures (maintained by liquid helium in the Dewar which also helps in SNR reduction). The arrangement of these superconducting loops responsible to acquire magnetic data divides them into two sensor types: Magnetometer and gradiometer. Both sensor types collect data but in a different way, and this allows for wide range of activity detection. In this study data from both magnetometers and gradiometers were analysed. MEG is primarily sensitive to tangential currents in the brain closer to the surface as compared to radial sources. Evoked MEG responses provide a more selective view of brain activity because only dipoles those are perpendicular to the cortical surface (leading to sulci focused activity) and close to it contribute strongly to the magnetic field.

Figure 2.2 306- Channel Elekta Neuromag® TRIUX™ similar to the one available at the Aston Brain Centre, Aston University, comprising of 102 magnetometers, and 204 gradiometers.

2.6 Screening Measures

The flow chart below (Figure) describes the process of participant selection for this study. These measures are discussed in detail subsequently.

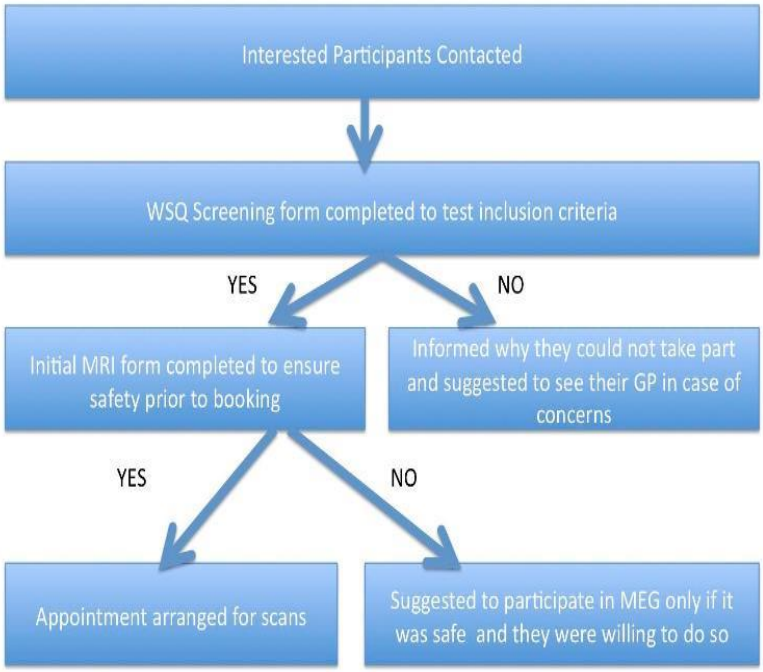


Figure 2.3 Participant selection process for this study

Two main screening measures were employed for this study: WSQ to identify participants with significant psychopathology not clinically identified and the MRI screening form to capture participants who could not undergo a neuroanatomical imaging study. Web screening questionnaire for common mental health disorders (WSQ), was developed in year 2009 at VU University Amsterdam. It is composed of 15 statements that were used to exclude any participants with mental health problems (http://www.webscreeningquestionnaire.org/). It assesses symptoms for generalized depression and anxiety, alcohol abuse, post-traumatic stress disorder, panic disorder with and without agoraphobia, social phobia, specific phobia, OCD, and alcohol abuse/dependence. Donker et al (2009) tested validity of this tool and reported a sensitivity between 0.72 and 1.00; estimates of specificity are: between 0.63 - 0.80 for social phobia, panic disorder with agoraphobia, agoraphobia, OCD, and alcohol abuse/dependence and appropriate for depressive disorder, GAD, PTSD, specific phobia, and panic disorder (without agoraphobia) sensitivity: 0.80 - 0.93; specificity: 0.44 - 0.51. Post WSQ, participants who were selected for MEG scan filled in the initial screening form for MRI. This form assess if there are any potential risks for participants, if they have any metal implants, or foreign metallic particles in their body. In case, there were participants who were safe to be in MEG, but unsafe for MRI, they were provided a choice to have only the MEG scan. Amongst thirty-four participants recorded, four did not have an MRI scan due to safety reasons and only took part in the MEG study.

2.7 Procedure

Prior to participant arrival we ensured that the MEG system was set in the upright position, that the system had sufficient helium level and sensors were well tuned. In case sensors were noisy, they were heated to remove any trapped magnetic flux. After the participants arrived at Aston University, they were taken into the auditory lab to measure their auditory threshold. Once that was done, participants were escorted to MEG acquisition room where they were first shown the equipment and provided general information to make them familiar with the surroundings. They were explained the task and its length, if they were satisfied screening form and consent form was then provided. After ensuring the participants were de-metaled. They were asked to sit in a chair for marking head digitization. Prior to this five pick up coils were attached on the participants: two on the mastoid position and three on the forehead just below the hairline. These areas were cleaned with alcohol wipe to remove any dead skin cells. Then they were asked to wear a pair of goggles that have a localizing reference sensor attached to the side. A digital pen attached to the goggle system in combination with the MEG Acquisition software was used to digitally mark the location of all Head Position Indicator (HPI) coils, measured with respect to the localizing reference sensor attached to the goggles. This step is crucial, as it stores information with respect to person's head shape and in case of any head movement whilst in the scanner. Digitization should cover the whole scalp including points that mark the edges of the nose as it improves surface-based registration accuracy. These head points for each participant were also aligned with the structural MRI of the individual while analysing the data. After the head shape was formed, participant was accompanied into the MEG scanner. They were provided with some brief instructions just before the recording such as instructions to avoid movements, eye-blinks and eye movements during the trials. This procedure was followed for both paradigms. After MEG scan, if participant had agreed to MRI scan, than structural MRI scan was carried out. During second paradigm, because same participants were recorded they were not required to have MRI.

2.8 Data Acquisition

MEG data was acquired with a 1000 Hz sampling rate, to allow a reliable identification of high-frequency brain oscillatory patterns. Data was digitally filtered between 0.1 and 330 Hz. All the data was recorded with Internal Active Shielding 'On'. This system employs the sensor array of the probe unit to measure the residual ambient field variations inside the magnetically shielded room. These signals are fed back to the coils inside the magnetically shielded room forming a closed control loop that effectively minimizes the external disturbances at the sensor area.

Apart from the measured brain signal, MEG data contains unnecessary environmental interference, biological noise or system-related noise. System related artefacts are commonly due to noisy sensors and can be reduced prior to recording by rejecting flat or noisy sensors or during pre-processing. In order to reduce environmental or biological noise, Elekta (Helsinki, Finland) scanner proposes two methods: single-space-separation (SSS) and spatial temporal filter (tSSS). In order to increase signal to noise ratio (SNR refers to ratio between the mean signal amplitude and standard error of the mean over trials) in Elekta system it is essential to apply either of these methods (Gonzalez-Moreno et al., 2014). Both methods aim at suppressing magnetic interferences coming from inside and outside the sensor array, reducing artefact in measurements, transforming data between different head positions (by removing any continuous head position information) and reducing the effect of head movement on data (Gonzalez-Moreno et al., 2014). The software which carried out these pre-processing methods if *Maxfilter 2.1*. In cases where the source of interference is located inside or very close to the sensor array, the use of spatio-temporal Maxwell filtering, (tSSS) is recommended, as it allows suppression of bodily sources of magnetic interference such as dental work, braces or any magnetized pieces in/on subjects head (Gonzalez-Moreno et al., 2014). In a comparative study (Gonzalez-Moreno et al., 2014), it was found that both SSS and tSSS increased signal to noise ratio by 100% and there were no significant differences between the two approaches. tSSS was applied on the data set presented in this study. Head position was transformed to default head position, which coincides the head and device coordinate axes. For continuous head positioning (tSSS) movement correction was applied. tSSS interference suppression was done and the data were transformed to the reference head position. Primarily,

with ERP data sometimes the peak amplitude can be affected due to artefact inclusion while recording the data set. After max filtering the file was divided into segments (epochs), the residual epoch file was then inspected visually and any trial containing artifactual signal was removed manually.

2.9 Data Analysis

The MEG data acquired during this series of studies was analysed in terms of source localization, time frequency analysis of responses in the source space, and functional connectivity of MEG sources. Due to the multiplicity of analysis levels in this study, we were not able to identify a single software analysis package that could perform all the stages within a single platform. For this purpose, Brainstorm 3 and Statistical Parametric Mapping 12 (SPM 12) were chosen, as these are user friendly, have GUI based interface, and are part of large active community. Brainstorm is a collaborative, open-source application dedicated to MEG/EEG data analysis (visualization, processing and advanced source modelling). Brainstorm project was initiated more than 10 years ago in collaboration between the University of Southern California in Los Angeles, the Salpêtrière Hospital in Paris, and the Los Alamos National Laboratory in New Mexico. This software has been widely used since its development (Tzelepi et al., 2010; Amor et al., 2009). There are brief tutorial sessions available to assist beginners with the understanding of the software (http://neuroimage.usc.edu/brainstorm/Tutorials). Data files are saved in the Matlab .mat format and are organized in a structured database with three levels of classification: protocols, subjects, and experimental conditions. Brainstorm does not extract cortical and head surfaces from the MRI, but imports surfaces from external programs (Tadel et al., 2011). To extract cortical surfaces the software Brainsuite 14a (http://brainsuite.org/2014/06/brainsuite-14a-released/) was used and the segmented data was imported into brainstorm (Shattuk & Leahy, 2002). For further details about this see 3.2.4.1.

The second software Statistical Parametric Mapping 12 is also free and open source academic software distributed under GNU General Public License developed by The Wellcome Trust Centre for Neuroimaging of the University College London. Both software tools are written in Matlab and have GUI interface which make it easier to run the data. The pre-processing methods for both are very much similar with an extensive pre-processing pipeline, with options to epoch the data, filter, remove

artefacts, baseline correction etc. Conversely, there are significant differences in methods for source estimation and models for time frequency and connectivity.

Initially, the data was analysed using SPM12, however, it was recognized that it is not possible to extract neural oscillatory information at source-based level in SPM, while Brainstorm had the appropriate feature to perform this. Nevertheless a drawback with brainstorm was that it doesn't have the capacity to perform group analysis. In order to perform group analysis, the data was exported into SPM and statics were run there. Also, the type of connectivity model used for ERP response was available only in DCM (Dynamic Casual Modelling) for SPM details about this can be seen in Chapter 4 (section 4.1.2.). In order to produce desirable results both software's were employed when and as required. Both sensor and source based analysis was performed for auditory stimulus, whereas only sensor based analysis was carried out on visual emotionally evoked auditory task as this was a pilot study using a novel stimulus, therefore, only preliminary results from few participants were reported. Analysis was carried out at three different levels: within individuals, between subjects and group analysis see Chapter 3, 4, 5 and 6 for further details

The behavioural measure data were entered in a spreadsheet and exported into SPSS Version 22.0 software package (IBM Corp. 2013, Armonk, NY) for statistical analysis. For the details on statistical tests carried out see Chapter 5.

Chapter 3: Characterization of the P50 ASG network in healthy participants

3.1 Introduction

3.1.1 Measurement of the P50 Response: methods and pitfalls.

The amplitude and latency of evoked responses can be measured using one of the following methods:

i) To define a time window for each waveform and identify the maximum amplitude in that time window; this is called peak amplitude measure.

ii) To define a time window and for each waveform being measured and calculate the mean voltage in that time window. This is known as mean amplitude measure and is widely reported in most EEG studies.

iii) To calculate the amplitude against baseline where the highest amplitude in selected time window is measured against baseline to get the correct measure of the amplitude relative to baseline.

iv) More recent method is to calculate the Global Field Power (GFP) as defined by Lehmann & Skrandies (1980). Using this method, "*Component latencies are defined as times of maximal values of the electrical power of the evoked field (a measure of field strength); this measurement is independent of the choice of the reference electrode as it considers information from all channels*". The GFP method determines the latency of an evoked response by defining the occurrence times of GFP maxima (Skrandies, 1990) in a multi-channel evoked potential recording. GFP is used to quantify the amount of activity, and it is computed as the mean of all absolute potential differences in the field corresponding to the spatial standard deviation.

It is critical to measure and report amplitude correctly, specifically when comparing amplitudes between two conditions. It has been suggested that mean amplitude is better than peak amplitude as the former is unbiased by noise levels while the latter is sensitive to noise levels, and more noise can lead to higher peak amplitude (Luck, 2005). While measuring mean amplitude, it is imperative to be restrictive of the temporal extent of the window in order to avoid inclusion of time points from adjacent components of the waveform as that would lead to inaccurate measurement. Peak measurement represents the weighted average of all conducting

fibres not just the fastest (represented by onset) and peak latency is determined from this peak measurement at which topography and sources are computed which makes them sensitive to represent not only the area of initial generation, but also spread in surrounding regions. In a comparative study, classical latency and GPF method was applied to determine peak latency of evoked potential recordings during oddball auditory paradigm. Findings from sixty-five healthy adults suggested steeper voltage gradients at peak GFP measure as compared to classical measure latency. There was a significant difference in the topography determined by both measures at N200 and P300. These results suggested that multichannel recordings can be more edifying and only GFP measure can lead to an unbiased data-reduction as it determines single momentary map in time which has maximal field strength (Hamburger & Burgt, 1991). A key factor that needs consideration while measuring either peak or average amplitude measure is the baseline noise, as it would contribute towards amplitude measure. This can be achieved by either calculating amplitude against baseline or apply baseline correction before measuring amplitude. In most cases, the baseline is based on the mean of the waveform computed across some pre-stimulus time window in that same waveform. Baseline duration can affect amplitude measure because shorter baselines are more sensitive to residual voltage fluctuations than if the baseline is scaled over a longer time window (Handy, 2005).

Another essential factor that could potentially affect the amplitude measure is low SNR. As discussed earlier, MEG or EEG data can be infested with environmental, biological or system related interference. It is essential to understand the effectiveness of pre-processing techniques vital to eradicate these unwanted noise sources. Apart from tSSS or SSS (offline noise reduction methods designed for the Elekta MEG equipment) which have been discussed in detail in section 2.8 (chapter 2), there are other methods described below which could be applied to remove external noise or non-biological artefacts. Signal Space Projection (SSP), unlike tSSS or SSS, is a real-time data visualization used for suppressing ambient magnetic interference by recording MEG data without a subject for few minutes (empty room recording). In this case, interference is statistically characterised using principal component analysis (PCA). PCA decomposes data and identifies subspace where external artefacts are reflected in sensor space (Uusitalo & Ilmoniemi, 1997). These components are then projected out from measurement data to reduce contribution from external artefacts. Due to the Magnetically Shielded Room (MRS), these components are stable over time until or unless magnetic environment experiences radical modification or due to artefact sources inside the room; in that case new computation will be required and this is one of the limitations of SSP. An

epoch-based method can be applied to identify artefacts based on the amplitude or spectral content of the signal (Gonzalez-Moreno et al., 2014). Filtering of the raw data on the other hand is not applicable since the brain signal of interest might be in the same frequency range as the artefact (Taulu & Hari., 2009). However, all of these methods can lead to some data loss, which could be preserved by applying a technique called Independent Component Analysis (ICA). ICA has been applied to remove artefacts as well as to decompose MEG/EEG data into separate components that are maximally independent (in statistical terms) (Vigario et al., 2000 & Tang et al., 2002). The limitation of ICA is that it requires visual identification of the artifactual components. In a recent study Gonzalez-Moreno et al. (2014) evaluated the effect of epoch- based artefact rejection vs. decomposition methods and found a 36% increase in SNR for ICA and a 5% increase for epoch-based artefact rejection. This study provided evidence that pre-processing method such as tSSS or SSS to MEG data are of significant value prior to further processing.

3.1.2 Cortical Source Localisation and the P50 ASG network

Most of the source localization methods rely on assumptions on underlying generators of the surface-recorded waveforms at the latency of interest or at the peak maxima. The relationship between observed data and its underlying primary source structure is dependent on the choice of models of the volume conductor (human head). The volume conductor is represented by the conductivity distribution of different tissues via which electric or magnetic fields transmit (Wolters & De Munck, 2007). However, a complete and realistic volume conductor model cannot be designed as some neurons (specifically interneurons) with closed field geometry don't produce externally measurable signal. Volume conductor models are the basis of inverse and forward models, but these are vulnerable to a priori assumptions on the geometry of generators, conductivity distribution and could influence the application of inverse and forward models in source analysis.

The parametric methods of source analysis are based on assumptions of sources being represented by a finite number of dipoles, the number of which is determined using non-linear optimization technique. In contrast, imaging methods also known as distributed source which are based on linear inverse solution and involve a huge number of dipoles distributed all over the brain or areas assumed to be activated as result of stimulus related activity (see Luck, 2005 for a review). Some of these techniques: dipole modelling, beamforming and distributed source approaches are discussed below.

i) Dipole Modelling – This technique is based on the assumption that the spatiotemporal distribution of voltage can be adequately modelled by a relativity small set of dipoles each of which has a fixed location and orientation but varies in magnitude over time (Scherg, Vajsar & Picton, 1989). Each dipole has five major parameters three indicating its location, and two indicating its orientation. It is also associated with a source waveform, which shows the estimated magnitude for that dipole over time. Dipole modelling has been used previously in auditory analysis (Pang et al., 2003) as it provides precise source location and strength of evoked response (Lutkenhoner, 2003). Nonetheless, there are certain limitations associated with this technique; it cannot measure changes in induced activity and is only suitable for evoked activity. Along with this dipole models are based on a priori knowledge, which can lead to biased information. As mentioned in Chapter 2, MEG is not sensitive to radial dipoles (the one's perpendicular to the surface), and only identifies sulci-focused activity. Due to these limitations, dipole modelling was not adopted as a method for ERP localization for this study.

ii) Beamforming- Beamforming methods were first applied to EEG/MEG data in the late 90' (Van Veen, 1997) and are therefore relatively new methods in MEG data analysis. Beamforming reconstructs the contribution of single location to the measured field (Vbra & Robinson, 1998). It creates a spatial filter, which blocks the contribution of all sources not equal to that single source. It is not based on the strength of the source, but on its variance and unlike dipole modelling does not require a priori specification of number of active sources.

iii) Distributed source approaches- Instead of using small number of dipoles to represent brain activity, it is possible to divide the brain into voxels and determine a pattern of activation values that will produce the observed pattern of voltage on the surface of the scalp. This approach uses MRI structural scan and divide cortical surface into hundreds or thousands of small vertices. A common type of distributed source approach is Minimum Norm Estimation (MNE). This method was initially proposed by Hämäläinen and Ilmoniemi (1994) which suggested that selecting one solution that both produces the observed scalp distribution and has minimum overall source magnitude called minimum norm estimation (MNE). MNE consist of both forward and inverse solution where former represents underlying current distribution in the sensor data while latter is computed by modulating amplitude of the dipoles to find a

solution which matches the measured data and represents the least overall power possible. A strong merit of MNE is that it remaps sensor data into a new domain that has more meaningful interpretation. There are more recent variants of this approach based on similar principle such as sLORETA and dSPM (which could be described as further implementations of MNE), Multiple Spare Priors (MSP) etc.

Some of the studies that have applied the above-mentioned techniques to P50 ASG are discussed briefly in this section. By means of EEG dipole modelling techniques researchers have identified bilateral sources of auditory responses in the temporal lobes and recent intracranial recordings have also identified frontal sources (Jensen et al., 2008; Oranje et al., 2006; Weisser et al., 2001; Korzyukov et al., 2007) of P50 ASG. Magnetoencephalographic (MEG) studies have also pointed towards bilateral sources in the temporal lobes in auditory P50 suppression (Farrell et al., 1980; Reite et al., 1988). Knott et al (2009), performed MEG auditory sensory gating study to localize the source of gating process and it was found that as suggested by previous studies (Thoma et al., 2003; Huang et al., 2003 Korzyukov et al 2007), both frontal (pre-central gyrus, post-central gyrus and middle frontal gyrus) and temporal areas are involved in sensory gating. Other areas might be responsible for sensory gating such as intra-thalamic and fronto- thalamic pathways regulating sensory transmission through thalamic relay nuclei, to nucleus reticularis thalami from basal forebrain nuclei. More recently, Bak et al, (2011) conducted a combined EEG and fMRI study to locate sensory gating sources in healthy adults. Using EEG data analysed using dipole modelling, they identified areas active during sensory gating that included the medial frontal gyrus, the insula, the hippocampus, and primary somatosensory cortex. These sources then corresponded to significant fMRI clusters located in the medial frontal gyrus, the insula, the claustrum, and the hippocampus (Bak et al., 2011).

3.1.3 Neural oscillatory patterns during P50 ASG

Rhythmic activity referred to as neural oscillations (Cohen, 2014) can be described by frequency, power and/or phase; power refers to amount of energy in each frequency band and phase can be described as position along a sine wave at any given point. As discussed in Chapter 1, the phase alignment model for ERP responses suggest that neuronal assemblies have the capacity to oscillate at

different frequencies when responding to sensory information; this shift in oscillations generate ERP response (partially). Although oscillations have been studied widely from a long time, it has only recently been applied to ERP data. There is mounting evidence to suggest that sensory processing is strongly dependant on cortical oscillatory activity (Fiser et al., 2004; Jansen & Brandt, 1991; Kisley & Gerstein, 1994).

A recent hypothesis known as “oscillatory hierarchy hypothesis” (Lakatos et al., 2005) suggests that the phase of lower oscillations modulate the amplitude of oscillations in the higher frequency band. This hypothesis was tested in four Macaque monkeys (Macaca Mulatta) measuring spontaneous as well as stimulus driven activity in the primary auditory cortex. Findings indicated that excitability of cortical neuronal assemblies during stimulus presentation was strictly dependent on the phase of spontaneous oscillations. This finding has been corroborated in further animal studies suggests that in rodent hippocampus (Buzsaki et al., 2003) and entorhinal cortex (Cunningham et al., 2003), gamma oscillation amplitude is dependent on theta oscillatory phase. Yet it is unclear if hierarchy of on-going oscillations is preserved during stimulus driven activity or not. There is no evidence yet to infer the geometry of neural circuitry of these on-going or stimulus-driven oscillations.

To understand neural oscillatory patterns, fMRI studies were designed and performed along with MEG/EEG to identify any association between BOLD fMRI response and oscillatory power observed primarily in visual tasks (Singh, 2012). BOLD fMRI response positively correlates with local field potentials power in the gamma (>30Hz) frequency range and negatively with alpha/beta frequency power. common studies using sensorimotor stimuli (Gaetz and Cheyne, 2003; Stevenson et al., 2011), visual motion perception, reading (Pammer et al., 2004), object perception (Maratos et al., 2000) and semantic processing (McNab et al., 2007). This notion about alpha-beta desynchronization and gamma synchronization is common to fMRI studies mainly visual and somatosensory. These findings are yet to be tested in the auditory domain using non- invasive techniques as these can assist in understanding the inhibitory process of P50 ASG. Below are some studies which have investigated neural oscillatory pattern during P50 ASG. Nonetheless these are yet inconclusive.

Hong et al (2008) evaluated rhythmic modulatory process of sensory input to examine underlying oscillatory processes. It was found that gating of auditory evoked oscillatory responses occur primarily at theta- beta frequency. On the other hand, it was also identified that gating of the theta (4-7 Hz) and alpha (8-12Hz) is heritable and predisposed for schizophrenia. The relationship between neural

oscillations and sensory gating is not yet clear. A recent study by Hall et al (2011), analysed the distribution of gamma and beta event related oscillations in response to conditioning and testing click stimuli. It was suggested that the components of information processing assessed by gamma (30-100 Hz) and beta (12-30 Hz) gating seem to be independent from those mediated by P50 suppression. Unlike, Hong et al (2008), Hall et al (2011), suggest that impaired event related oscillations are associated with Schizophrenia but are not related to genetic liability for the illness.

It is thus essential to understand how oscillatory pattern alters during S1 and S2 response. In this study, focus is laid upon understanding oscillatory changes in sensor as well as source space, as there are no studies to date reporting oscillatory modulation in source space during P50 ASG.

3.1.4 Aim

The overall aim of this study was to calculate gating suppression and localize cortical sources involved during P50 ASG process, and to investigate neural oscillatory patterns within those sources.

3.2 Methodology

3.2.1 Participants

Twenty-seven healthy adults in the age group 18-59 years were recruited for this study. For recruitment details refer to Chapter 2. Six participants who were recorded were excluded from further analysis due to noise contamination in their data. Three participants from the remaining twenty-one did not have an MRI scan due to safety concerns; their MEG data was included in the study and the Colin 27 MNI template was used (Tadell et al.,2011).

3.2.2 Auditory Stimulus

A double-click paradigm with the features as described in the Figure 3.1 was used for this study.

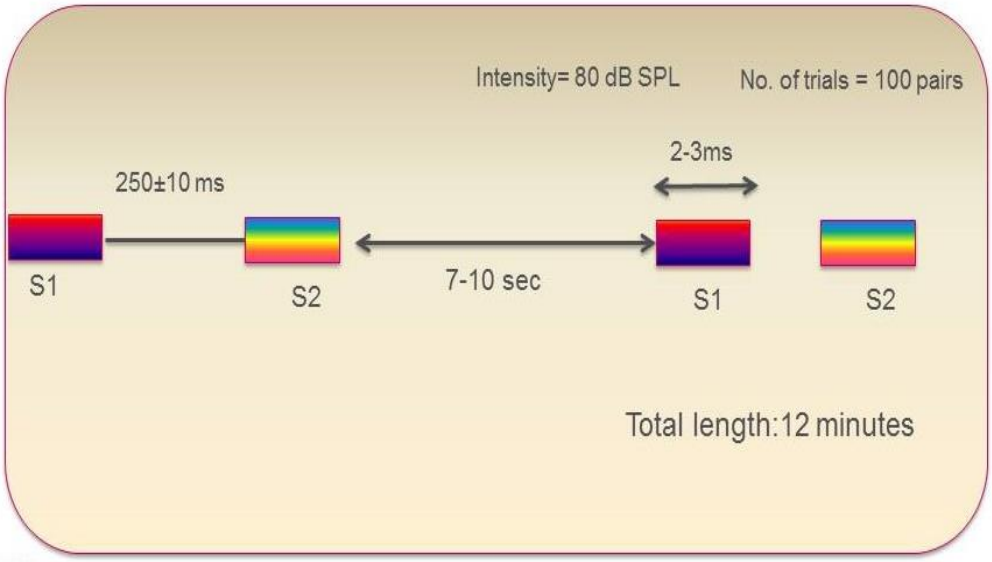


Figure 3.1 Auditory stimulus design. S1 and S2 represent 3 ms duration square-wave clicks.

3.2.3 MEG data collection and procedure

Data for this study was collected on the Elekta Neuromag® Triux™ system. Participants were screened and consent form was signed after carefully screening for metals. A Polhemus Isotrack system was used to obrain the participants' head shape, the 3D location of scalp fiducials and of 5 position coils. Participants were seated in the scanner in the upright supine position. While the participant waited for further instructions from the researcher, they watched a silent video. Channels were inspected for noise and trapped flux and recordings were started when these had been minimised. Once satisfied with the quality of the signal, instructions were given to the participant through the intercom to inform them about the initiation of stimulus after measuring head position. For all recording sessions, data was collected at sample rate of 1000 Hz. To ensure auditory evoked response was present, an on-line average was set up which was used for the purpose of viewing only.

3.2.4 Data Analysis

For this study, the data was stored in raw .fif file (approximately 1GB per recording) and was post-processed (tSSS) using the MaxFilter 2 Elekta software. This process was discussed in detail in Chapter 2. Following this, Maxfiltered data file was pre-processed in both brainstorm and SPM12. The details below explain the pre-

processing and analysis in Brainstorm followed by analysis in SPM 12. The purpose behind Brainstorm analysis was to process the Maxfiltered file, and extract the average P50 response from epoched trials and identify its peak latency in each participant. Cortical sources at that peak latency were then computed on individual MRI following segmentation of anatomical images and creation of the head model in the Brainsuite software platform. This allowed the computation of sources of the P50 response in each participant in their individual MRI space. Time frequency analysis was then performed on those extracted sources to determine neural oscillatory pattern associated with P50 response and its suppression during second condition. Steps performed to achieve this output are described below in detail.

3.2.4.1 Anatomical data

Brainstorm provides few options to extract cortical information from the MRI including Freesurfer, Brainsuite or use of Brainstorm itself. However, prior to cortical extraction it is essential to create a NiFti file (represents a simple, compact image format highly used for scientific analysis of brain images) for the T1 weighted MRI of the participant. This task was achieved using MRIcron (Rorden, 2007), software used to convert Dicom images (176 files) of MRI into a NIfTI file format. Once NIfTI file was created for each participant, it was further processed in Brainsuite (Magnetic Resonance Image Analysis Tools) to extract cortical information.

In Brainsuite individual models of brain structures are produced based on T1 weighted MRI of the head using different MRI analysis sequences. These steps can be performed as a batch or individually. The first step of skull striping was performed separately for each individual to ensure that there were no extra regions remained. Since every participant has different head shape it is important not to use only default diffusion constant and edge constant as these can be altered depending on the results from skull stripping. For smaller heads, these parameters were changed from default value to confirm correct skull stripping. The procedure followed thereafter is presented below as a flowchart process.

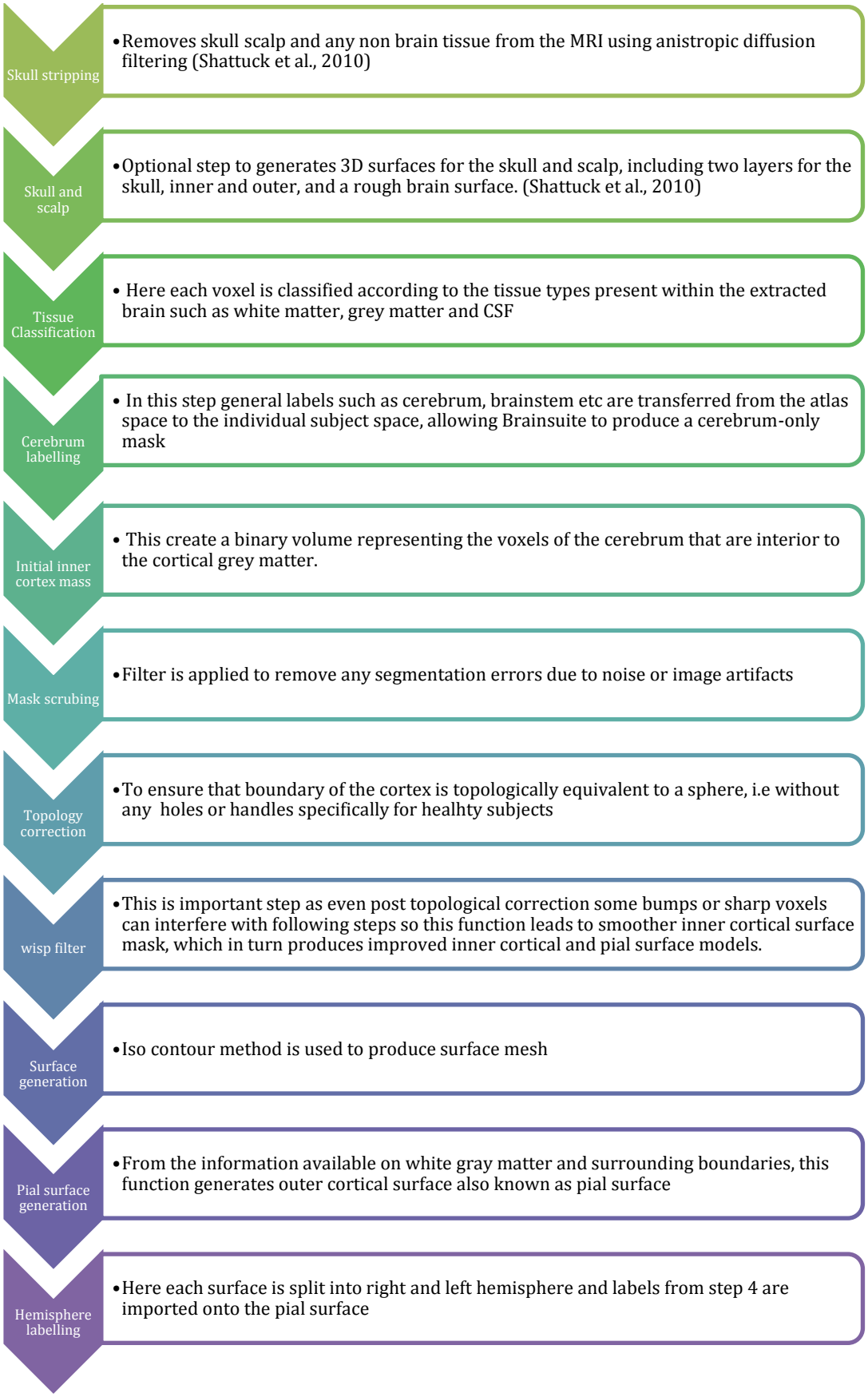


Figure 3.2 Flowchart of cortical extraction steps in BrainSuite.

The next step involved surface and volume registration, where brain segmentation and surface extraction methods were applied to create label volumes and align subject model to atlas surface model. Each individual has a different head shape and size, in order to align each subject to atlas model it was essential to perform volume registration. A brief summary of the procedures involved is presented below in flowchart diagram Figure 3.3.

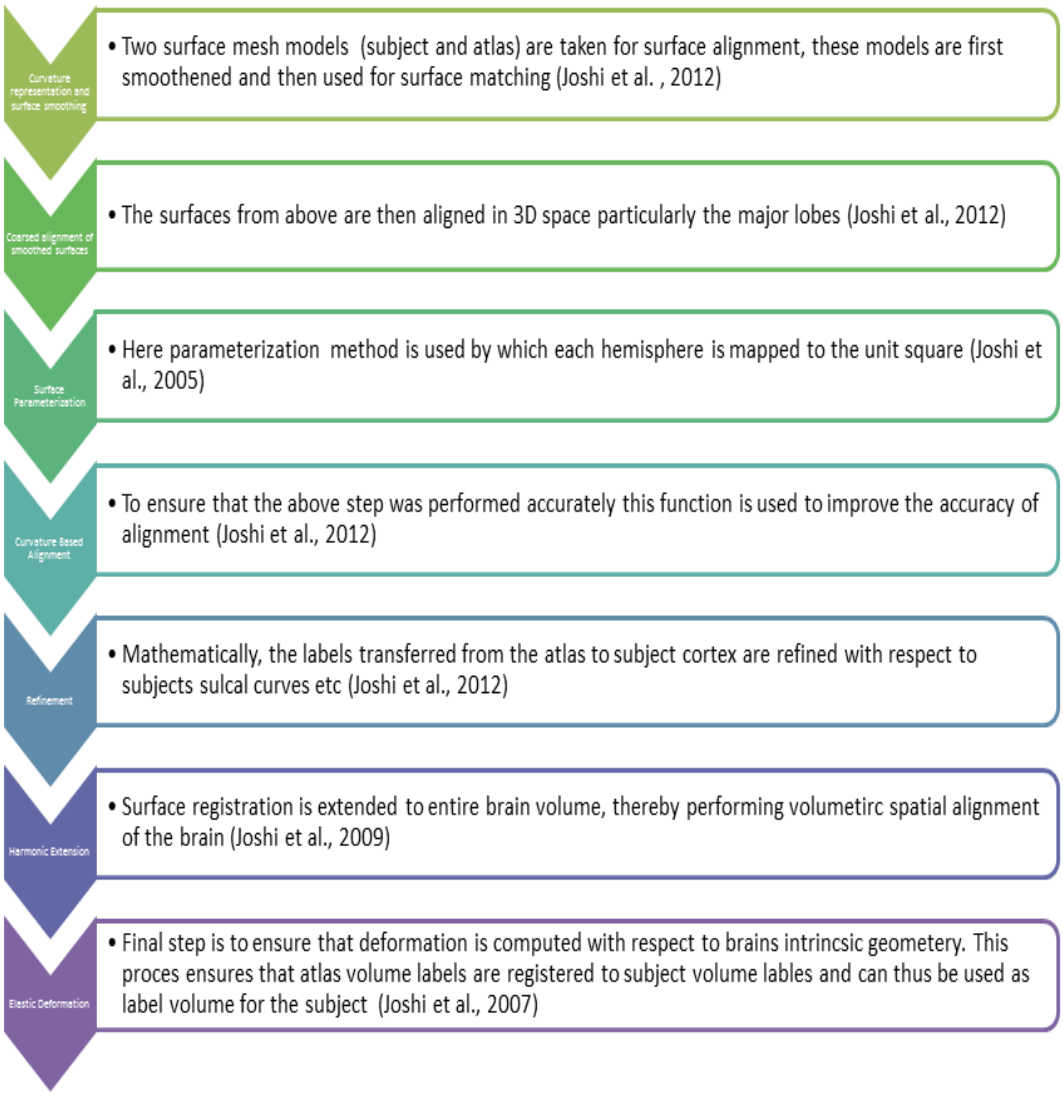


Figure 3.3 Represents surface and volume registration steps following steps in Figure 3.2

The output from BrainSuite was exported into Brainstorm where three points were chosen to define the Subject Coordinate System (SCS): Nasion (NAS), Left pre-auricular point (LPA), Right pre-auricular point (RPA). Other three were selected

to define the Normalized coordinate system (NCS): Anterior commissure (AC), Posterior commissure (PC), and any Interhemispheric point (IH). Once this task was performed and checked, the MRI and other cortical surface files for each individual were ready to be used in conjunction with their functional data. Volume registration was performed on each individuals' MRI due to variability in head shape and size.

3.2.4.2 Functional Data

A brief summary of the analysis pipeline as discussed later (in section 3.2.4.2, 3.2.4.3, 3.2.4.4 & 3.2.4.5), is presented in flowchart diagram Figure 3.4.

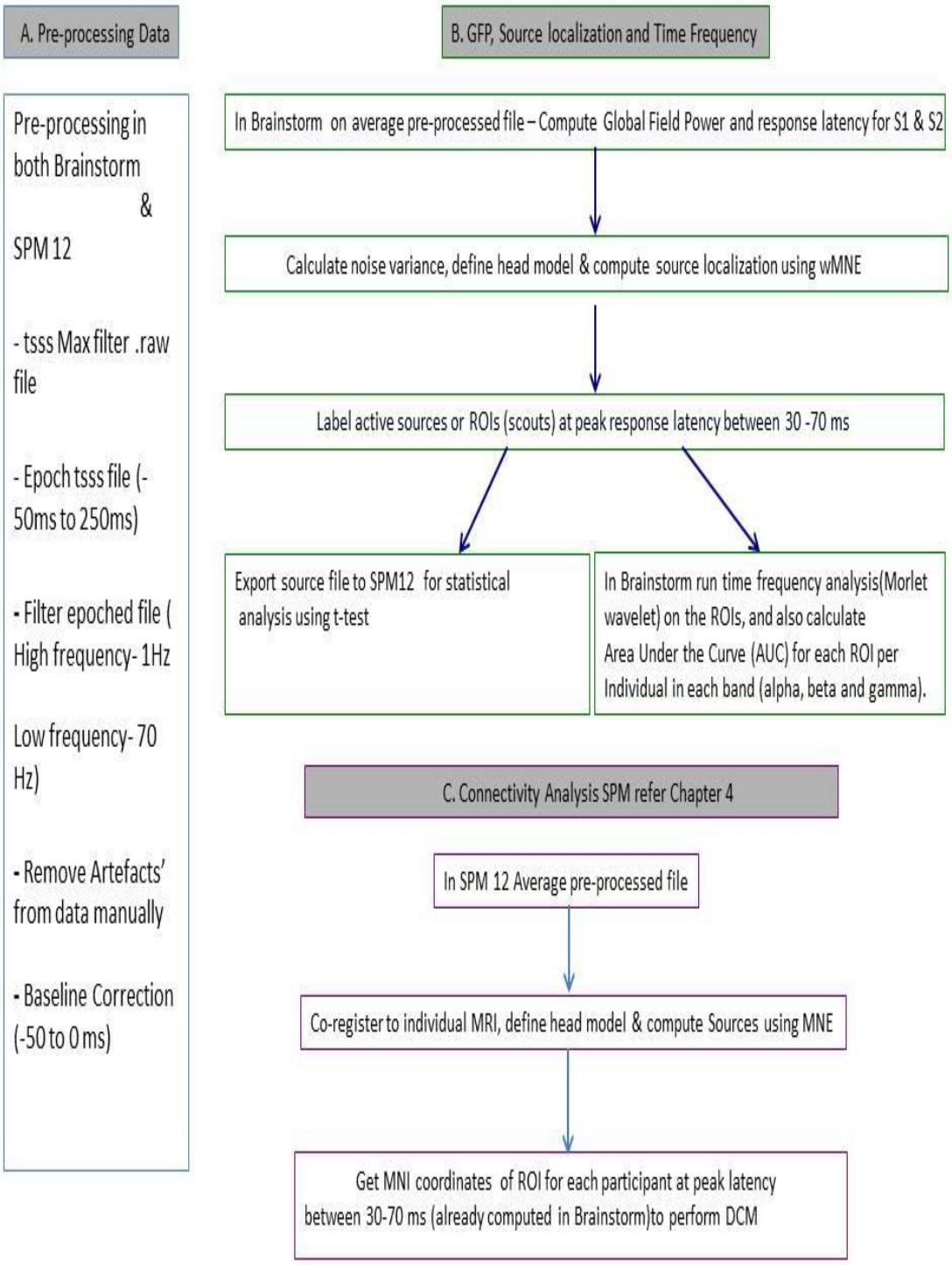


Figure 3.4 Flowchart displaying analysis pipeline in Brainstorm & SPM12.

Pre-processing

The ‘tSSS’ Maxfiltered raw file was imported as functional data in Brainstorm. Two stimulus triggers were chosen, and epoch length was defined prior to importing the file. The two stimulus channels were STI001 and STI002 for condition S1 and S2 respectively. The epoch length was -50 to 250 ms for each condition. This epoch length was chosen to avoid any overlap between first and second click, particularly considering late ERP responses.

This data was then filtered using a FIR filter (filter whose impulse response is of finite duration) with low-pass of 70 Hz and high-pass of 1 Hz. These filter settings were chosen carefully after considering present literature on P50 ASG (Patterson et al., 2008) as mentioned above in the introduction. After the data file was filtered, each trial was manually checked to remove any major artefacts such as eye blinks, MCG or muscular artefacts. After artefact removal, we ensured that each subject had same number of trials for each condition. The original recordings had 100 trials, but after pre-processing an average of 80 trials for each condition were kept. Baseline correction was applied in the -50 to 0 ms time window. Subsequently an average was computed for each condition for all 80 trials for each subject. This average was arithmetic mean of the group of trials per condition.

Head model

For MEG data source localisation, the overlapping spheres model was chosen as it gives better results than the single sphere model. Overlapping sphere produces more focal results, when compared to other head models (Tadel et al., 2011). The overlapping spheres method is based on the estimation of a different sphere for each sensor. Instead of using only one sphere for the whole head, it estimates a sphere that fits locally the shape of the head in the surroundings of each sensor.

Noise covariance

This step is a requirement prior to source reconstruction; it estimates noise level in the recording by providing a diagonal matrix (one value per channel in time domain) or full matrix. It identifies the noise of all the sensors which makes it easier to remove any sensors with excess noise and to quickly check the quality of the recordings. For this study diagonal matrix was chosen as suggested in the manual and it is easier to identify noisy channels as compared to the whole matrix (Tadel et al., 2011).

Source Estimation

The Weighted Minimum Norm Estimation (wMNE) method was applied on the head model to localise cortical sources at peak latency for each individual as mentioned earlier. According to wMNE, at each vertex of the cortical surface there is only one dipole. A brief overview of this method was provided above in the introduction section, as suggested previously, wMNE is a quick efficient way to compute and display (Tadel et al., 2011). Since it produces one value per vertex, it can be represented well on cortical map. Here a region of interest was chosen during time window 30-70 ms based on previous literature (Picton et al., 1974; Korzyukov et al., 2007 &Wang et al., 2014). An approximation of peak latency of P50 response in each individual from the average response was also considered while defining the time window of interest, the first most positive peak in time window 30-70 ms referred to as P50 response of the individual.

In Brainstorm region of interest is referred to as a scout: which is a subset of vertices of chosen surface. Each scout was about 5mm in size and was named individually.

Time frequency decomposition

To capture oscillatory components in time series, complex Morlet wavelets were applied to the continuous signal and the analysis was conducted in the frequency band 8-90 Hz. These wavelets have the shape of a sinusoid, weighted by a Gaussian kernel, and were therefore used for time frequency decomposition. This technique was applied at both sensor and source level (on scouts) as discussed in section 3.2.4.3 and 3.2.4.4.

3.2.4.3 Analysis Pipeline for SPM 12

The objective of investigating data in SPM 12 was to identify if there were significant differences between conditioning and testing condition. Since SPM has a robust way to run statistical tests to identify any such differences at sensor as well as source level, data was analysed with the standard parameters. The pre-processing steps were similar to those in Brainstorm. Epoch length, filter and baseline correction were exactly same as those uses in the Brainstorm processing, with the only difference in the detection of artefacts for which the SPM has built in visual artefact rejection function. This was used to identify any major artefacts, but the trials were visually observed and to maintain consistency between the two analysis pipelines, the same trials were rejected for both brainstorm and SPM. Single trials (80 per condition) were averaged within conditions. Head model was prepared for the average file using individual head meshes describing the boundaries of different head compartments based on the subject's structural scan which was already accessible (imported as Dicom file).

In order for SPM to provide a meaningful interpretation of the results of source reconstruction, it should link the coordinate system in which sensor positions are originally represented to the coordinate system of a structural MRI image (MNI coordinates). This was achieved by applying a forward model and inverse solution reconstruction following co-registration of individual's MEG data with their MRI.

Forward model in SPM - this refers to computing for each of the dipoles on the cortical mesh the effect it would have on the sensors, single shell head model was chosen for this MEG study as recommended by Ashburner et al., 2014. In contrast to recommended multiple spheres for Brainstorm.

Inverse Solution- for reconstruction based on an empirical Bayesian approach to localize the evoked response, inverse reconstruction was performed on the pre-processed (averaged) data set of each individual was chosen. Minimum Norm Solution (IID) was applied to compute inverse solution as same method was applied to Brainstorm dataset.

Analysis was performed in both sensor and source space to ensure consistency in findings, and to confirm reliability of sensor space analysis relative to source space. This strategy was chosen as some studies report only sensor based data while others report only on source space results. In this thesis, the aim was to perform and report findings from both sensors as well as source space.

3.2.4.4 Analysis in sensor space

Within subject

Peak amplitude and latency for conditioning and test conditions for each participant was calculated from the average file of each participant after calculating the Global Field Power (GFP). A GFP script was written in Matlab, to compute the time course of the GFP in the time window between 30 and 70 ms for S1 and S2 conditions. The sensory gating ratio (S2/S1) was calculated by dividing the amplitude of the response to the S2 by the amplitude of that obtained for the S1 condition.

Statistical analysis was performed on the image data in SPM to evaluate any within subject differences at sensor level. The epoched file for each participant was converted into 2D scalp time image (scalp map where 2D MEG sensors are projected on to a flat surface) and a statistical two-sample t-test was performed on each participant's images for both S1 and S2 in the time window -50 to 250 ms. Within subject analysis was performed for each participant. To examine any difference between two conditions T contrast (S1 –S2) and (S2-S1) was applied which computes difference in one condition relative to the other. (Mathematically, T contrast can be defined as T= contrast of estimated parameters/ $\sqrt{}$variance estimate) These revealed regions within the 2D sensor space and within time window -50ms to 250ms where, S1 and S2 trials differ significantly, having corrected for multiple t-tests across pixels and time. For each subject the MEG channel (sensor) with highest signal strength in the associated time window was chosen during the above mentioned two sample t-test on images. This channel is referred to as the supra-threshold channel as it shows the greatest S1/S2 difference over the epoch (-50 to 250 ms) (see Table 3.1).

Between subjects

Data distribution was inspected for normality for S1 and S2 conditions in SPSS using tests for normality. Paired t-test was performed to identify between-subject differences in the GFP for S1 and S2. To display between subjects differences in the two trials, the averaged file for each participant was converted to 2D scalp time image and statistical t-test was performed on it to examine statistical results for condition effects and T contrast used was same as above (S1-S2) (S2 – S1). Supra-threshold channel (channel with highest signal strength) for each contrast was chosen by using the same method as used above.

In Brainstorm, t-f analysis was performed on each supra-threshold channel for all subjects and paired t-test was performed to identify any significant differences between oscillatory pattern in S1 and S2 between subjects. The frequency bands over which data was analysed were alpha band (8-12 Hz), beta band (13-29 Hz) and gamma band (30 – 90 Hz).

3.2.4.5 Source Space Analysis

Within subjects

In Brainstorm, wMNE was computed for each participant and for each condition. The cortical sources activated at the peak latency for each individual during S1 and S2 were determined, and labelled as '*scouts' (as described in Brainstorm)* or regions of interest for each participant and were saved in their respective file. For example, Participant A, has peak latency of 58 ms for S1 as computed from GFP, displays strong activation in right STG, this area is then labelled, and saved as a region of interest (scout) for Participant A.

Since it is not possible to perform higher-level statistics in Brainstorm, the source volume map was imported into SPM 12 where statistical analysis was performed on the sources. In this process, two NiFti files were generated, each file containing 80 volumes, one per trial for each condition. This step was performed for each participant separately; however the parameters for time and volume options were kept same throughout.

Specify 2nd-level analysis in SPM using two sample t-test to compare sources of activation during S1 and S2, differences between two conditions were examined

using t contrasts (S1 –S2) and (S2 –S1) entered in SPM as (1 -1) and (-1 1) respectively for each participant (see Figure 3.8).

As mentioned earlier, there were scouts (regions of interest) labelled for each participant and each condition. These scouts were than used to compute the time-frequency maps for both conditions. Morlet wavelet transformation was used in the frequency of interest being 8Hz to 90 Hz. There were four scouts for each condition and time-frequency analysis was performed on all of those scouts, from the computed power spectrum, the area under the curve (AUC) was estimated using trapezoidal area calculation using a purpose-written script in Matlab .The AUC was integrated for three frequency bands Alpha Beta and Gamma. From total AUC (8to 90Hz), relative power in each band was computed and statistical analysis was performed to determine any differences in each frequency band for each condition within subject. This analysis was performed on the dominant hemisphere area, for example if participant x had right hemisphere as dominant then right temporal and right frontal was chosen over left hemisphere response. The dominant area for temporal and frontal was determined from scout amplitude, the scout with the highest amplitude during evoked response was considered as dominant.

Between Subjects

In Brainstorm, the individual MRI was replaced by Colin 27 MNI template, the average source file for each participant was imported into SPM 12 in a NifTi format as it was done earlier for epoched file. The same two sample t-test was performed comparing all subjects across two conditions using contrasts (S1 –S2) and (S2-S1) to observe any significant differences in two conditions across subjects.

From the source level time-frequency analysis the AUC for dominant hemisphere was considered for each participant due to variance (the source amongst left and right STG as well as left and right IFG which had highest peak amplitude relative to the other was considered as dominant; two sources per individual instead of four were considered) and paired t-test was performed in SPSS (after the data set met assumptions for this) to identify differences in Temporal region Alpha S1 vs Alpha S2 (8-12 Hz), Beta S1 vs Beta S2 (13-29Hz), Gamma S1 vs Gamma S2 (30-90Hz), and same comparison was made in Frontal region scouts.

In Brainstorm, t-f (8-90Hz) was computed on each scout for all subjects, where same scout was compared from each condition for all participants using t -test.

The t-values were obtained in Matlab and looked upon using t table for any significant differences (See Figure 3.11) Maximum value between 30 -70 ms was obtained using Matlab.

Group Analysis

Grand mean was computed in SPM 12 to determine source localisation at group level. The sources of activation were displayed on template MRI (Colin 27) see Fig.3.12. The MNI coordinates are mentioned in table 3.2.

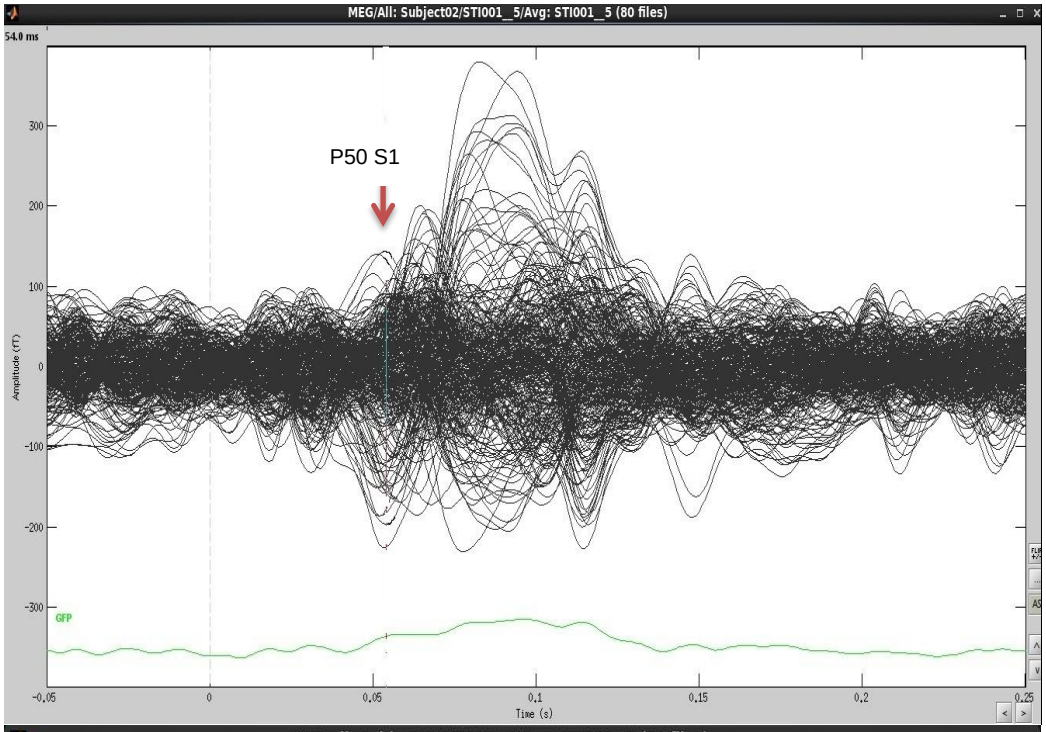
3.3 Results

3.3.1 Findings in Sensor Space

Within subject

Figure 3.5 shows average P50 response for S1 and S2 in an individual participant. The average amplitude measured using the GFP was 228.42± 83.86 for S1 and 148±57.8 for S2, which was [t (20) = 3.511, p=0.002]. The mean latency of S1 was 52± 7.8 ms and that of S2 was 52 ± 8.2 ms (n.s.).Suppression index ranged from 0.5 to 0.9 (average 0.66±0.15). The GFP during both conditions at peak latency as well as gating ratio for both conditions can be seen below in Figure 3.6 and Figure 3.7.

A.



B.

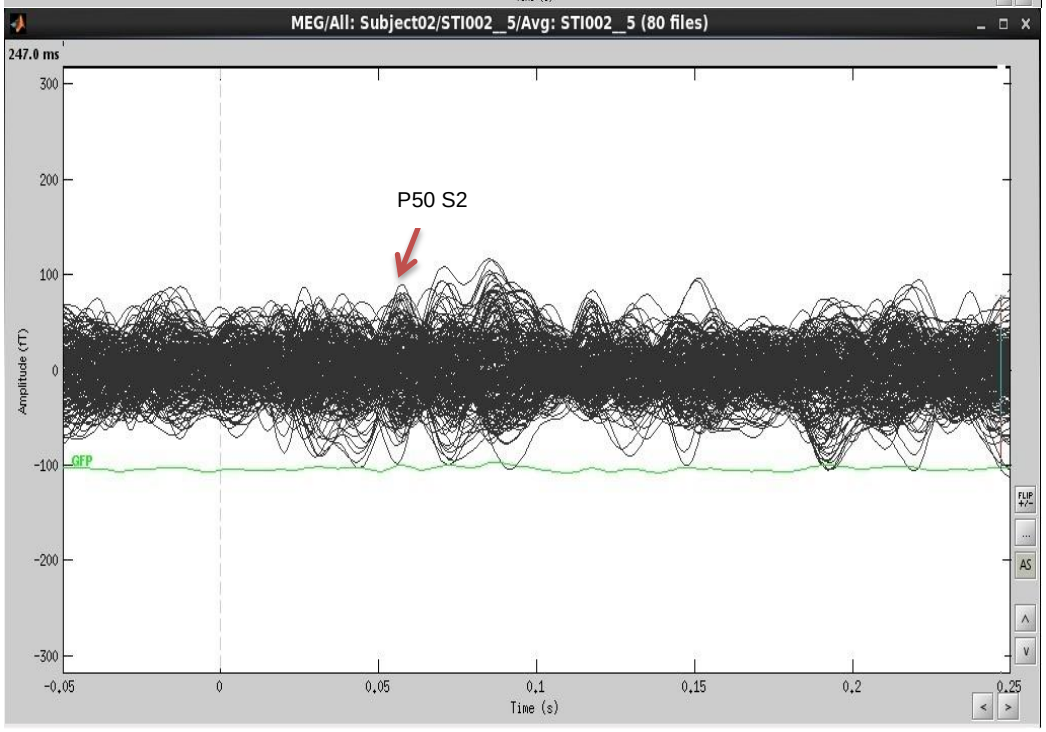


Figure 3.5 Displays average P50 response for both S1 (A.) and S2 (B.) in an individual participant. (y axis = Amplitude in femtoTesla, x axis = time in seconds; green line marked GFP represents the Global Field Power).

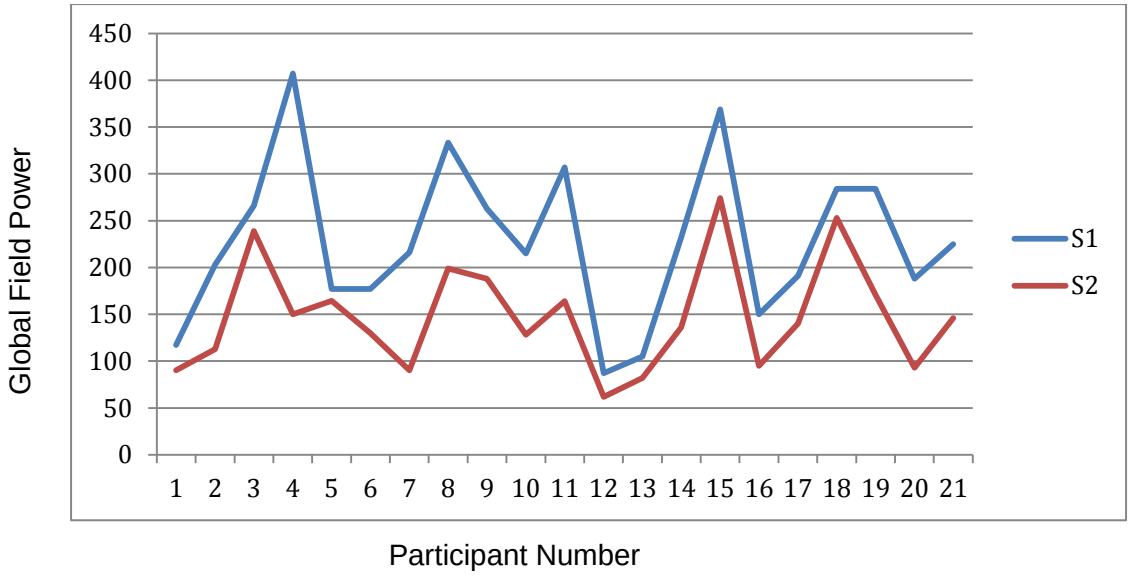


Figure 3.6 Global field power for each participant for the S1 and S2 conditions at peak latency in the time window 30-70 ms.

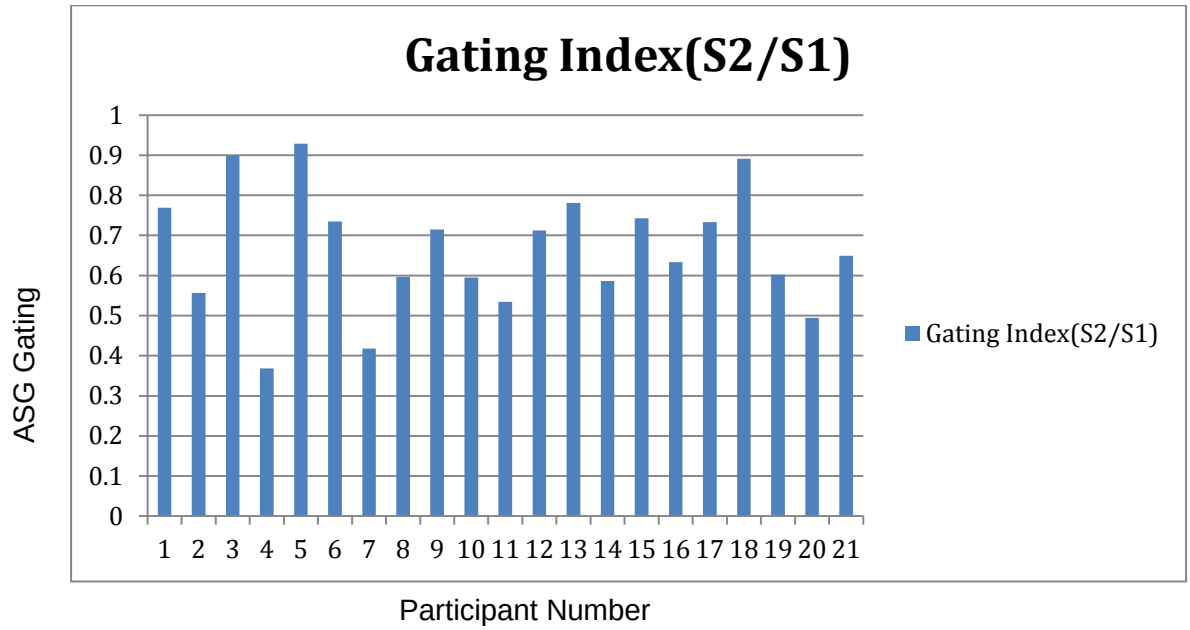


Figure 3.7 Sensory gating index computed for each participant to identify the amount of suppression during second stimulus.

A significant within subject difference between S1 and S2 was observed in t-statistics images ($p<0.05$). These findings are presented in Table 3.1.

Participant	Supra threshold channel S1-S2 (1 -1)	Supra threshold channel S2-S1 (-1 1)
01	MEG1521, t=3.58 p 0.08, 45 ms	MEG0541, t=3.48 p 0.20, 64 ms
02	MEG 1322, t=6.65 p 0.00, 63ms	MEG0132, t= 4.06 p 0.02, 52 ms
03	MEG1931, t=4.45 p 0.01, 40 ms	MEG0641, t=4.50 p 0.001, 55 ms
04	MEG2411, t=6.46 p 0.00, 61 ms	MEG0231, t=7.02 p 0.00, 49 ms
05	MEG1141, t=3.86 p 0.14, 54 ms	MEG0431, t=4.85 p 0.01, 46 ms
06	MEG2011, t=4 p=0.040, 46 ms	MEG0231, t=4.11 p 0.033, 57ms
07	No Supra threshold channel	MEG1521, t=3.52 p 0.176, 70ms
08	MEG1341, t=6.13 p 0.00, 62 ms	MEG0241, t=6.78 p 0.00, 60ms
09	MEG1922/21/0443 t=4.15 p0.015 33	MEG1231, t =3.89 p 0.036, 52 ms
10	MEG1311, t=5.46p 0.00 68ms	MEG 0531, t = 5.94 p 0.00 65ms
11	No Supra-threshold channel	No Supra-threshold channel
12	MEG1441, t=3.99 p0.040, 68ms	MEG1411, t=3.99 p0.040 54ms
13	MEG2221, t=6.14 p0.00, 50ms	MEG0431, t=6.28 p0.00 55ms
15	MEG1331,t= 7.63 p0.00, 48 ms	MEG0231, t=8.93 p0.00 49ms
16	MEG1341, t=3.46 p0.090 67 ms	MEG0231 t=3.19 p0.286, 48 ms
17	MEG1131, t= 7.02 p 0.00 56 ms	MEG 0121 t=4.53 p0.00, 63 ms
18	MEG1421, t = 3.91 p 0.04 53 ms	MEG 2221 t= 4.08 p 0.018, 57 ms
19	MEG1421, t=4.40 p0.013 53 ms	MEG2221 t=4.08 p0.018, 57 ms
20	MEG0721, t=4.06p0.038, 68ms	No Supra threshold channel
21	MEG1131, t=4.55 p0.00, 57ms	MEG1811 t=5.50 p0.00, 51 ms

Table 3.1 Supra-threshold channels identified in SPM 12 from two sample t-test on epoched image file (both conditions) for each participant. Channel number, significance level and latency of the ERP.

Between Subject

- Amplitude

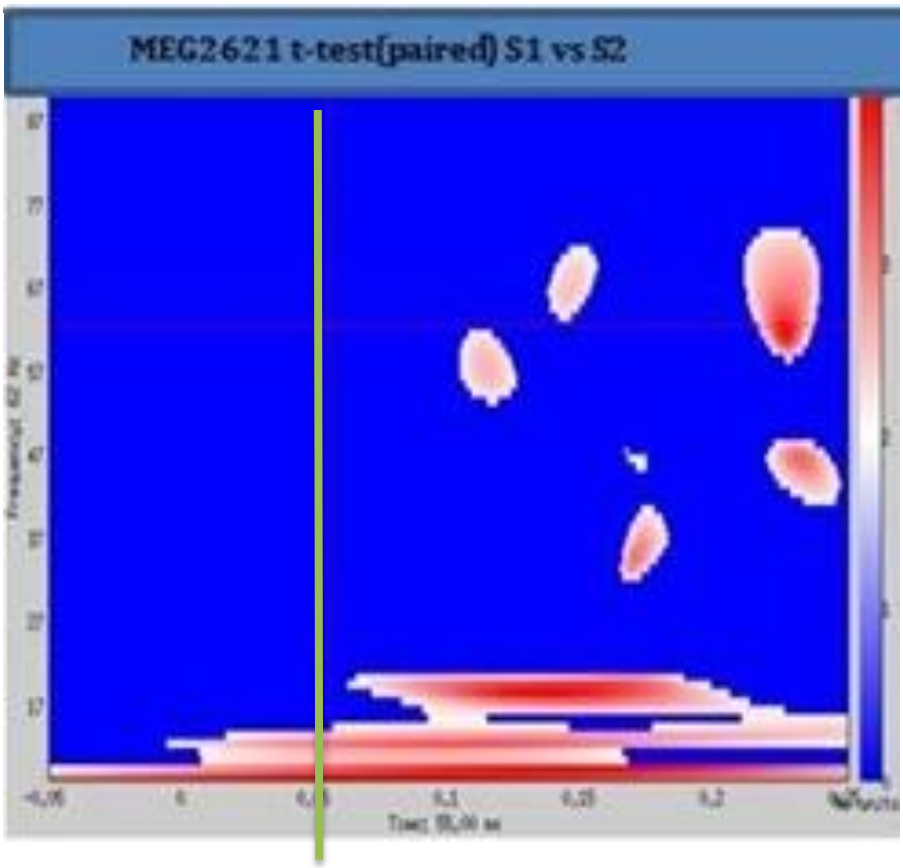
There was significant between subjects difference in GFP for S1 and S2 condition [t(1,20)=6.52, p 0.001]. In SPM 12, supra-threshold channels (those with the largest signal strength between the 2 conditions) for the S1-S2 contrast were MEG 2621 (Right Temporal) t = 5.58, p=0.004 at 68ms and MEG0511 (Left Frontal) t= 3.63, p= 0.008 at 54 ms latency for the S2-S1 contrast.

- Time-frequency analysis

In the right temporal sensor MEG 2621, power was significantly higher for S1 condition (t ≥ 2.12, p 0.05) in the 12-16 Hz and 19-21 Hz frequency bins at an average peak latency of 52 ms (shown in Figure 3.8). In this sensor we observed a power decrease (t ≥ -2.16,p 0.05) in 41-44 Hz and 71-88Hz frequency bins during S1 as compared to S2 condition in same time window. The t-values were extracted in Matlab from the data file relevant to the graphs. In Figure 3.8, alpha synchronization can be seen throughout the time window (250 ms) during S1 as compared to S2

In left frontal sensor (MEG 0511), there was a significant decrease in 8-12Hz which can be seen in Figure 3.8 B. and decrease at18-19 Hz during S2 condition as compared to S1 and at 65Hz there was significant increase in power during S2 which can be seen as gamma burst around 58 ms in Figure 3.8 B. (for any value t ≥2.12, p≤ 0.05 indicated significant differences depending on sign of the t-value(+/-).

A.



B.

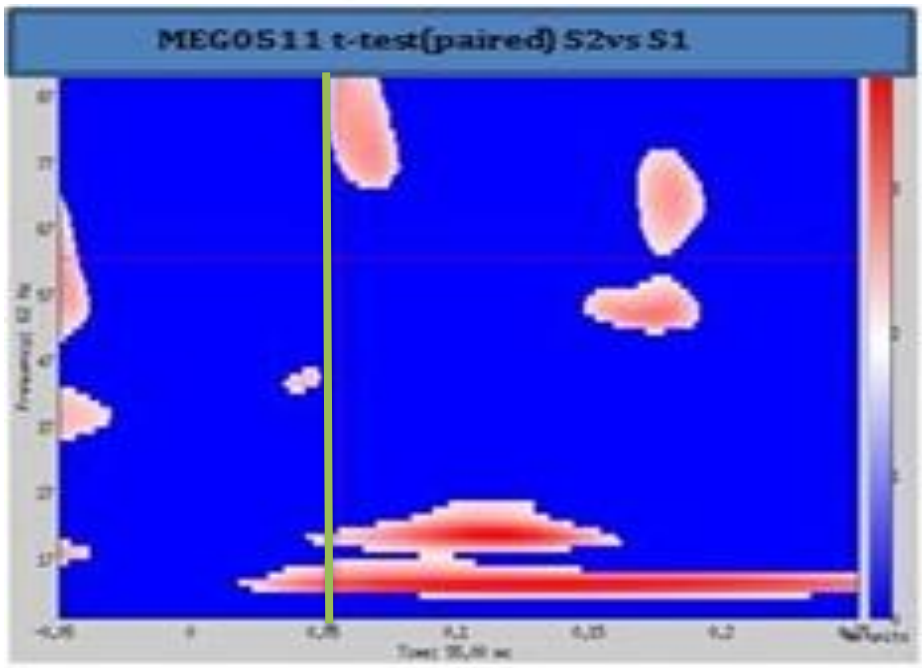


Figure 3.8 Time frequency plot for A. MEG2621 temporal channel, and B. MEG0511 frontal channel. This map was computed as result of t-test performed on this channel for both S1 and S2 between all subjects. (green line in the graph represents 50 ms, y axis= frequency 8- 90 Hz, x axis = time in seconds; *the colour bar on the right side of the graph represents t-values, with red indicating frequency bin and time point with higher t-value however increase or decrease was reflected by positive or negative sign of t value which was extracted from t-test output file using Matlab).*

3.3.2 Findings in Source Space

Within Subject

- Source Localisation

At peak latency four regions: Bilateral Superior Temporal Gyrus and Bilateral Inferior Frontal Gyrus displayed strongest activation. The results can be seen in Figure 3.9 in an individual participant.

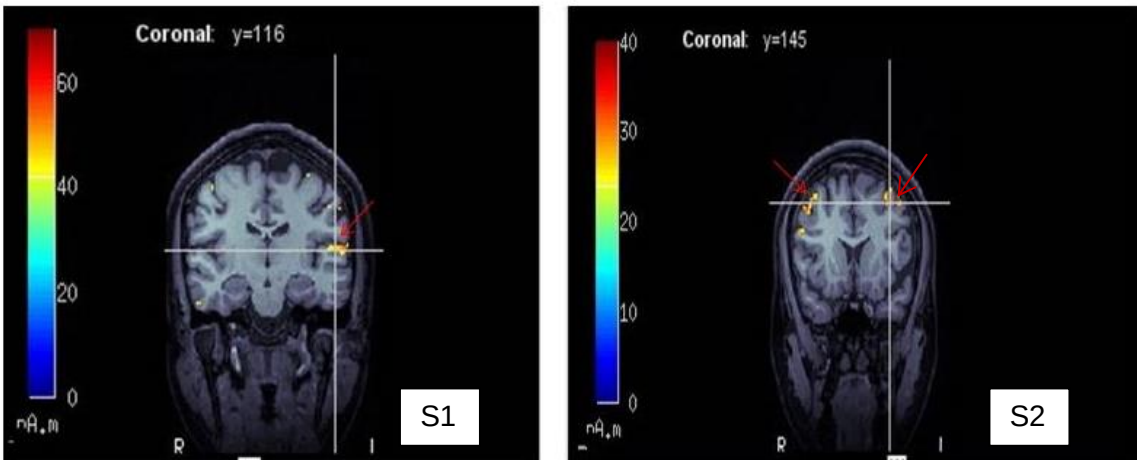


Figure 3.9 wMNE (imposed on individual MRI coronal view) areas of activation in individual participant at their peak latency amplitude during S1(STG) and S2(IFG) condition (colour bar represents strength of source activation, red = strong, blue = week)

Between Subject

- Source Activation

Stronger bilateral temporal region activation was observed between subjects (on MNI template file), during S1 as compared to S2 at significance level p≤0.05, t(1, 20) = 6.58 for right superior temporal gyrus (RSTG) and t(1, 20)=6.09 for left superior temporal gyrus (LSTG).

Differences observed during contrast S2-S1, suggested strong activation in Frontal Region during S2 as compared to S1 condition[t (1,20)= 5.09 for Right frontal gyrus, and t (1,20)= 4.95 for Left frontal gyrus].

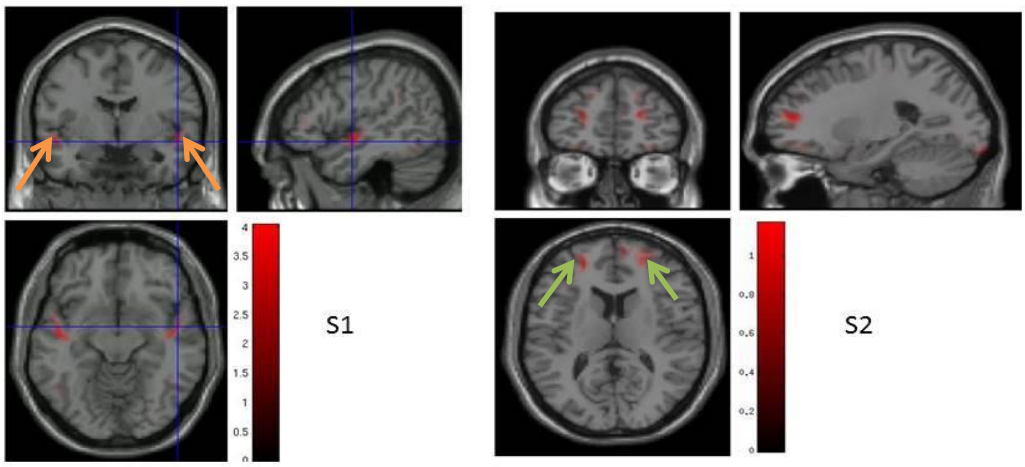


Figure 3.10 Shows source activation across participants during S1 and S2 (STG during S1 represented with orange arrows; IFG during S2 represented with green arrows (color bar represents strength of source acitvation)

Group Analysis

- Source localisation

From the grand mean average the sources active during ASG time window during S1 and S2 were Bilateral Superior Temporal Gyrus, Bilateral Inferior Frontal Gyrus. Along with this, strong activation was seen in para-hippocampal gyrus (PHG) Table 3.2 and Figure 3.12.

MNI coordinates for S1	**Region**	**MNI coordinates for S2**	**Region**
47 -31 17	RSTG	51 -46 14	RSTG
-48 -30 11	LSTG	-52 -41 11	LSTG
23 8 -16	RIFG	45 28 -16	RIFG
-25 8 -18	LIFG	-46 28 -13	LIFG
-30 10 -17	LPHG	NA	NA

Table 3.2 Represents MNI co-ordinates of sources active during S1 and S2 condition on grand mean average.

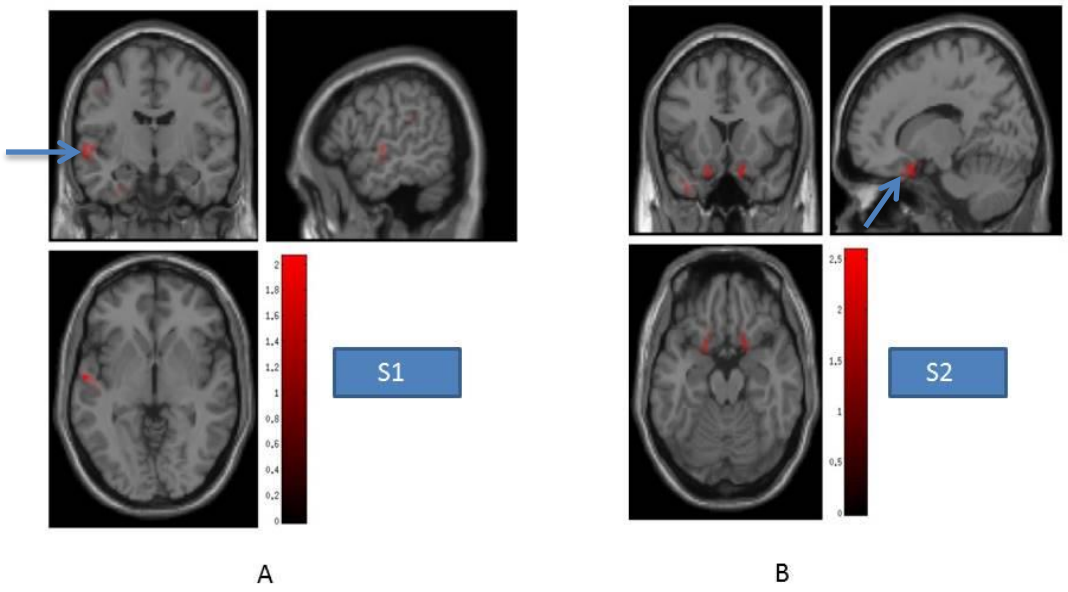


Figure 3.11 Shows source activation during S1 (A) and S2 (B) (represented with arrows). Stronger activation in temporal region for S1 can be seen (red area) whereas activation is stronger in frontal region for S2.

Between Subject

- Time frequency (applying AUC in source space)

Higher power in 8-12 Hz frequency band was observed for the S1 condition as compared to S2 in the Superior Temporal Gyrus of the dominant hemisphere ($t=3.159$, $p <0.05$).

Power in the inferior frontal gyrus in beta band (13-29 Hz) was greater in response to the first click as compared to second click ($t = 2.334$). However, power was reduced in 30-90 Hz gamma frequency band in IFG during S1 as compared to S2 ($t = -2.37$).

Average AUC for all participants in each frequency band can be seen below in the pie chart diagram. This average AUC was calculated by considering measures of the dominant hemisphere for each individual.

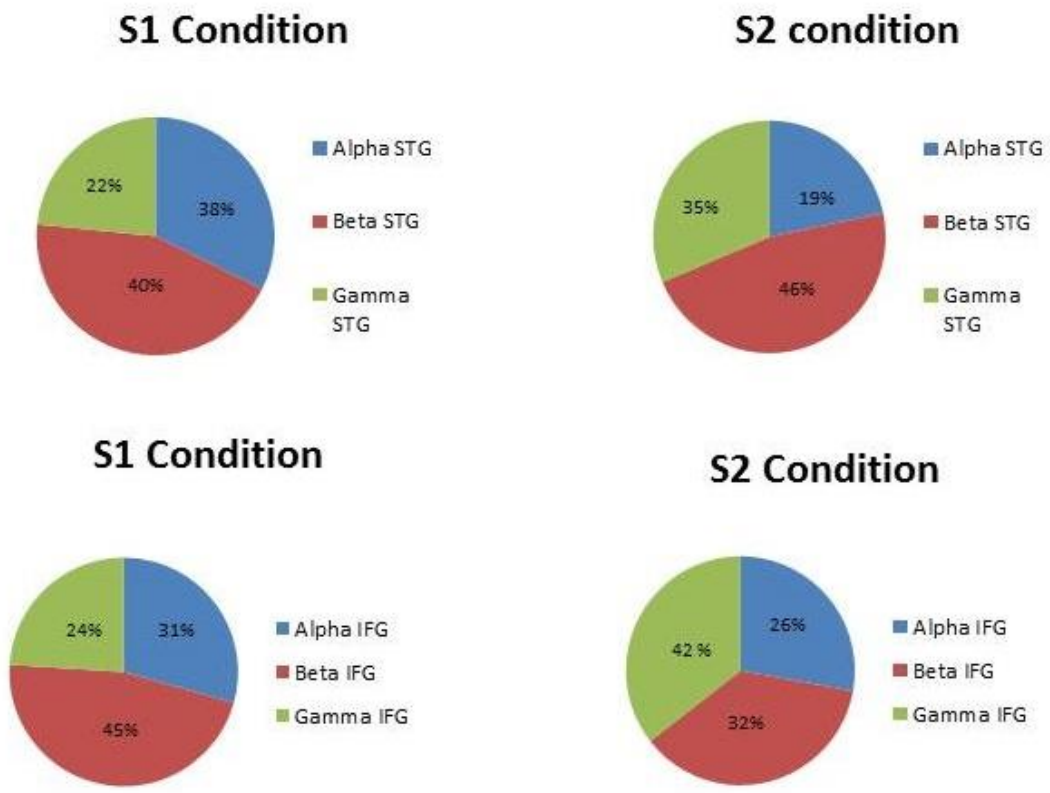


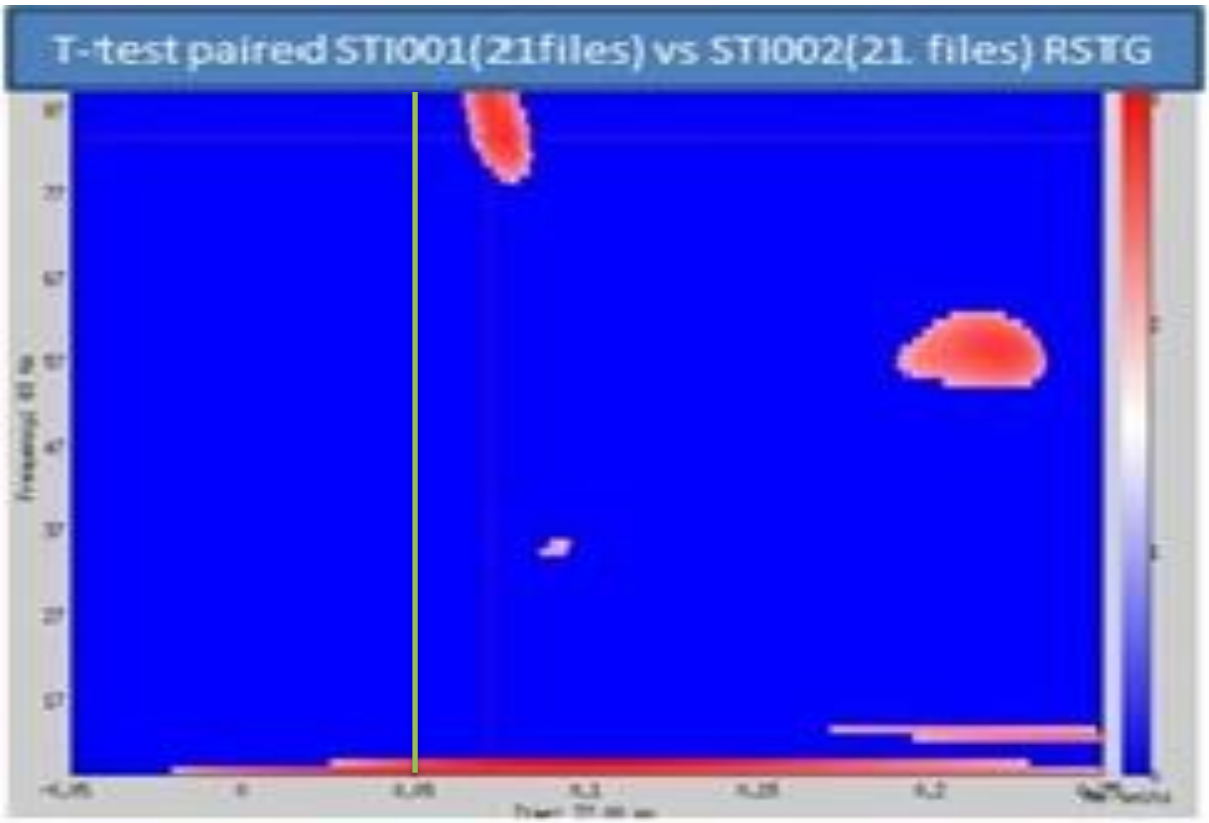
Figure 3.12 Represents average AUC for all participants in dominant temporal (STG) and frontal scout(IFG) (region of interest) in each frequency band (8-12 Hz alpha; 13-29Hz beta & 30-90Hz gamma) during S1 and S2.

- Time Frequency (direct measure on scouts)

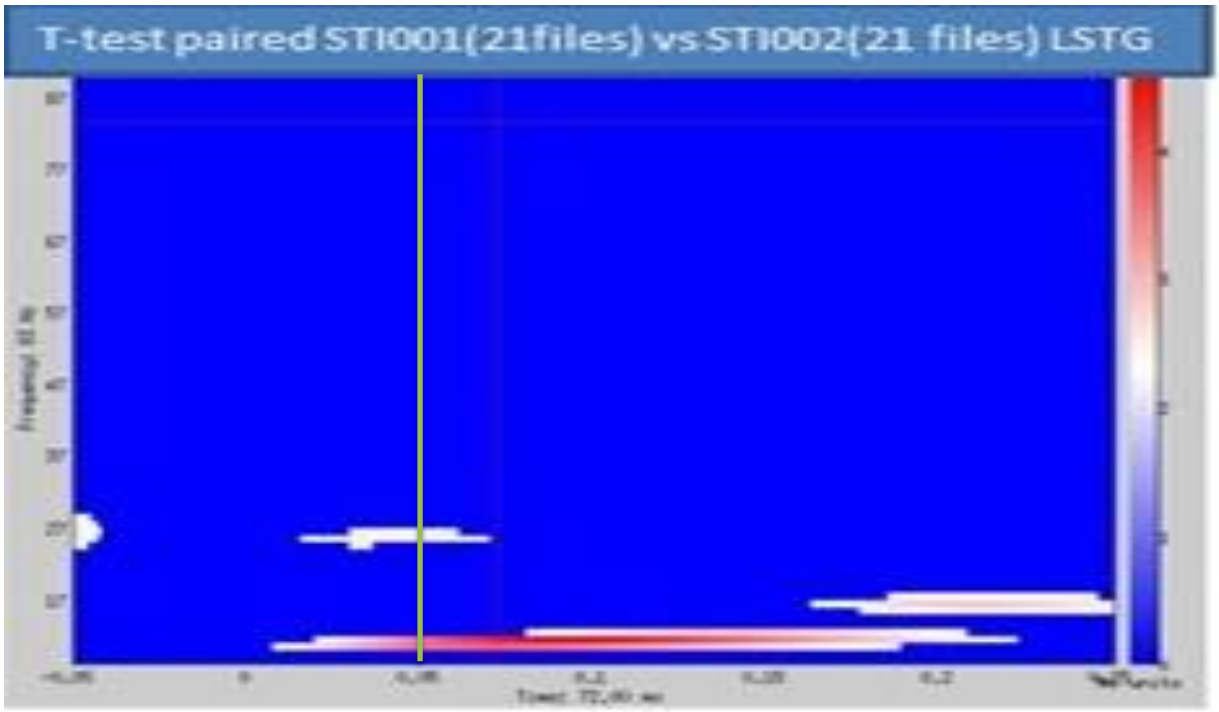
As compared to previous results these are not performed on dominant hemisphere; t-f was measured on all four scouts. For these results any t value higher than 1.73 was significant at p≤0.05. Higher power at 8Hz, 9Hz,30 -35 Hz and 79-90 Hz (S1> S2 at 8 Hz, 9 Hz, 30-35 Hz and 79-90Hz) in RSTG was observed. In LTSG, higher power at 10 Hz ,11 Hz and 24-27Hz was seen during S1 as compared to S2.

In RIFG, significantly higher power was observed in 12-15Hz and 17-19 Hz during S1 as compared to S2. In LIFG, higher power was observed in 13-15 Hz and 17-28 Hz during S1 compared to S2. However, between 51-52 Hz and 56-60 Hz power was significantly higher during S1 as compared to S2.

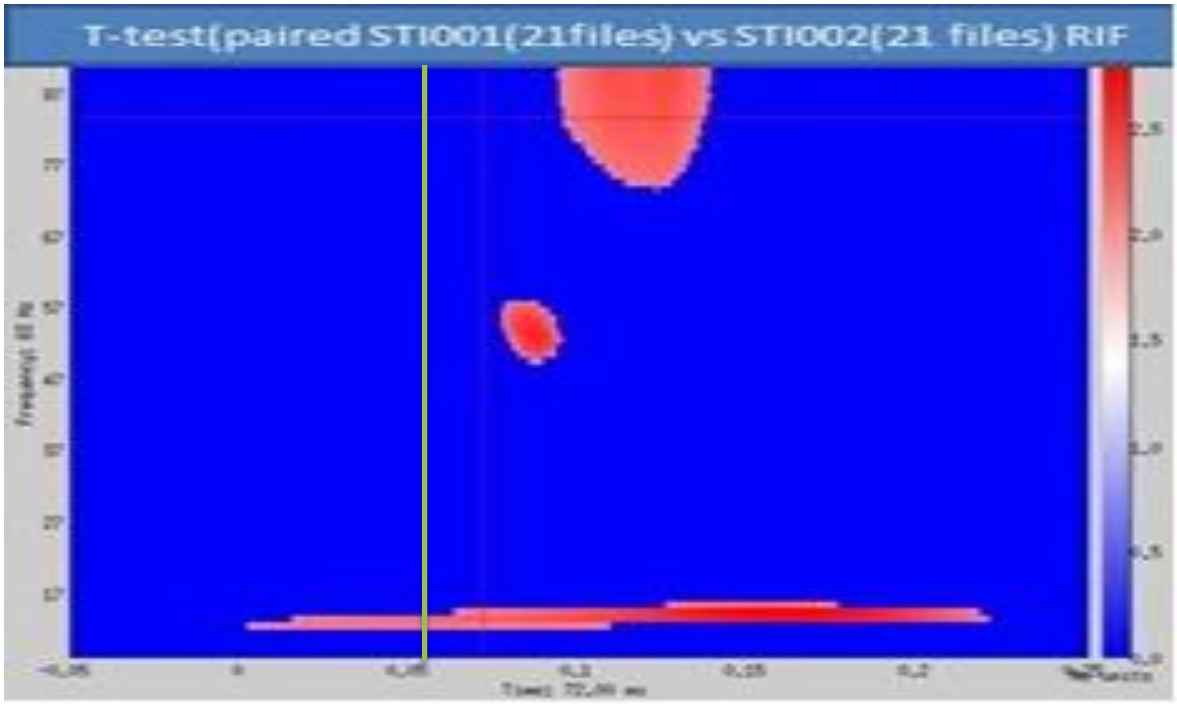
A.



B.



C.



D.

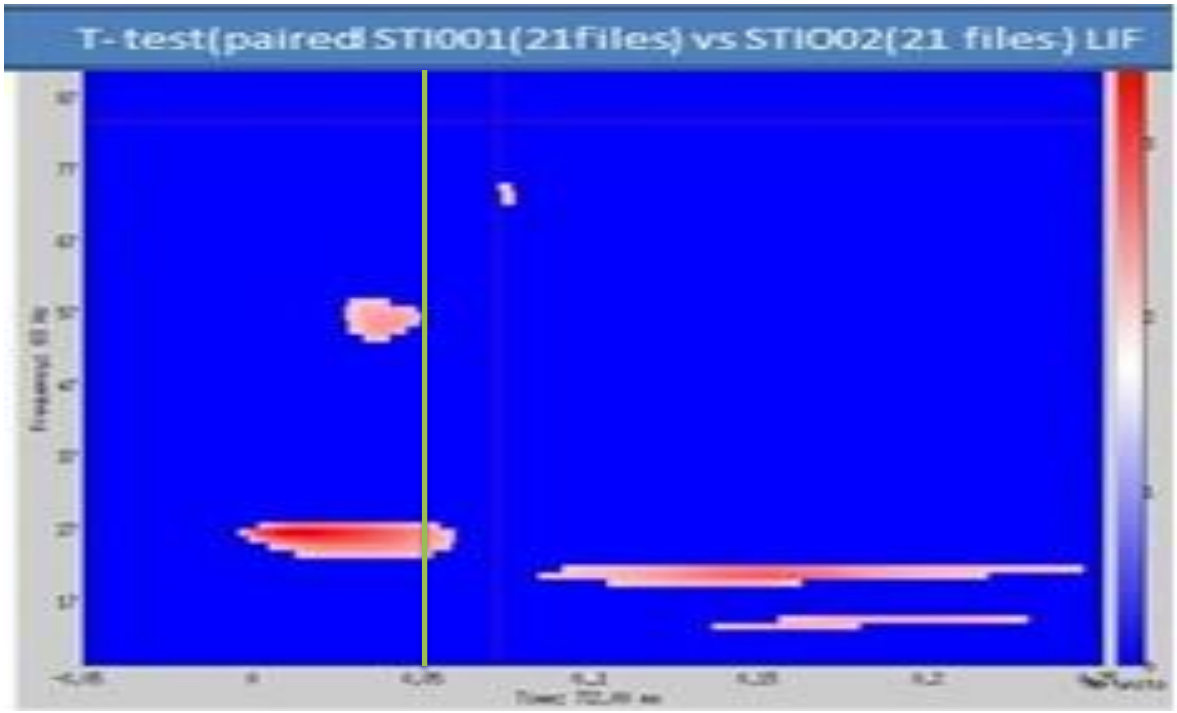


Figure 3.13 Paired t-test output between 18 subjects for each scout A. RSTG, B. LSTG, C. RIFG, and D. LIFG. (where green line on the graph represents point at time 50 ms, y axis = frequency 8-90 Hz(displayed from 0-17-27-37-47-57-67-77-87 Hz), x axis = time in seconds, colour bar on the right side of each graph represents the t-value at any given time point and frequency bin, where red represents higher t-value, these t-values were extracted from the output file using Matlab approximate range of t values = 0 to 4).

3.4 Discussion

The aim of this study was to characterise topographic, temporal and spectral properties of P50 ASG in healthy participants. The data in this study indicates that P50 ASG is a dimensional measure with significant differences in the amplitude measure of first click as compared to second click in participants. Furthermore, our data confirms that the processing of the first stimulus had a significant effect on that of the second stimulus in all recruited participants. The direction of this effect was towards an attenuation of the response to S2 with respect to S1. This finding is in line with evidence accumulated over the last decades and replicated in a recent study (Knott et al., 2014). The physiological explanation of this at systems level is still somewhat elusive, as is its relationship with subjective reports from individuals at perceptual level and with personality profiles.

3.4.1 Source localisation

Our findings confirm previous MEG sensor-level studies (Edgar et al., 2003; Huotilainen et al., 1998; Makela et al., 1994), which have shown sensitivity of temporal sensors in detecting changes in sensory processing during a paired click paradigm. However, the relationship between sensor location and underlying anatomical structures is not sufficiently accurate to infer direct involvement of specific cortical structures, partly due to the variability in head shape and sensor position with respect to the scalp surface. The effect of this variability is evident from the nomenclature of supra-threshold channels in some individuals as parieto- temporal (Table 3.1). Source space analysis of our data identified a stronger activation in the STG for S1 compared to S2, while S2 was associated with stronger activation in the IFG as compared to first click. This finding can be interpreted as suggestive of a temporal lobe contribution for the initial processing of the auditory stimulus and that the frontal lobe is a significant contributor of the suppression phenomenon. This is a novel non-invasive confirmation of the intracranial findings recorded in patients undergoing pre-surgical assessment due to drug-resistant epilepsy (Korzyukov et al., 2007) and indicated that MEG can be used effectively to understand sensory gating

phenomenon. At technical level, the analysis supports the suitability of distributed source models to investigate this aspect of auditory sensory processing.

3.4.2 Neural Oscillatory Pattern

Findings from this study correlate to the fMRI studies mentioned above, which suggest alpha-beta desynchronization is associated with gamma synchronization (Singh, 2012). Two ways were chosen to ensure reliability of results from AUC and t-f maps on each scout between all subjects. The only finding which was not matching with our results from AUC was gamma increase in right temporal scout during S1. This could possibly be due to high signal to noise ratio as this power was measured directly from the scout across all subjects. Moreover, for AUC analysis, only the dominant hemisphere was considered, while this was not the case for scout input. Unlike Hall et al (2011), from this study it can be stated that event related beta and gamma oscillations are not independent of P50 ASG processing. It can be stated that in the temporal region there is a significant reduction in alpha power during S2 click, while there is a notable reduction in beta band as well but it is not at same level of significance ($p<0.05$). In frontal regions, a strong increase in gamma band power was accompanied by strong reduction in beta band during S2, suggesting beta desynchronisation accompanied by increase in gamma power. These findings connected well with the sensor level t-f results as well. Unfortunately, due to short epoch length t-f measures in theta and delta band could not be calculated, and the results remain limited to alpha, beta and gamma band. Since there are no similar studies that have looked upon t-f analysis at source level during P50 ASG, it is stimulating to report these findings.

3.4.3 Possible Limitations of Auditory Stimulus and Analysis Method

Auditory stimuli were presented at the same SPL level for all individuals. An alternative strategy could have been selecting stimuli at HL intensity. This should be only a very minor confound in our sample, given the relatively small variance in hearing thresholds measured with tonal audiometry between participants. Previous studies using 70 dB to 90 dB SPL stimuli indicated no intensity-related differences in

sensory gating (Freedman et al, 1987; Clementz et al., 1998; Brinkman & Stauder, 2007).

Pre-stimulation baseline was used to assess noise covariance in individual trials**.** This is a commonly used method, but it means that everything in pre-stimulation baseline is going to be attenuated in the source reconstruction, noise and brain activity. So stimuli have to be distant enough in time so that the response to a st**i**mulus is not recorded in the "baseline" of the following one which was not a major concern in this study. However, it would have been better to measure resting state baseline and use that instead or pre-stimulation baseline, as pre stimulation baseline was 50 ms and it has been suggested in literature that anything less than 100 ms could be noisy.

Both software were used alternatively to meet analysis requirements, which has been an advantage as it confirmed the findings from one to another. In brainstorm the source localisation was measured using MNE as that is the option provided. This technique has been criticized as it is biased towards sources that are near the surface as compared to deep sources (Hämäläinen & Ilmoniemi, 1994) Magnetic signals are largest for superficial dipoles that run parallel to the surface of the skull and fall off rapidly as the dipole become deeper and or perpendicularly oriented. In SPM, Multiple Sparse Priors (MSP) is recommended over MNE, but to reduce variation in results Minimum Norm solution was chosen. However, a separate analysis was performed using MSP, it was found that same regions (same MNI coordinates) were activated in all individuals as with Minimum Norm, so no major drawbacks associated with it. In terms of t-f analysis, longer epoch length would have been advantageous to perform analysis in lower frequency bands, but then both conditions would have been incorporated into single trial, and results would be very subjective.

Chapter 4: Investigation of P50 ASG brain networks using MEG connectivity measures

4.1 Introduction

The two fundamental aspects of brain organization in human beings are functional segregation and integration. Functional segregation refers to the presence of specialized neurons, which are organized into distinct neuronal groups based on their common functionality. These specialized sets of neurons selectively respond to specific input features or combination of features (Tononi & Sporns, 2003). Functional integration refers to interaction among these specialized or segregated sets of neurons; how these interact is largely dependent upon the sensorimotor or cognitive context (Friston, 2003). Functional integration is evaluated by observing the correlations among activity in different brain regions, or elucidating activity in one area relative to activities in other regions (Tononi & Sporns, 2003). Both functional segregation and integration can affect how brain structures operate, in that the integrated action of specialized neurons can exert specific causal effects on other neurons. Functional segregation has been characterised using neuroimaging techniques and these techniques are now being applied to understand functional integration. Compared to segregation, functional integration is more challenging to measure. Investigating connectivity between structures is an elegant way to explore these relationships. Previous knowledge on synaptic connectivity was obtained in non-human primates (Jones, 1993; Levitt, 2003). This was achieved using tracers into target brain areas to identify the anatomical pathways. More insight was gained from post-mortem studies observing patterns of transport of tracers injected in specific brain regions (Ramnani & Miall, 2001; Kobbert et al., 2000). Even though these techniques provide in-depth knowledge about connectivity between individual synapses, their invasiveness makes these methods unsuitable for use in humans. With advancement in technology, measuring connectivity patterns in humans has become possible thanks to methodologies such as fMRI, MEG and EEG.

Three level of connectivity are currently defined: structural, functional and effective connectivity.

1. Structural connectivity refers to the presence of neural pathways between two regions as well as their associated structural characteristics measured by parameters such as synaptic strength or efficiency (Sporns, 2003). Currently, structural connectivity is investigated using powerful non-invasive techniques such as Diffusion Tensor Imaging (DTI), which explains structural connectivity between brain regions by providing detailed 3D probabilistic representation of white matter structure.

2. Functional connectivity refers to the statistical dependencies between regional time series. Measures used to understand functional connectivity are phase synchronization temporal correlations and coherence (Li et al., 2009).
3. Effective connectivity represents casual (directed) influences between neuronal populations. It measures the influence one neuronal system exerts over another at synaptic or population level (Friston et al., 2003)

For this study focus is laid upon effective connectivity, due to its ability to reveal patterns of integration within a distributed system (Friston et al., 1997). Effective connectivity can be studied through model comparison or optimization; it depends on both mathematical and neuroanatomical models. The former suggest "how" areas are connected while the latter are used to identify "which" areas are connected (Tononi & Sporns, 2003). Some of the methods used to measure effective connectivity are discussed below.

1. Structural Equation Modelling (SEM) - This method is based on the variance-covariance structure of the data rather than considering variables individually; it was initially applied to neuroimaging by McIntosh and Gonzalez-Lima in 1991. SEM is the method of choice to analyse models consisting of multiple regions of interest.
2. Multivariate Autoregressive Models (MAR) - This approach is used to model the temporal effect across different variables such as – in the case of functional neuroimaging - region of interest, without using state variables. It has been used to investigate both temporal and spectral processing during fMRI and EEG studies (Harrison et al., 2003).
3. Granger Causality - This model was originally developed in economics and has been recently applied to brain connectivity studies. It uses temporal

precedence to identify direction and strength of causality information in the data. This model helps to identify whether history of one of the time courses can be used to predict the current value of another. In neuroimaging Granger Causality Index is computed with respect to a single reference region selected a-priori (seed region) (Harrison et al., 2003).

4. Dynamic Casual Modelling (DCM) - This model unlike the others is dynamic (nonlinear state-space model in continuous time) and designed to measure connectivity at neuronal level. It estimates coupling among brain regions and how that coupling is influenced by experimental manipulations (Friston et al., 2003)

Unlike DCM, most regression methods do not allow testing for directionality/casualty measure between regions of interest. SEM and MAR have been used to model correlations at the level of the observed fMRI time series, whereas DCM can be used to model connectivity at neuronal level as well. Due to the non-linear dynamic nature of DCM, this measure was chosen for this study to understand underlying mechanisms of P50 ASG.

4.1.1 A bit more detail on DCM.

DCM was developed in 2003 (Friston et al., 2003) and implemented in Statistical Parametric Mapping (SPM) software, initially developed with fMRI studies in mind and later developed to be applied on MEG and EEG data. DCM is a hypothesis-specific technique not exploratory in nature. The hypothesis and output is formulated based on a-priori physiologically plausible hypotheses on neural function specific to the tasks and stimuli used during the experiment. In DCM the input (external or contextual) can be described as the casual or explanatory variable that comprises the conventional design matrix and the *parameters* are considered to be the measures of effective connectivity. In DCM inputs can affect the responses either by eliciting changes in neuronal activity (state variable) directly or by changing the effective connectivity (interactions) between regions of interest (Friston et al., 2003). This is the paradigmatic case for sensory inputs, which could be modelled as causing direct responses in primary visual or auditory areas (Friston et al., 1997). DCM was first designed to understand the dynamic interaction in a network model consisting of few sources from the measured data (Friston et al., 1997). Essentially, DCM attempts

to provide neurophysiological interpretation of the neuronal activity by defining the spatial distribution of its generators and their relationship during the execution of a task (Kiebel et al., 2009). DCM is based on Bayesian statistics by which each parameter is constrained by a prior distribution to attain precise results. The principles and implementation as it relates to our study design will be discussed in detail below.

DCM is a causal modelling procedure for dynamical systems in which the simple impression is to treat the system of interest, in this case the brain, as an input-state-output system (Friston et al., 1997). By perturbing the system with known inputs, measured responses are used to estimate various parameters that direct the evolution of brain states. Although, there are no restrictions on the parameterization of the model, a bilinear approximation could produce a simple re-parameterization in terms of effective connectivity. Parameter estimation using fairly standard approaches to system identification that rest upon Bayesian inference are the first steps of the procedure. Considering that a vast majority of neuro-imaging studies rely upon design-based experiments, DCM can potentially act as a useful complement to existing techniques.

4.1.2 Different Models of DCM

Dependent on the nature of stimulus and the type of hypothesis, a range of DCM models can be chosen to analyse MEG/EEG data such those for evoked responses, for induced responses, for cross spectral densities etc. Based on Jansen and Rit's model (1995), DCMs for MEG/EEG data adopt a neural mass model to elucidate source activity in terms of collective dynamics of the interaction between inhibitory and excitatory sub-population of neurons (please refer back to Chapter 1 for further details). This model follows the activity of a source using three neural subpopulations, each assigned to one of three cortical layers. The excitatory pyramidal cells receive excitatory and inhibitory input from local interneurons (via intrinsic connections), and send excitatory outputs to remote cortical areas via extrinsic connections (Kiebel et al., 2006).In this modelling process (Figure 4.1), bottom up, top down and/or lateral connections can be investigated (Friston et al., 2003; Mechelli et al., 2003). These connections can be examined either individually or in conjunction with each other depending on the testing hypothesis.

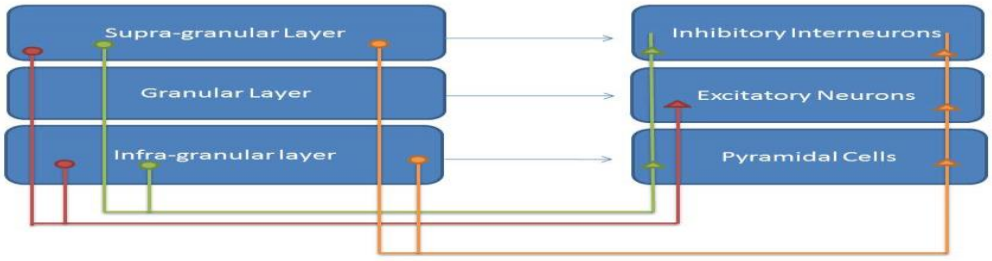


Figure 4.1 Shows the composition of neurons in the three layers and illustrates bottom up (red), top down (green) and lateral (orange) connections.

These processes are termed differently in DCM; bottom up connections are referred as forward connections and top down as backward connections following the terminology used by Ungerleider et al., (1998). An example of how the model can be designed is presented in Figure 4.1, in which modulatory processes, often known as top-down processes, are shown. These are mediated anatomically by 'backward' connections from higher to lower areas which both originate and terminate in infra- and supra-granular layers as seen in the Figure 4.1 .

4.1.3 Bayesian inference

Bayesian inference is a powerful statistical framework applied in dynamic system; it updates coherently the probability for a hypothesis as data is observed (Marreiros et al., 2010). Since DCMs are dynamic models Bayesian inference is the most suitable statistical approach for model estimation. This method is based on the 'prior' distribution (which refers to the distribution of parameters before any data is observed) in combination with 'likelihood' of parameter (given an outcome) to provide a 'posterior' distribution (distribution of parameter after taking into account observed data, e.g. neuronal coupling strength) (Penny et al., 2004). As a part of the estimation procedure, prior density is established from the mean and standard deviation of a coupling parameter, which represents its posterior distribution. This process identifies the probability on which the connection exceeds some specified threshold (Friston et al., 2003). Classical models assume unconstrained access to all brain regions as they infer that activations are caused directly by experimental factors, as opposed to being mediated by afferents from other brain areas (Friston et al., 2003). Bayesian

inferences disdain many of the challenges encountered with classical inference and can be used flexibly to characterise brain responses (Friston, 2002). Bayesian inference is utilized by Bayesian model selection in DCM, which assists in determining the best-fit model.

4.1.3.1 BAYES' FACTOR

The Bayes' factor is a summary of the evidence provided by the data in favour of one scientific theory, represented by one statistical model, as opposed to another. It is calculated based on the probability of two different models, parameterized by model parameter vectors for those models (Penny et al., 2004). Bayes' factor is a statistical measure, similar to P values in classical statistics and has a range that identifies the strength of the models created. Bayes' factor guards against overfitting, as it automatically includes penalty for including too much model structure. An interpretation of Bayes' factors according to Raftery (1995) is shown below:

i. 1–3 (50–75) Weak
ii. 3 – 20 (75– 95) Positive
iii. 20 -150 (95-99) Strong
iv. >150 (99) Very Strong

Bayes factors can be interpreted as follows: provided hypothetical models A and B, a Bayes factor of 20 correspond to a belief of 95% in the statement 'hypothesis A is true'. This corresponds to strong evidence in favour of A. If one wishes to make decisions based on Bayes factors, some cut-off value is required. In Bayesian decision theory, the choice of cut-off is guided by a 'loss function' or 'utility' that captures the costs of making false-positive and false-negative decisions (Bernardo and Smith, 2000).

DCM uses the probability of data (model evidence) - given some model and priors - to identify the best model. The most likely model is the one with the largest log-evidence. Conventionally a log-evidence greater than 3 provides strong evidence. The absence of any difference in the log evidence suggests that the two models are either too similar, the data are too noisy or the data might not have fitted well (SPM manual, 2012).

4.1.4 DCM Validity

Two types of validities are tested in DCM model. Face validity, refers to the notion that recognition procedure to identify estimation and inference effectively

proposes what it is supposed to. In an fMRI study on auditory perception, a range of hyper-parameters (noise level, slice timing, artefacts) was tested and it was observed that broadly the system was robust to most violations assessed (Friston, 2002). Face validity was specifically observed to learn the effect of noise, and it was found that noise did not lead to false inferences such that the posterior densities are always in range of true values even at high levels of noise (Friston et al., 2003).Thereby, suggesting high validity of the results obtained without being influence by noise levels in the data set.

Predictive validity measures the consistency of the effective connectivity estimates and their posterior densities, thereby providing evidence that reproducible results can be achieved from independent data. Predictive validity was assessed over multiple sessions using empirical data from an fMRI study of single words processing at different rates over a number of sessions using over 120 scans. It was found that the reproducibility of forward connections was very strong, backward connections were somewhat weaker but certainly greater than 0. These studies suggested that the analysis of independent data acquired using same stimulus, subject and scanning session, produces remarkably similar results.

4.1.5 Aim

In this study, focus is laid on identify the dynamics underlying the process of ASG using DCM modelling. We aim to identify the model that best explains the interactions between cortical structures during S1 and S2, by determining the connectivity patterns between regions of interest.

4.2 Methodology

4.2.1 Participants

For this study, the analysis was conducted on the dataset collected from the twenty- one participants included in Chapter three of this thesis. Participants were healthy adults in the age group 18-59 years with no personal or history of psychiatric or neurological disorders. For additional details on participant recruitment as well as inclusion exclusion criteria refer to section 2.2.

4.2.2 Auditory Stimulus

The classic double click paradigm with two clicks (N= 100 pairs) presented at 80dB binaurally at inter trial interval of 250±10ms and inter stimulus interval of 7-10 seconds (Chapter 3 (Figure 3.1)) was used to collect the data the using the MEG system.

4.2.3 Data Analysis

In this study effective connectivity was measured using DCM for evoked responses -ERP model. This model use neural mass models to explain source activity in terms of the collective dynamics of the interacting inhibitory and excitatory subpopulations of neurons, based on the model of Jansen and Rit (1995). Data was pre-processed and analysed in Brainstorm (Tadel et al., 2011) and SPM 12 (Wellcome Trust Centre for Neuroimaging, UCL); for full details on the pre-processing steps (epoch -50 to 250 ms, filter 1-70Hz, artefact rejection, baseline correction -50 to 0, average of 80 trials) see Chapter 3. For DCM, the SPM 12 pre-processed average file with both S1 and S2 conditions and head model information was loaded into DCM interface. This was the same file on which inverse solution was performed and sources of activation in the time window of interest (30-70 ms) were extracted. Connectivity was estimated in the 0 to 70 ms time window, the same time window used for sensor and source-space analysis of the P50 response presented in earlier chapters. Both S1 and S2 trials were selected; the 0 1 contrast (the way in which conditions are compared relative to each other in DCM) was chosen to determine the model that best explained the S2 trial data and the 1 0 contrast was chosen to identify the model that best explained the data during the S1 trial. In ERP DCM, contrast 0 1 computes the best model for condition 2 relative to condition 1, while 1 0 represents vice versa. 'IMG' function was chosen to define a priori cortical surfaces that were activated during S1 and S2 trial. The details on features available in DCM can be seen in figure 4.3 below. These were the four regions of interest (*scouts* in Brainstorm) LTSG, RSTG, LIFG, RIFG (process explained in Chapter 3) and their MNI coordinates. The model below explains the three models that which were considered (feed forward, feed backward and feed forward-backward) and the MNI coordinates for each subject for four regions. Each

model (forward, forward-backward and backward) was evaluated for each individual and for both S1 and S2 trials' using the MNI coordinates of each individual to reduce the variance.

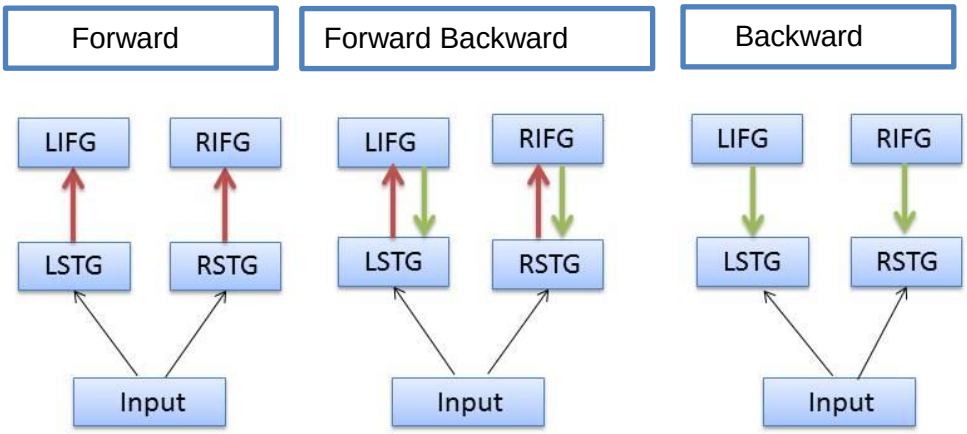


Figure 4.2 Represents three models: forward (left), forward-backward (middle) and backward model (right) computed for each individual with MNI coordinates for the four sources. Input refers to the bilateral auditory stimulus; red arrows indicate forward and green arrow backward connections.

The performance of the three models was compared using Bayesian Model Selection to determine which model best explained the data for each condition. For this analysis fixed effects (FFX) were chosen under the assumption that the optimal model would be the same for each subject. This assumption is justified when studying a basic physiological mechanism that is unlikely to vary across subjects. A between-subject method was applied; first the connectivity model (three models) was generated for each subject, then the best-fit model was chosen using Bayesian Inference.

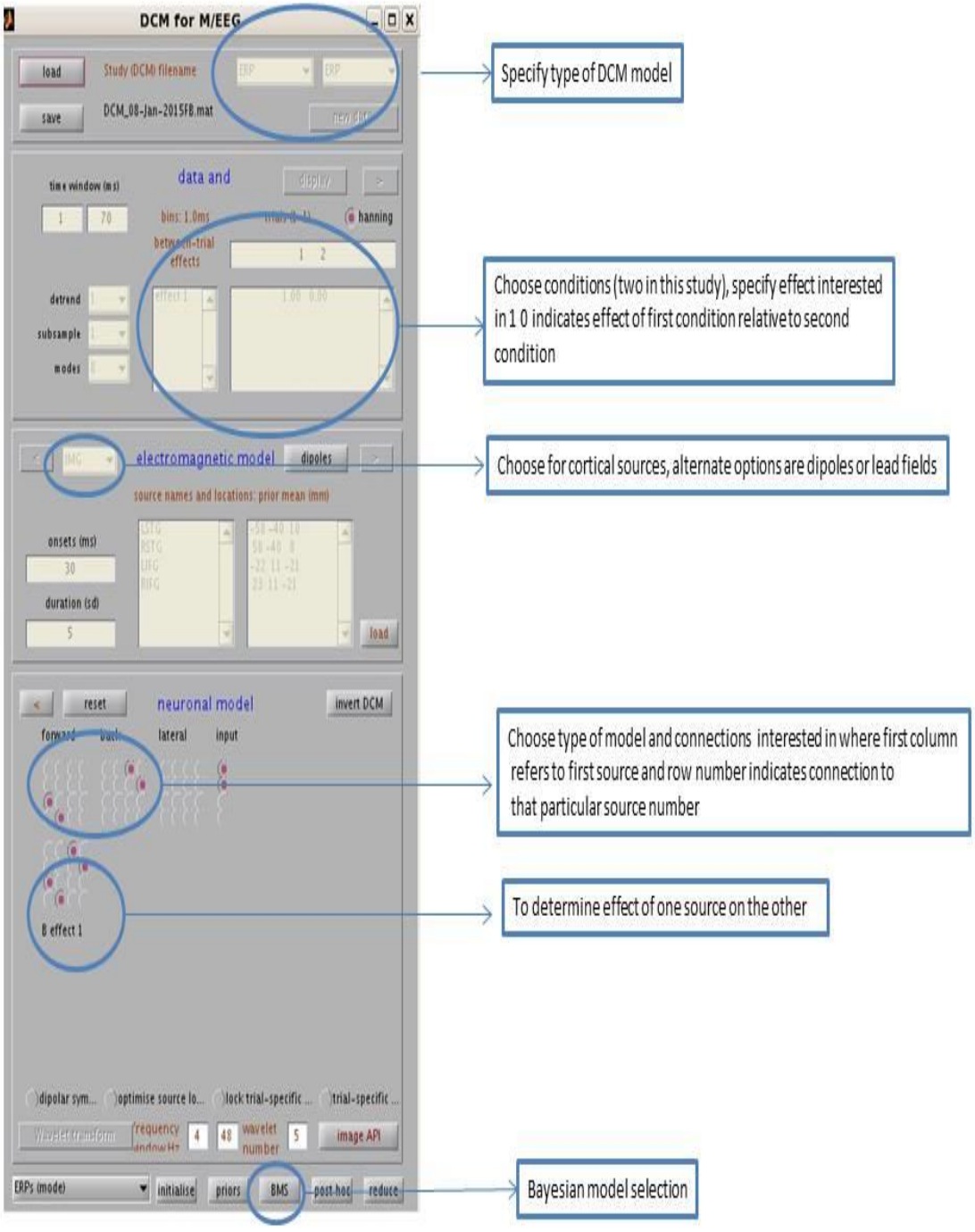


Figure 4.3 Illustration of features available in DCM for ERP model (SPM, 2012).

4.3 Results

4.3.1 Findings at Individual Level

The input received by bilateral auditory cortex was consistent throughout all participants. The input level (the external auditory input received by LSTG and RSTG) was same (predicted vs actual) see Figure 4.4.It was observed that at an individual level, most data for S1 was explained by the forward model while that or S2 was explained best with the backward model as shown in Figure 4.5

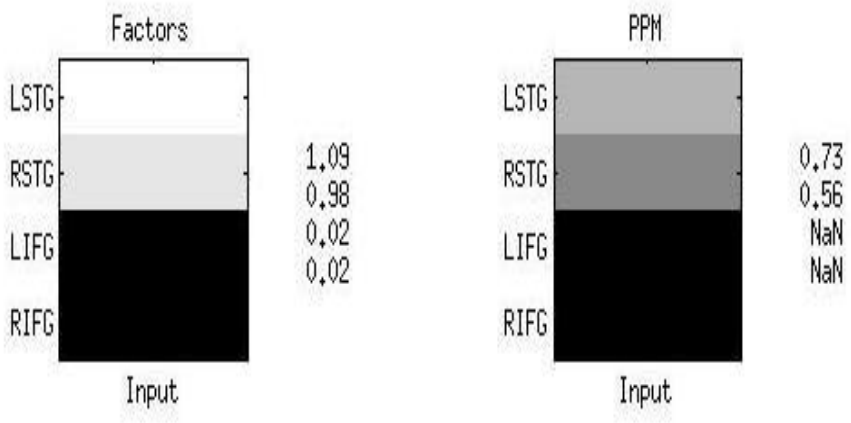


Figure 4.4 Input level in one subject with respect to predicted input (PPM) for LSTG and RSTG.

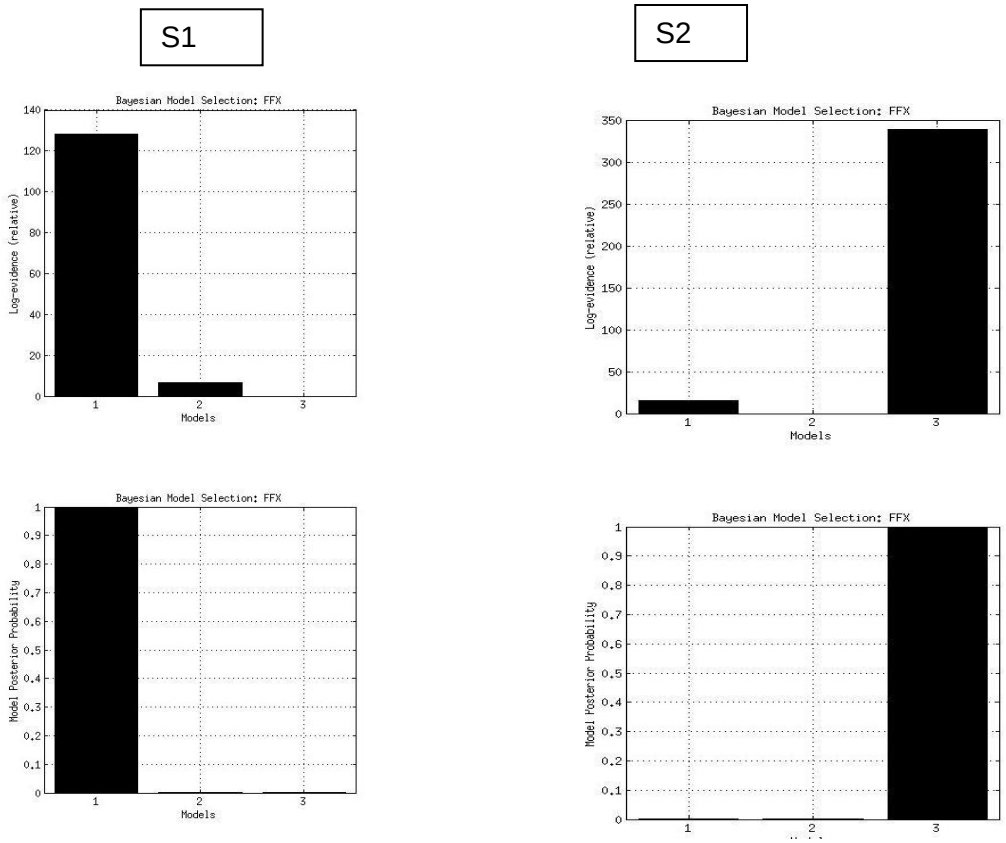


Figure 4.5 Histograms represent the posterior probability for each model from BMS results. (model 1= forward, 2= forward-backward, 3 = backward)

In Figure 4.5, the forward model (LSTG-LIFG & RSTG-RIFG) was the best at explaining the S1 response while the backward model (LIFG-LSTG &RIFG-RSTG) explained better S2 response. Trial specific effects are defined by the strength of coupling between two regions of interest during each condition. Considering the best-fit model from Figure 4.5, connection strengths for S1 and S2 (trial specific effect) (here 100% represents the connection strength for the baseline condition). Results show strong bilateral STG to IFG connection strength in S1 compared to S2, while connection strength between bilateral IFG and STG was observed during S2 relative to S1.

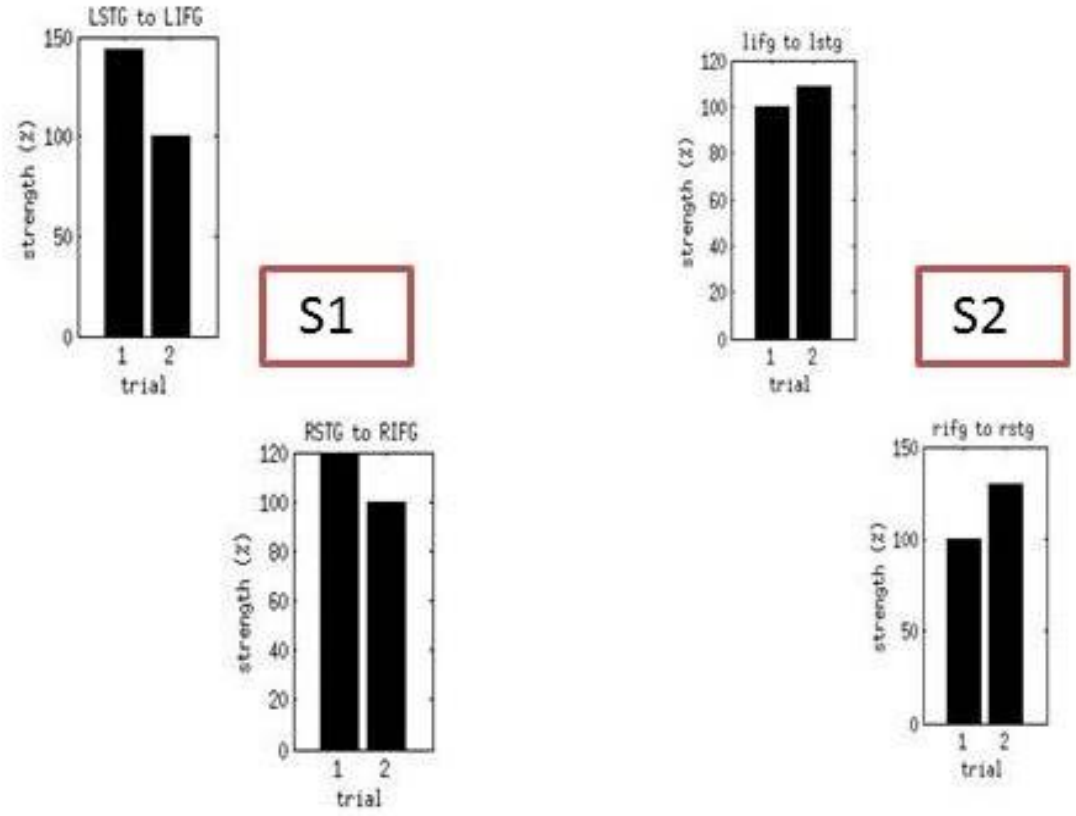


Figure 4.6 Shows trial specific effect in forward model for S1 and backward model for S2 in the individual subject from Figure 4.5

4.3.2 Findings Between Subject

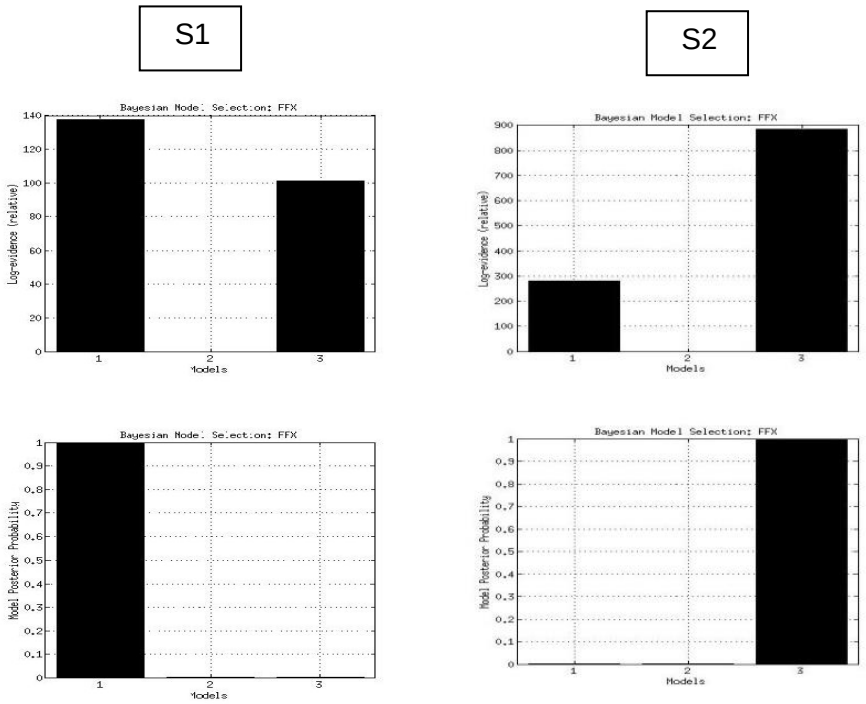


Figure 4.7 Illustrates posterior probability and log evidence for three models between twenty subjects for each condition S1 and S2 (Model 1= Feed forward, 2= Feed forward-backward, 3= Feed backward).

The model that best explained S1 was a feed forward one (LSTG-LIFG & RSTG- RIFG) with 140 log- evidence value and posterior probability of 1. The difference between log value for both models is between 20 -150 suggesting 95-99% in favour of model 1.

The model that best explained S2 was feed-backward model (LIFG-LSTG & RIFG-RSTG), with log evidence value of 890 and posterior probability of 1.0. Bayes factor is greater than 150 indicating 99% evidence in favour of model 3 in S2. The input into auditory cortex was strong and it was same for all participants across both trials.

4.4 Discussion

There is very limited literature on the DCM connectivity model for auditory tasks and there is only one study so far on mismatch negativity (Kiebel et al., 2007). Prediction of the best model relies on accurate parameter selection. In this study, one

of the most important of these parameters is the input to auditory cortex. It was observed that the level of volley of thalamic input arriving at the cortex was the same in all individuals. For the temporo-frontal (forward) model, the strength was greater during S1 relative to S2 while the opposite was true for the fronto-temporal (backward) model. For three participants, the forward-backward model best explain the data during S1 and S2 condition. This pattern could possibly be due to the lower GFP for S1 seen in these participants, or less suppression of the S2 response compared to the other participants. This finding at individual level confirmed the validity of our choice of avoiding the analysis of grand-average data. Temporo-frontal connections play a significant role during processing of the first click and the directionality suggests a temporal drive on the frontal regions. Backward connections from the frontal to the temporal lobe regions appear to be critical to explain the physiology of the S2 condition, possibly due to a modulatory drive. In the context of the DCM framework our findings can be interpreted at cellular network level hypothesising that processing of the first stimulus is associated with an initial activation of the stellate cells in the STG and that these further activate the pyramidal cells. GABAergic interneurons do not appear to be significantly involved in this initial ERP response. Processing of the second stimulus on the contrary is characterised by a strong activation of GABAergic interneurons in the IFG that drives STG structures, as explained by the backward model. This phenomenon suggests a role of inhibitory interneurons during S2. In terms of P50 ASG, this is the first whole-brain neuroimaging evidence to suggest an important role of the frontal cortex in auditory sensory gating. Previously, only an intracranial EEG study in patients with drug-resistant epilepsy (Korzyukov et al., 2007) had provided evidence of the temporo-frontal dynamics in P50 ASG. Earlier, only animal studies (refer to Terrance et al., 2011) had suggested the role of frontal cortex during S2 responses. Even though the temporal lobe is the main generator for P50 response, the suppression of S2 is a result of inhibitory activity occurring in the frontal cortex. This inhibitory activity of the prefrontal cortex is indirectly supported by a Magnetic Resonance Spectroscopy (MRS) study that measured GABA levels in healthy controls and patients with schizophrenia, showing that GABA levels in the prefrontal cortex were significantly lower in schizophrenics than in healthy adults (Marsman et al., 2014). This evidence is in agreement with our findings; low GABA levels in patients with schizophrenia could result in reduced excitation of inhibitory inter-neurons in the frontal cortex, leading to reduced P50 suppression in this clinical group. Findings from Chapter 3, suggest synchronization of gamma oscillations in IFG during S2 condition; generation of gamma oscillation is associated with activity of inhibitory interneurons thereby

providing additional evidence on the possible role of interneurons during suppression (refer to Chen et al., 2014).

Advantages

1. DCM helps to infer parameters which cannot be directly observed with M/EEG.
2. It is a hypothesis based model which helps to understand the causal relation between sources.
3. A powerful feature of DCM is that it combines the spatial forward model with a biologically informed temporal forward model, unfolding for example the connectivity between sources.

Limitations

1. The option to choose between two or more alternative models can lead to a problem known as ‘over fitting’, which can be achieved by including variety of unnecessary parameters.
2. The true model identified by DCM is amongst the pre-prepared models, so if there is a different theory it might remain uncovered (Stephan et al., 2010).

Chapter 5: P50 ASG and Personality Dimensions

5. 1 Introduction

The P50 ASG has received significant attention in the last decade as a relevant sensory-level intermediate phenotype in patients with schizophrenia. The evidence of abnormal P50 suppression in this patient group has been considered to account for aspects of the schizophrenia spectrum phenotype such as its correlation with severity of negative symptoms (Thoma, et al., 2005) and invoked in the pathogenetic mechanisms of delusions and hallucinations (Waters et al., 2003). More recently evidence of impaired P50 suppression has been documented in patients with schizotypal personality as well as mood disorders (Cabranes, et al., 2012) suggesting that the P50 ASG might be an intermediate phenotype associated with specific personality dimensions rather than a diagnostic tool for categorical diagnoses. In this line, data that emerged for the study presented in Chapter 3 is strongly supportive of a dimensional nature of P50 ASG in healthy adults; whether and how behavioural or personality traits might account for this variability is an interesting issue worth exploring. Behavioural studies found both personality and behaviour to be impaired in non-psychotic relatives of schizophrenia patients. A frequently reported association is with measures of schizotypal personality (Schizotypal Personality Disorder or STPD), similar qualitatively but less severe (Mohanty et al., 2005) than in affected relatives. A few studies have investigated the association between schizotypal personality features and P50 ASG in the general population and found strong correlation between high levels of schizotypy and reduced P50ASG (Evans et al., 2007; Wan et al., 2006). A recent study (Park et al., 2015) reported that when compared to low schizotypal, high schizotypal individuals (who scored above average on both cognitive disorganisation and impulsive nonconformity dimension) displayed early sensory gating deficits. Cognitive disorganisation refers to tendency for thoughts to become derailed or disorganised while impulsive nonconformity refers to disposition of unstable mood and behaviour. These two dimensions of STPD are reported also in other psychiatric disorders and often co-exist with avoidant personality, borderline personality, paranoid personality disorder, depression and social anxiety. The association between behavioural and personality measures and P50ASG are discussed below in further detail.

5.1.2 P50 ASG, behaviour and personality measures

Anti-Social Personality Disorder (ASPD)

A strong association between ASPD and impaired higher order information processing as revealed by early ERP components has been reported (Bauer, 2001; Chang et al., 2010). Studies indicated that early gating process might be abnormal in ASPD and that the abnormalities in later ERP components are only a consequence of early earlier processing difficulties (refer to Lijffijt et al., 2012). The findings from these studies indicated that the story is slightly more complex than first hypothesised suggesting that while no difference in P50 ASG or S1 S2 amplitudes are seen between healthy controls and ASPD as a whole, ASPD participants with higher impulsivity and additional ASPD co-morbidities had higher P50 ratio and reduced P50 difference score. This was interpreted as indicating that sensory gating is impaired only in subjects with more severe ASPD, particularly those with impulsive nonconformity (Lijffijt et al., 2012). Impulsivity involves dysregulation of early behavioural responses to stimuli, resulting in action without the conscious decision to act, and is a prominent feature of bipolar disorder (Moeller et al., 2001). P50 amplitudes and/or gating are reduced in conditions with impulsivity as prominent feature other that antisocial personality disorder (Lijffijt et al., 2009c), such as impulsive aggression (Houston and Stanford, 2001) and bipolar disorder (Moeller et al., 2001).

Borderline Personality Disorder (BPD)

One study in the literature has so far investigated the association of P50 ASG deficits and Borderline Personality Disorder (Grootens et al., 2008). This study reported higher S1 amplitude in BPD participants compared to healthy controls and stronger P50 suppression. It was proposed that gating is intact in BPD participants unlike in other psychiatric disorders.

Attention Deficit Hyperactivity Disorder(ADHD)

Deficits in attention and information processing are a dominant feature in patients with ADHD (Biederman, 2005; Faraone et al., 2000). Furthermore,

subjective patient reports often include discomfort when exposed to sensory stimuli as if they were being overloaded by the environmental stimulation. A recent study in adults with ADHD reported P50 ASG deficit along with poor performance on attention-related cognitive tasks (Holstein et al., 2013). The deficit was primarily due to differences in the S_2 but not S_1 amplitude; this was interpreted as suggestive of impaired central inhibitory activity (White and Yee, 1997; Ghisolfi et al., 2004). A further study showed that infants with reduced P50ASG ranked higher at three years of age on parent-reported problems in attention, anxiety/depression and externalizing problems measured with the Child Behaviour Checklist (Hutchison et al., 2013). This body of evidence support a relationship between P50 ASG and dimensional aspects of personality.

Anxiety and Depression

Neural mechanisms involved in anxiety have likewise been linked to inhibitory gating (Grunwald et al., 2003). Anxiety is a multidimensional construct linked with negative mood and emotion and influenced by cognitive, affective, physiological, and behavioural components (Corr and Fajkowska, 2011). Extreme levels of anxiety can characterize clinical diagnostic categories such as panic disorder and this has been reported to be associated with reduced P50 suppression. Deficit of P50 suppression was positively correlating with severity of anxiety disorder and negatively associated with benzodiazepine use (Ghisolfi et al., 2006). The infant P50 ASG study (Hutchinson et al., 2013) mentioned above similarly proposed association between higher score on anxiety/depression and reduced P50ASG. Reduced P50 ASG was reported in both treatment resistant and non-treatment resistant depression patients as compared to healthy adults (Wang et al., 2009).

Creativity

The investigation of schizotypy and total creativity as assessed by three self-report creativity measures demonstrates a consistent relationship between schizotypy and creativity (Batey & Furnham, 2008). Among dimensions of schizotypy, unusual experience and impulsive nonconformity are positively correlated to creativity whereas cognitive disorganisation has a negative correlation (Batey & Furnham, 2008). Recently, the relationship between P50 ASG and two measures of creativity - divergent thinking and real world creative achievement was investigated

(Zabelina et al., 2015). The study suggested that the former was negatively correlated with P50 ASG and the latter measure was positively correlated. Divergent thinkers show strong sensory gating in the very early (50 ms after stimulus onset) stages of the sensory processing stream, whereas people who reported higher number of creative achievements showed reduced sensory gating. This finding was interpreted as indicative that low sensory gating might be beneficial to real world creativity by allowing the expansion of attention focus, while divergent thinking is reliant on efficient filtering processes.

From above mentioned studies, it is evident that personality and behavioural measures are significantly linked to the P50 ASG phenomenon. However, as this is a relatively recent line of research, very little prior knowledge is available to inform how to adequately power such studies and to gain insight on the dimensionality of this phenomenon in healthy individuals.

5.1.3 Aim

In this study we examine the relationship between a broad range of behavioural /personality measures and P50 ASG using self-report questionnaires. The information will be critical to adequately power further studies.

5.2 Methodology

5.2.1 Participants

The twenty-four participants recruited for the first MEG study (Chapter 3), completed three sets of self-report questionnaires after their scanning session, either at the end of the procedure or if not convenient or possible, after taking the questionnaire home and filling it in their own time. These were healthy adults in the age group 18-59 years with no history of psychiatric or neurological disorders. For additional details on participant recruitment as well as inclusion exclusion criteria refer to Chapter 2. The number of participants who filled in each questionnaire was different as some participants were uncomfortable in providing their personal information particularly by responding to the questions prescribed by the ASEBA (Achenbach System of Empirically Based Assessment).

5.2.2 Questionnaires administered

ASEBA- the adult self-report (ASR) questionnaire, which forms part of the ASEBA assessment has been designed to measure adaptive functioning, empirically based syndromes, substance use, internalizing and externalizing problems in the 18-59 age group (Achenbach & Rescorla, 2003).This measure comprises of 123 statements and provides information on syndrome scale: internalizing problems (anxiety/depression, withdrawal, somatic complaints), externalizing problems (aggressive behaviour, rule breaking behaviour and intrusive behaviour), thought problems and attention problems. The DSM-oriented scale provides measure on depression, anxiety, somatic problems, avoidant personality, ADHD and antisocial personality. Each statement is rated on a 3 point scale, where 0= not true of me, 2= very true of me. These scores are then entered in the automated Assessment Data Manager Software (ADM) designed specifically for ASEBA measures (Achenbach, 2000). After all the scores are entered into the system, they are automatically computed and results are produced with t-score, raw score, and percentile for each of the above mentioned measures. Each statement is categorised under each measure for example when scored for statement 25, 30,42,48,60,65,67,69 and 111 are calculated it gives a total score for withdrawn syndrome (See Appendix 4, for overview of output). Using this technique each score is computed automatically in ADM. These scores are then divided into three ranges: normal, borderline = 93^{rd}-97^{th} percentile and clinical range > 97^{th} percentile.

SIAS - this twenty-statement measure was designed to assess social interaction anxiety. It measures the anxiety experienced while interacting with others, and has been explained in detail in Chapter 2. It is used to assess prevalence, severity and treatment outcomes of social phobia and social anxiety disorders. Experiences are rated on five-point scale from 0 (not at all characteristic of me) to 4 (extremely characteristic of me). Maximum score that can be achieved on this scale is 60, with cut off of 34 suggestive of social phobia and 43 or higher indicating social anxiety. In this scale, scoring on items 5,9,11 are reversed (which means 0=4 while 4=0) to assess response validity (Mattick and Clarke, 1989).

ASP- Adult Sensory Profile (Brown and Dunn, 2002) enables to determine individuals' sensory processing preferences based on four categories presented in a model of

sensory processing: low registration, sensation seeking, sensory sensitivity, and sensation avoiding refer to Figure 5.1.

	Behavioural response in accordance Passive	**Behavioural response to counteract Active**
Low Threshold	Low Registration	Sensation Seeking
High Threshold	Sensory Sensitivity	Sensory Avoiding

Figure 5.1 Dunn's Model of Sensory Processing (1997).

Table 5.1 Description of Sensory Processing Models (Brown & Dunn, 2002).

This self-report questionnaire measures six sensory processing features: Taste/smell processing, movement processing, visual processing, touch processing, activity level and auditory processing. Each category comprises of different number of items in total there are 60 items, rated on 1-5 point scale, where almost never = 1 and almost always = 5. The maximum score that can be achieved in each of the four quadrants is 75. Score in each category is then entered into one of the five classified columns (based on performance of individuals without disabilities): much less than most people, less than most people, similar to most people, more than most people and much more than most people.

5.2.3 Data Analysis

For the analysis, we used sensory gating measures [P50 ASG ratio (S2)/(S1)] obtained in study 1 presented in Chapter 3.

1. ASEBA- the scores for each questionnaire were entered into SPSS Version 22.0 software package (IBM Corp. 2013, Armonk, NY). Correlation analysis using Kendall's Tau was performed to determine association between P50 ASG ratio (gating ratio S2/S1) with measures of ASEBA questionnaire (ASR-Syndrome scale, internalizing, externalizing and total problems as well as measures from DSM Oriented Scale)

2. SIAS – the relationship between social interaction anxiety scores with P50 ASG ratio (S2/S1) was determined using Pearson's correlation analysis in SPSS as assumptions for this test were met.
3. ASP-Pearson correlation was used also for the analysis of adult sensory profile raw scores and P50 ASG ratio.

5.3 Results

Of the 24 participants recruited, 17 completed the ASEBA questionnaire, 19 completed the SIAS questionnaire and 15 completed the ASP.

1. ASEBA scores and sensory gating

Positive correlation was found between internalising problems and P50 ASG ratio (r = 0.470, p=0.010, see Table 5.4). Significant correlation was observed between anxiety/depression problem, and P50 ASG ratio (r = 0.369, p= 0.048, see Table 5.2); a similar effect was seen for somatic complaint problem and P50 ASG ratio (r = 0.372, p=0.047, see Table 5.3). From DSM-Oriented scale ADHD scores were positively correlated with P50 ASG ratio (r = 0.393, p= 0.043, see Table 5.5).

Correlations

			Anxiety depression	gatingratio
Kendall's tau_b	Anxiety depression	Correlation Coefficient	1.000	.369*
		Sig. (2-tailed)	.	.048
		N	17	17
	Gatingratio (ASG)	Correlation Coefficient	.369*	1.000
		Sig. (2-tailed)	.048	.
		N	17	17

*. Correlation is significant at the 0.05 level (2-tailed).

Table 5.2 Kendall's Tau correlation between ASG and Anxiety depression scores on ASEBA.

Correlations

			Gating ratio	Somatic Complaint
Kendall's tau_b	Gating ratio(ASG)	Correlation Coefficient	1.000	.372*
		Sig. (2-tailed)	.	.047
		N	17	17
	Somatic Complaints	Correlation Coefficient	.372*	1.000
		Sig. (2-tailed)	.047	.
		N	17	17

*. Correlation is significant at the 0.05 level (2-tailed).

Table 5.3 Kendall's Tau correlation between ASG and Somatic Complaint scores on ASEBA.

Correlations

			Gating ratio	Internalizing problem
Kendall's tau_b	Gating ratio	Correlation Coefficient	1.000	.470*
		Sig. (2-tailed)	.	.010
		N	17	17
	Internalizing problem	Correlation Coefficient	.470*	1.000
		Sig. (2-tailed)	.010	.
		N	17	17

*. Correlation is significant at the 0.05 level (2-tailed).

Table 5.4 Kendall's Tau correlation between ASG and Internalizing Problem scores on ASEBA.

Correlations

			ADHD	Gating ratio
Kendall's tau_b	ADHD	Correlation Coefficient	1.000	.393*
		Sig. (2-tailed)	.	.043
		N	17	17
	Gating ratio (ASG)	Correlation Coefficient	.393*	1.000
		Sig. (2-tailed)	.043	.
		N	17	17

*. Correlation is significant at the 0.05 level (2-tailed).

Table 5.5 Kendall's Tau correlation between ASG and ADHD scores on ASEBA.

In this group of adults with no prior history of psychiatric or behavioural disorders, a few participants were in the borderline or clinical range on some behavioural measures of ASEBA. Scores for each participant on the four measures can be seen in the graphs below.

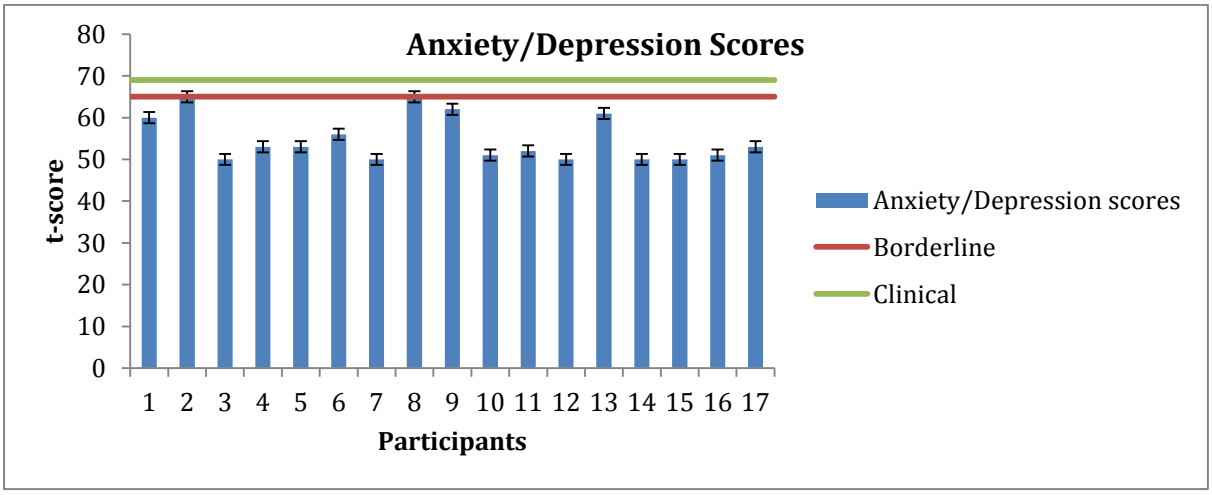


Figure 5.2 Graph represents distribution of anxiety/depression t-score on ASR syndrome scale across all participants.

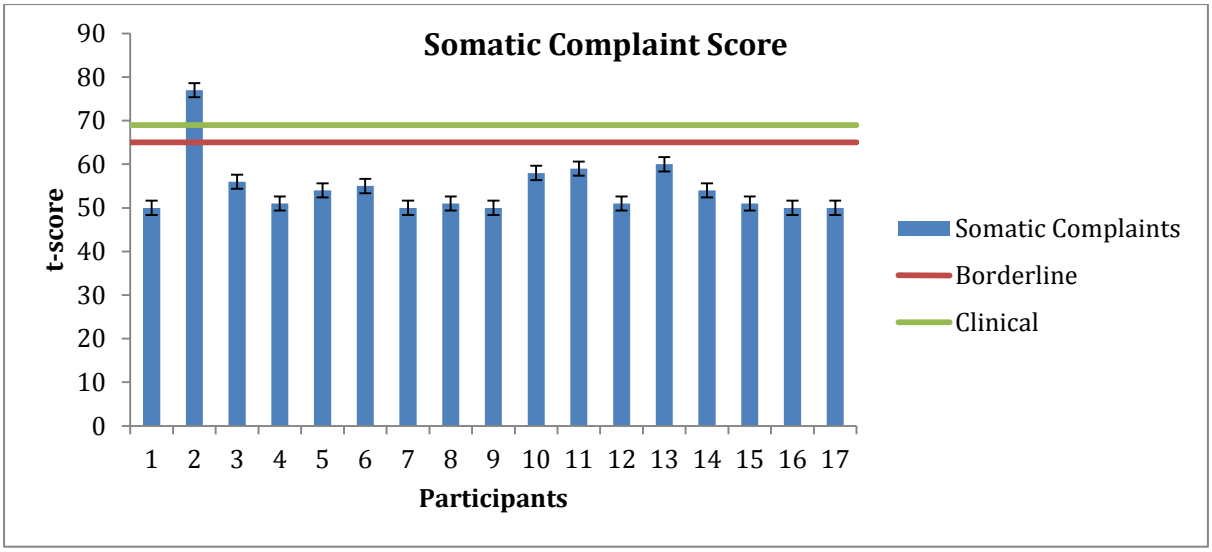


Figure 5.3 Graph represents distribution of t-score on somatic complaints measure on ASR syndrome scale across all participants.

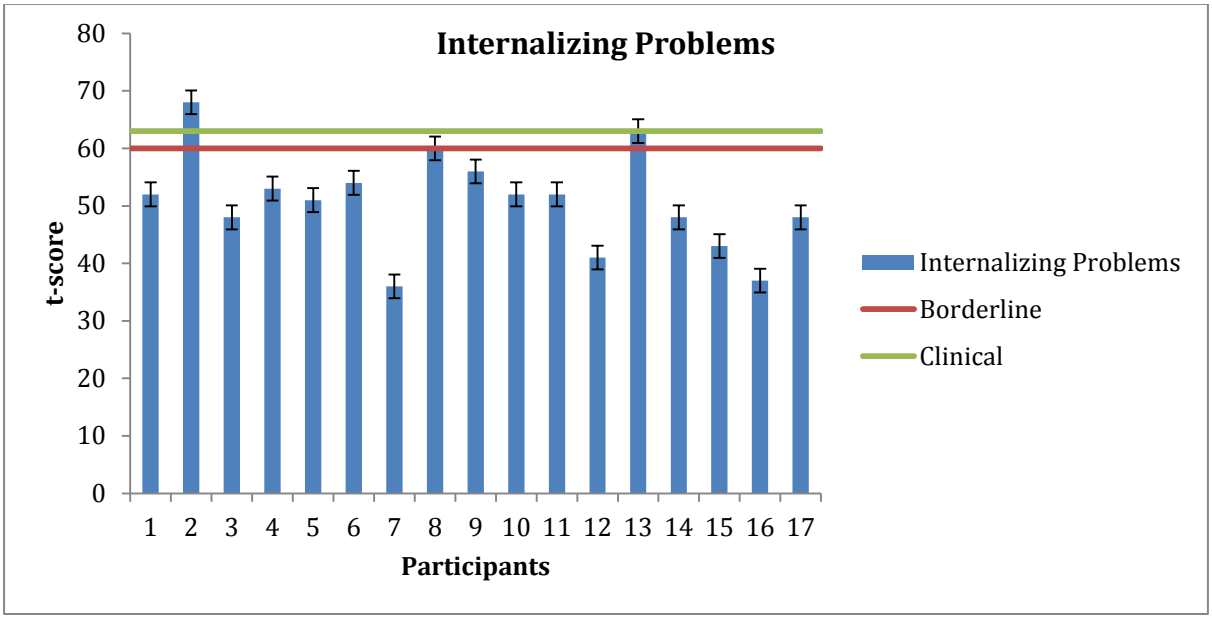


Figure 5.4 Graph represents distribution of t-score on internalizing problems across all participants.

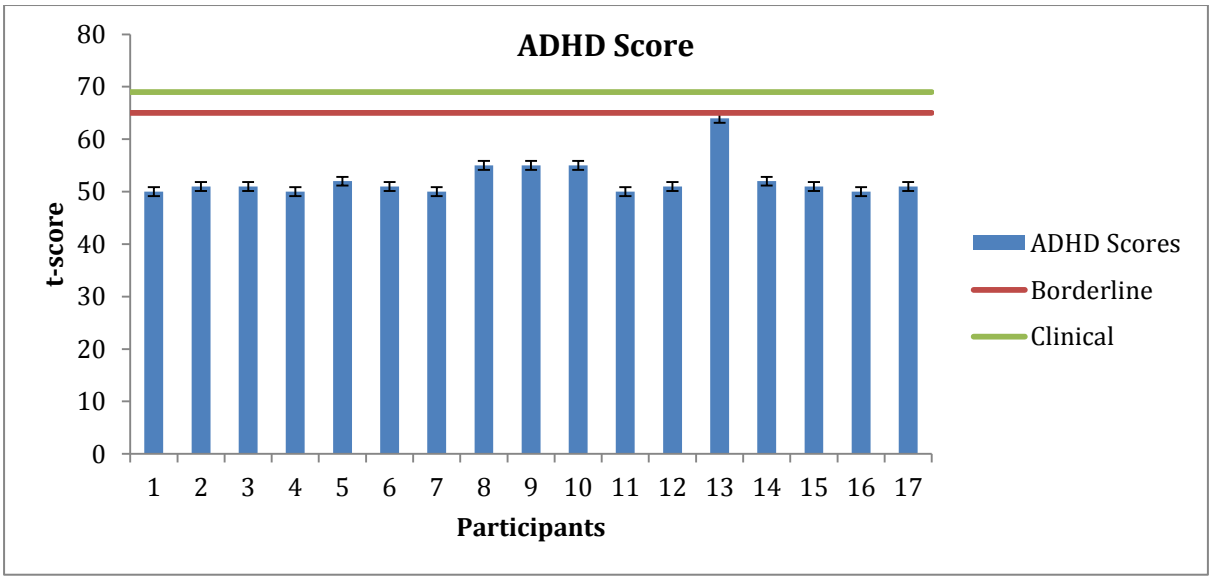


Figure 5.5 Graph represents distribution of ADHD t-score on ASR DSM oriented scale across all participants.

2. SIAS scores and sensory gating

A positive correlation was found between social interaction anxiety scores and P50 ASG ratio after Bonferroni correction (Pearson's r= 0.639, p= 0.003, see Table 5.6). The distribution of SIAS scores across all participants can be seen in Figure 5.6 below.

Correlations

		Gating ratio	SIAS score
Gating ratio	Pearson Correlation	1	.639**
	Sig. (2-tailed)		.003
	N	19	19
SIAS score	Pearson Correlation	.639**	1
	Sig. (2-tailed)	.003	
	N	19	19

**. Correlation is significant at the 0.01 level (2-tailed).

Table 5.6 Correlation between ASG and SIAS scores in 19 participants.

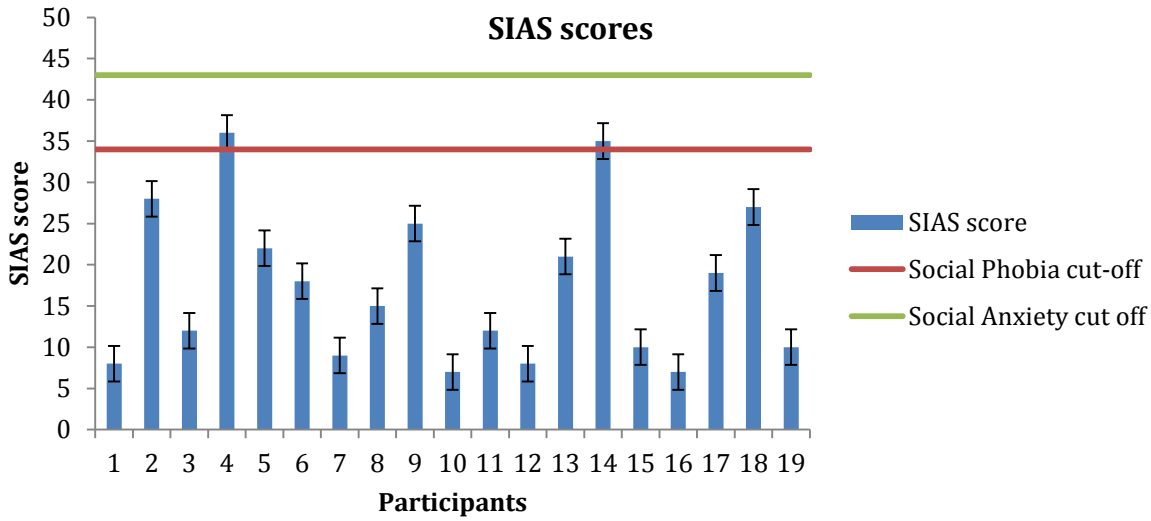


Figure 5.6 SIAS scores across all participants with red line indicating cut off for social phobia and green line suggesting social anxiety.

3. ASP and sensory gating

The mean value of 15 participants for each sensory processing pattern can be seen in Figure 5.7. No significant association was found between sensory processing patterns (low registration, sensory sensitivity, sensory seeking and sensory avoiding, see Table 5.7) and P50 ASG ratio as most participants scored similar to healthy people for each category.

Figure 5.7 Mean value of 15 participants in each sensory processing pattern; each mean value falls in similar to most people range as seen in the green rectangular box. (Symbol representation: (++) much more than most people, (+) more than most people, (=) similar to most people, (-) less than most people, (--) much less than people.

Correlations

		Gating ratio	Low Registration
Gating ratio	Pearson Correlation	1	.189
	Sig. (2-tailed)		.537
	N	15	15
Low Registration	Pearson Correlation	.189	1
	Sig. (2-tailed)	.537	
	N	15	15

Correlations

		Gating ratio	Sensation Seeking
Gating ratio	Pearson Correlation	1	-.202
	Sig. (2-tailed)		.508
	N	15	15
Sensation Seeking	Pearson Correlation	-.202	1
	Sig. (2-tailed)	.508	
	N	15	15

Correlations

		Gating ratio	Sensory Sensitivity
Gating ratio	Pearson Correlation	1	.026
	Sig. (2-tailed)		.933
	N	15	15
Sensory Sensitivity	Pearson Correlation	.026	1
	Sig. (2-tailed)	.933	
	N	15	15

Correlations

		Gating ratio	Sensation Avoiding
Gating ratio	Pearson Correlation	1	.168
	Sig. (2-tailed)		.582
	N	15	15
Sensation Avoiding	Pearson Correlation	.168	1
	Sig. (2-tailed)	.582	
	N	15	15

Table 5.7 Shows correlation between ASG and sensory processing patterns (No significant correlations were observed)

5.4 Discussion

The findings from this study suggest that participants with reduced P50 suppression scored higher on self-reported problems in anxiety/depression, somatic complaints and internalizing problems, and had higher scores on the DSM-IV (APA, 1994) oriented scale for ADHD measured by ASEBA. These results are supportive of the findings in the infant P50 ASG study (Hutchinson et al., 2013), where high scores on attention and anxiety/depression in the overall externalizing symptoms strongly correlated with diminished P50 ASG. This finding can be interpreted hypothesising that preschool externalising symptoms predict later internalising symptoms, possibly because children with early externalizing symptoms may find it challenging to form relationships with peers, and this may later lead to internalising symptoms like anxiety and depression (Hutchinson et al., 2013). Furthermore, social anxiety and social phobia were found to be strongly associated with P50 ASG as well, suggesting that higher scores on SIAS might be indicative of reduced P50 suppression. When we consider that schizotypal personality traits co-occur with social anxiety, this ASG finding is not unforeseen. However, none of the participants scored higher than 43, indicating no one was identified with clinically relevant social anxiety disorder. This is the first study to have measured the relationship between ASEBA scores, social anxiety and P50 ASG. No correlation found between the four sensory processing patterns of the ASP (low registration, sensory sensitivity, sensory seeking and sensory avoiding) and P50 sensory gating. There is no previous evidence to benchmark our findings against. The sample size for this part of the study ended up being very small and we cannot exclude that the negative finding might be related to the study being underpowered. We will need a much larger sample to formulate firm conclusions, given the relatively small variance in the recruited sample. Results from this study however suggest that P50 gating deficit is strongly linked with behavioural and personality traits, thus questioning the role of P50 ASG measure as potential endophenotype for schizophrenia.

5.4.1 Behavioural measures and P50 ASG

Unexplained or multiple somatic symptoms are strongly associated with coexisting depressive and anxiety disorders (Kroenke, 2005). DSM-IV (APA, 1994) presents six somatic symptoms associated with generalized anxiety disorder: restlessness, increased fatigability, difficulty in concentrating, irritability, muscle tension, and sleep disturbance. Studies suggest that about 50% of the patients report

somatic symptoms exclusively when presenting their depressive disorder. A close relationship between depressed mood and symptoms of pain, especially of chronic pain, has been established in many empirical studies (refer to Kapfhammer, 2006). The co-existence of these two conditions could possibly explain the strong correlation of P50 ASG not only with anxiety and depression but with somatic complaints as well. Previous studies have shown that GABAergic systems play an essential role in the pathophysiology of anxiety and depression. Depressed patients tend to show reduced GABAergic function as suggested by pharmacological, as well as neuroimaging studies (refer to Kalueff &Nutt, 2007). Similarly, the GABAergic system is an important target of the treatment of anxiety and depression, and received significant attention in the development of pharmacological interventions for anxiety and mood disorders (Krystal et al., 2002; Nutt et al., 2002). As discussed in chapter 3 and 4, low levels of GABA specifically in prefrontal cortex have been reported in schizophrenia patients as well and this deficit is cardinal to impaired sensory gating (Marsman et al, 2014). The strong correlation between high anxiety (as well as social anxiety/ depression score) and high P50 ASG ratio could both be explained by low GABAergic function. The evidence provided in chapter 4 suggesting that P50 suppression is best explained by fronto-temporal connections and the knowledge of the importance of GABAergic transmission in these networks could be interpreted as supportive of significant role of inhibitory connectivity on both the P50 ASG and dimensional aspects of mood. Furthermore, evidence suggests that the prefrontal cortex reported to play significant role in P50 suppression, also has a crucial role in voluntary suppression of sadness, and chronic incapacity to suppress negative emotions, a major factor in the origin of depression and anxiety (Levesque et al., 2003).

The results from current study do not allow a distinction between inattention and hyperactivity and this limits the possibility to formulate a strong conclusion. As mentioned in the introduction impulsivity has been strongly correlated with high P50ASG ratio and it co-occurs with other behavioural measures (anti-social personality, schizotypy). P50 ASG deficit in ADHD could also be related to ineffective GABA transmission, as shown in an MR spectroscopy study performed in adults with ADHD (Edden et al., 2012). Insufficient norepinephrine and dopamine levels, which impair prefrontal cortex function in ADHD, could possibly lead to P50ASG deficit in this clinical group considering the crucial role prefrontal cortex in suppression phenomena. In particular dopamine has been reported to stimulate postsynaptic receptors which are responsible for suppression of irrelevant stimulus (Arnsten,

2009) and reduced levels of this neurotransmitter has been reported in ADHD patients.

Chapter 6: Effect of Visual Emotional Stimuli on P50 ASG

6.1 Introduction

As mentioned earlier in chapter 1, no studies so far have investigated whether sensory gating is modulated by concurrent processing of stimuli of other modality and in particular the relationship between processing stimuli with emotional valence and sensory gating. Throughout chapters1 to 5 we were able to characterize the spatio-temporal properties of P50 ASG; in this chapter the focus is on evaluating whether face stimuli with positive and negative emotional valence have any influence on P50 ASG.

Face processing can be represented as a two-component process: perception of the physical properties of the stimulus and emotion recognition. From a cognitive neuroscience perspective (LeDoux, 1993) cognition and emotion are seen as separate but closely interacting processes. It has been proposed that processing and responding to emotionally evoked information appears to be involuntary and precede conscious perception as well as cognitive processing. The term 'emotion' has been described as an "intensive, adaptive and phasic change in multiple physiological systems including somatic and neural components in response to the value of a stimulus" (Adolphs, 2002). Studies have suggested that human beings can differentiate, classify and identify emotions solely on the basis of the geometric visual properties of stimulus image. Prior to understanding emotion recognition and identification, it is vital to discuss the specific properties of face processing since the face is the primary structure to be visually processed before examining any other features of the individual (gender, age, emotion etc.).

6.1. 2 Spatial processing of face perception and facial expression

Based on previous findings from neurophysiological and neuroimaging studies (Allison et al., 1999; Bentin et al., 1996), Haxby et al. (2000) proposed a neural model to explain the networks involved in face perception and their spatial localisation. This model identifies two systems, which Haxby defines as *core* and *extended*. Core system comprises of occipito-temporal visual extrastriate areas that play a crucial role in the visual analysis of faces; the extended system comprises other neural systems whose functions are not primarily visual but that play a

significant role in extracting critical information from faces such as emotion, personal identity, name, and spatially directed attention.

A recent fMRI mapping study (Rossion et al., 2012) distinguished the areas involved in perception of face vs inanimate objects such as cars. It was found that the occipital lobe, the fusiform area, the superior temporal sulcus and the amygdala all played a crucial role in discriminating faces from the inanimate objects. Recognition of emotional facial expressions draws not only on brain areas involved in visual processing of the structural aspects of the face, but also recruits brain areas involved in processing the emotional information. Further fMRI studies have suggested that along with the occipito-temporal and fusiform gyrus which plays a prominent role in the processing of facial emotional expression, the prefrontal areas, the right anterior cingulate, the right inferior parietal cortex and the mesial temporal lobe structures (amygdala and hippocampus) are also involved in the analysis of faces and facial expressions. As far as processing the emotional aspects of face perception, increased activity is observed in both right fusiform gyrus and amygdala when looking at faces displaying emotions (sad, happy, fearful) as compared to neutral faces (Vuilleumier & Poutois, 2007). Neuroimaging studies have reported activation of the amygdala to fearful faces (Breiter et al., 1996; Whalen et al., 1998; Vuilleumier et al., 2001), whereas activation in the insula and basal ganglia has been associated with processing of facial expression of disgust (Phillips et al., 1997). However, a meta-analysis of fifty-five neuroimaging studies concluded that amygdala activation is not specific to fearful faces, as it is present in other emotional contexts as well, thus suggesting that the amygdala responds to the salience of the emotional stimuli rather than to specific emotional categories (Phan et al., 2004). Although there is an extensive literature on anatomical sources involved during emotional facial perception, we are far from having identified a single neural network that accounts for the complexity of this process. Since face perception findings were based on behavioural and neuropsychological studies, while we have detailed knowledge of the neural networks and neuroanatomical structures involved in the process, less is known about the temporal properties of this complex process. Similarly, Haxby's model postulates a distributed neural system for face perception but is unable to account for the temporal aspects of this progression. To overcome this issue, Adolphs (2002), modified Haxby's model to include temporal information related to face processing. This model is discussed in the next section.

6.1.3 Temporal processing of face perception and facial expression

With the help of EEG and MEG studies, face-specific modulation of ERPs were investigated to determine the time course of modular processes involved during facial identification. These studies consistently report that faces are able to elicit a negative potential at a latency of 170 ms, and that this response has a topographic distribution with maxima in the lateral posterior temporal regions (Bentin et al., 1996; Eimer, 2000). This response was specific to faces and was not recorded when non-face stimuli were presented. The N170 is the most consistently reported response associated with face perception. The strongest response specific to face processing has been observed between 140 and 170 ms in the fusiform gyrus (Bentin et al., 1996; Halgren et al., 2000). However, several studies have shown that the first response to face stimuli occurs much earlier, between 50 and 90 ms post-stimulus in the occipito-temporal cortex, and it can be associated with categorization of visual stimuli (Van Rullen & Thorpe, 2001). A later response specific to emotional face expressions was proposed to occur in the occipital cortex between 80 and 110 ms post-stimulus (Pizzagalli et al., 1999; Halgren et al., 2000). According to Adolph's model (Figure 6.1), face perception occurs around 170 ms, and this is followed by emotion recognition between 170 to 300 ms. Post 300 ms the sensory and perceptual processing is followed by cognitive processing which can last a few seconds depending on the task.

Figure 6.1 Temporal processing of emotional facial expressions and its neural networks taken from Adolphs (2002).

Recently, studies have focused on the N170 to determine if this face-selective component was modulated by the type of emotions expressed by the face stimuli. While some studies reported amplitude modulation as a result of an emotional effect (Vuilleumier & Pourtois, 2007), other studies found no differences (Krolak-Salmon et al., 2001). Nevertheless, several studies have reported influence of emotional expressions on late ERP responses, from around 200 ms post-stimulus onset (Krolak-Salmon et al., 2001; Sato et al., 2001). It has been observed that late ERP responses to emotional facial expressions continue over a prolonged period of

time following stimulus onset (Krolak-Salmon et al., 2001; Ashley et al., 2004) and that this is not specific to the type of emotional expression, possibly reflecting more complex cognitive processes related to emotion processing (Vuilleumier and Pourtois, 2007).

6.1.3 Effect on visual and auditory processing

Studies conducted on healthy individuals, found that emotional visual stimuli had substantial effect on visual evoked potentials (VEPs), specifically on the late component P300 (refer to Yamashita et al., 2005), suggesting a potential interference due to emotional processing. However, the effect of emotional visual stimuli on auditory information processing has not received much attention. A mismatch negativity (MMN) study was performed on seven healthy adults, in which participants were shown pictures from International Affective Pictures System (mutilations, mushrooms and pleasant sceneries shown for 20 s each) while a tonal auditory stimulus was presented. It was found that MMN was very similar during neutral and negative slide viewing, but was significantly attenuated during viewing of positively valenced slides. This was interpreted as reflecting a potential modulation of stimuli with positive valence (signal of non-threatening environment) and low arousal on the MMN response (Surakka et al., 1998). A MEG study investigated the effect of visually evoked emotional stimuli using pictures from International Affective Picture System on auditory sensory gating (Yamashita et al, 2005). Participants were instructed to view slides of varying emotional valence and arousal prior to the presentation of clicks. This study found that, contrary to neutral and positive slides, negatively valenced slides significantly reduced the P50 suppression, suggesting that negative emotional stimuli might modulate sensory gating. However, no study to date has investigated the specific effect of emotional face perception on P50 ASG in healthy adults.

6.1.4 Aim

The objective of this study was to determine the effect of an emotionally evoked visual stimulus on P50 ASG.

6.2 Methodology

6.2.1 Participants

Thirteen healthy participants (5 males, 8 females) with normal or corrected to normal vision (mean age 34, S.D. 11 years) gave full informed consent to take part in the study, which was approved by the Aston University Human Science Ethical Committee. These were taken from the same participant pool that was recruited to take part to the study described in chapter 3. The inclusion exclusion criteria were same as first study. Participants abstained from having caffeine prior to the study to ensure consistency with first study.

6.2.2 Experimental Design

As briefly described in Chapter 2, the paradigm was designed based on the only previous MEG study (Yamashita et al., 2005). Emotional face stimuli and auditory clicks were presented using a script developed in Presentation (NeurobehaviouralSystems, Inc.) and participants viewed the computer monitor through a projector placed in the shielded MEG room. Considering the time it takes to process facial features and its emotional properties, the image was displayed for 500 ms. An inter-stimulus interval of 9.5s – 1s (at random) was chosen to allow the return of neural function to baseline prior to the presentation of the paired clicks. These were presented with a stimulus onset asynchrony of 250 ms. The inter trial interval was randomised between 8-9 s. Stimuli corresponding to three types of facial emotions were chosen randomly from the NIMSTIM database (Tottenham et al., 2009, details explained in chapter 2): these were classified as Neutral, Happy and Fearful. Each emotional face was chosen randomly not selected by the gender or ethnicity of the person in the picture. There were 16 pictures in total, four for each emotional representation (neutral, happy and fearful). Each picture was shown 10 times randomly. As a result, each emotion was repeated 40 times, resulting in 120 trials in total for pictures as well as paired clicks. This study lasted between 20 and 22 minutes. For this study, the response to the auditory click paradigm without any interruption by visual stimulus was required as a baseline measure, which was recorded during study 1 mentioned in chapter 3. The procedure for preparing participants for the MEG recording and data acquisition parameters were the same as those reported in chapter 2.

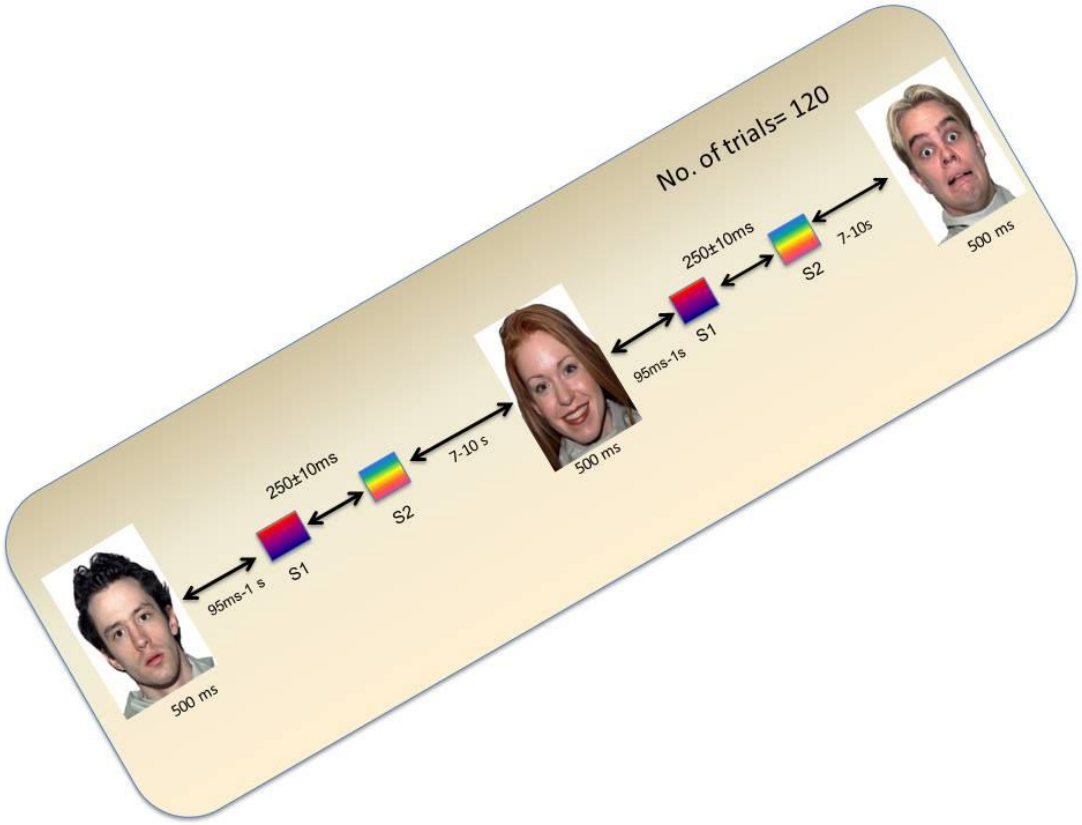


Figure 6.2 Stimulus design for the emotional face study, where face stimulus is followed by the paired-click auditory stimulus (ITI- 7-10s, ISI-95ms-1s).

6.2.3 Modifications of the paradigm: new evidence

In the new paradigm, each face was shown for 6 seconds (instead of 500 ms) based on Yamashita et al., 2005 and the ITI was shortened from 7- 10 s to 2-3 s to reduce the length of the paradigm all the other aspects of the stimulus were kept same. Due to time constraint only two participants were tested with this new stimulus design.

6.2.4 Data Analysis

The ERP responses from this study were analysed at sensor level, to identify significant differences in the gating ratio as a function of the emotional valence of the

emotional stimuli preceding the paired clicks. The amplitude and latency of the P50 component for S1 and S2 were computed using the GFP as discussed in Chapter 3. These S1 and S2 responses followed by each condition will be referred to as N1 and N2 (following neutral stimulus), H1 and H2 (happy condition), F1 and F2 (fearful condition), and S1 and S2 (for baseline condition from Study 1, chapter 3). As mentioned in Chapter 1, P50 has high test-retest reliability and validity, therefore we used the latency intervals of S1 and S2 from the baseline measure collected in the previous study.

The data set was analysed in Brainstorm software (Tadel et al., 2011). The raw data file was tSSS max filtered using Maxfilter 2.1 software (details explained in Chapter 2). The epoch length of the max filtered file was -2 s to 2 s, in order to include face ERP as well as responses to the paired clicks. The epoched data was filtered (High Pass 1 Hz, Low Pass 70 Hz). Filtered data was visually inspected for the presence of artefacts in the window of analysis. Baseline correction was applied -2000 to 0 ms. Average was calculated on the whole dataset and 40 trials for each condition were averaged. From the average data, GFP was calculated for all three conditions for the S1 and S2 P50 responses to obtain the amplitude measure for each category (N1, N2, H1, H2, F1 and F2). To investigate within subject differences, the non-parametric Friedman's test was applied followed by Wilcoxon Signed Rank test after Bonferroni adjustment was made. Since GFP measures were normally distributed, between subjects One Way ANOVA was performed to compare three conditions against baseline.

6.3 Results

Within Subject Analysis

P50 Auditory Sensory Gating Ratio (GR= S2/S1 P50 amplitude) was compared in all four conditions (N2/N1 =NGR, H2/H1 = HGR, F2/F1 = FGR and S2/S1 = BGR). Significant difference in the gating ratio between four conditions was found ($\chi 2$ (3) = 19.06, $p<0.001$). Post hoc analysis with Wilcoxon signed rank tests was conducted with a Bonferroni correction resulted in a significance level p= 0.012. There no significant differences between gating ratio for three conditions (neutral, happy or fearful (HGR-NGR z= -1.05, p= 0.91; FGR-NGR z= -1.75, p= 0.86; FGR-HGR z= -1.05, p=0.91). The gating ratio was significantly lower for baseline as

compared to the three conditions with emotional face stimuli (BGR-NGR z= -3.11, p =0.002; BGR-HGR z= -3.18, p=0.001; BGR-FGR, z= -3.11, p=0.002).

After modification to the paradigm the results from two participants indicate that normal suppression was observed in those two participants following emotional face perception (Participant 1 NGR = 0.73, HGR=0.74, FGR=0.61, BGR = 0.64; Participant 2 NGR =0.75, HGR=0.60, FGR =0.52, BGR = 0.55). Contrary to what was observed in the same participants during the short presentation experiment, suppression was strongest in clicks presented post fearful faces, negative emotion (fear).

Between Subject Analysis

There were no significant differences in the S1 amplitude for neutral, happy, fearful faces when compared to participant's baseline response. However, S2 amplitude was significantly different in three emotional face conditions as compared to baseline S2 response. Gating ratio suggests that suppression following face stimulus response was very weak compared to that measured in the baseline condition. The average amplitude responses for three conditions during paired click and baseline response can be seen in Table 6.1 below along with the respective average latencies.

	Baseline	Neutral	Happy	Fearful
Mean S1 amplitude (uV)	212.16±70(S1)	224.92±62(N1)	225.76±57(H1)	225.23±70(F1)
Mean S2 amplitude (uV)	141.88±63(S2)	213.84±48(N2)	218.30±48(H2)	215±55 (F2)
Mean Latency S1 (ms)	53±7	56±4	58±6	55±4
Mean Latency S2 (ms)	52±7	53±4	54±5	52±4
GR (S2/S1)	0.66	0.95	0.96	0.95

Table 6.1 Descriptive statistics across all participants Global Field Power S1 and S2 for each condition.

A significant difference between S1 and S2 amplitude in the baseline condition was found ($t(1,12) = 2.49$, $p=0.028$), whereas no significant difference was observed between amplitude N1 and N2, H1 and H2, F1 and F2 ($t(1,12)= 0.575$, $p=0.576$; $t(1,12)= 0.426$, $p=0.678$; $t(1,12)= 0.375$, $p=0.714$ respectively).

The S1 amplitude between baseline and each condition (N, H, F) was compared using One Way ANOVA (between subjects); no significant differences in the S1 amplitude across all four conditions (baseline S1, N1, H1 and F1.) ($F(3,48)=0.132$, $p=0.941$). However, significant differences in S2 amplitudes were observed across four conditions ($F(3,48)= 4.46$, $p =0.008$). Post hoc analysis using Tukey's HSD was performed and no significant differences were observed in the S2 amplitude of three emotional conditions (N2, H2, F2) while significant differences were observed in S2 amplitude for baseline measure against S2 for three conditions. Data showed that S2<N2, S2<H2 and S2<F2 at $p<0.05$, suggesting that S2 amplitude for the baseline measure was significantly less than S2 amplitude across three conditions.

6.4 Discussion

Findings suggest that P50 ASG is modulated by exposure to emotional visual stimuli in healthy adults. We found no difference between S1 amplitude for baseline and that of the three emotional face categories. However, S2 baseline amplitude was significantly lower compared to that recorded after presentation of the face stimuli. These results support the view that P50 ASG is affected by the exposure to face stimulus prior to the double clicks, in the direction of reducing the suppression of the response to the second click. In a study by Schupp (1999), positive shift occurred in long-latency ERPs around 200-300 ms after picture onset (for affective stimulus as compared to neutral), reaching its maximum amplitude approximately 1 s after picture onset, and was sustained for the 6 s picture presentation period. The results of this study failed to replicate the finding (Yamashita et al., 2005) that suggested that modulation of the P50 ASG is different for stimuli of different valence. In this study the stimulus was derived from the International Affective Picture System (Mutilations, buildings and pleasant landscapes), and shown for a longer period 6s as compared to our study, in which the stimulus was presented for short period of time 500 ms, only sufficient for recognition of the emotional and not the cognitive aspects of the stimulus. Findings from the modified stimulus where face was presented for 6s, encourage us to investigate this effect more systematically in a future development of the current study. It is possible that the P50 suppression phenomenon was concurrent with residual cognitive processing of the emotional face perception of the previous stimulus, which might have resulted in a weak suppression.

From the current study, it can be suggested that either emotionally evoked visual stimuli alter P50 auditory sensory gating or it could be due to face perception itself as the neutral condition showed similar effect as happy and fearful. These findings provide evidence which reports emotional face perception as a complex process, with long processing time window (6s). Recent study examining effect of emotional processing on P50 gating in bipolar disorder, reported that processing of disgust emotion reduced the gating ability (stronger S2 amplitude) in this clinical group as compared to processing of neutral face (Vuillier et al,.2014). It was found that compared with controls, patients with BD failed to engage prefrontal cortical structures while processing the disgust emotion, and instead they activated the hippocampus and caudate This evidence suggests that patients have greater engagement in bottom-up processes during disgust processing while controls activate top-down processes (refer to Vuillier et al., 2014). Findings from chapter 4,

provide evidence on the crucial role of top down processing during suppression, thereby suggesting that top-down processes are dysfunctional in bipolar disorder, and this may be more evident when concurrently processing the disgust emotion. As mentioned above in section 6.1, schizophrenia patients show robust recognition to fearful emotion, so a similar study as above, might facilitate understanding of emotional dysfunction during P50 ASG in this clinical group. Neurophysiological and neuroimaging studies (Allison et al., 2000; Haxby et al., 2000), report that facial stimuli are processed in a distributed neural system, which seemingly differ depending on type of emotion. It has been indicated that superior temporal sulcus plays an important role in processing dynamic extended features of faces specially emotional expression(Schupp et al., 2004), and from our findings in chapter 3, this region is the main generator of auditory response. Along with this, prefrontal cortex is reported to be strongly involved when emotional pictures are presented for long period of time capturing both early and late processing components. Whereas, fast picture presentation processes early components only (Schupp et al.,2004), this might affect the findings in our study, as prefrontal cortex is strongly associated with P50 suppression as identified in chapter 3. Yet, more understanding might be gained if data is analysed to source level, to understand processing of emotional face and areas involved. It is not yet clear how multisensory processing occur at neuronal level within auditory or visual regions, specifically regions in temporal association cortex (Stein & Stanford, 2008).

6.4.1 Future recommendations

The influence of emotional stimuli on gating ratio is still largely unexplored. Due to the dimensionality of this neurophysiological marker, it might be beneficial to extend the recruitment to increase the power of study. An even less explored area is the effect of emotional/affective valence of stimuli presented through the auditory pathway. Since brain regions involved in emotion processing and sensory gating overlap, it will be intriguing to examine neural network during multimodal processing as investigated by Vuillier et al.,2014. The Montreal affective voices used for fMRI studies could be a good starting point but require significant adaptation and validation before it can be used in MEG studies due to their long duration.

Chapter 7: General Discussion

7.1 Key Findings

P50 ASG as described earlier, is a process by which irrelevant information is filtered-out in the early stages of sensory processing, reducing sensory overload and thereby facilitating efficient cognitive processing. There is an increasing body of evidence to suggest that its function is impaired in certain clinical disorders such as schizophrenia, for which it has been proposed as a candidate endophenotype. In contrast, there is limited information from human studies regarding its neural bases; this was the foremost purpose of our study. Neuroimaging techniques are eminently suitable to deconvolve the time-course and spatial properties of the P50 ASG phenomenon and among these techniques Magnetoencephalography offers the best combination of temporal and spatial resolution with the added advantage of allowing the characterisation of the spectral properties of this response.

Our findings were able to provide further evidence in favour of a crucial role of the superior temporal gyrus and of the prefrontal cortex in the gating process (Thoma et al., 2003; Huang et al., 2003; Korzyukov et al., 2007). Connectivity analysis of the response to paired-click stimuli gave the first confirmation from non-invasive studies of the intracranial finding of Korzyukov et al. (2007) that the frontal cortex has a direct modulating effect (backwards connections in the DCM modelling) . Nonetheless, compared to intracranial recordings, MEG allows investigating connectivity patterns at the whole brain level and is a critical advantage for future studies intended at verifying whether candidate psychiatric disorders present abnormal connectivity patterns during sensory gating. Due to its non-invasive nature MEG can be applied to understand sensory gating process better in infants and young children.

Data from this study on connectivity pattern of P50 ASG using DCM indicated that first click (S1) requires temporo–frontal connections (STG-IFG) and that these are driven by excitatory pyramidal cells (based on forward connection model).The second click (S2) can be explained by backward connections from the frontal to the temporal lobe. According to the DCM analysis, processing of the second click is characterized by strong activation of GABAergic interneurons in the IFG that drive the STG node of the network. These findings confirm the inhibitory nature of the gating suppression, and provide evidence for Cromwell's (2008) proposal based on neural memory trace hypothesis. The significant role of the prefrontal cortex in the S2 response suppression, could possibly explain P50 ASG

deficit in patients with prefrontal dysfunction/damage. The P50 ASG abnormalities would therefore be the expression of abnormalities at neural network level, rather than a diagnostic tool of any specific disorder. Role of prefrontal cortex also supports findings from Brinkman & Stauder, 2007, which suggests that sensory gating varies in young children below 8 years and matures when child is around 8 years old. This could possibly be explained due to frontal lobe development during early childhood.

The measures of connectivity pattern during P50 ASG supports the classical model of ERP generation, indicating the role of cortical cells (pyramidal –excitatory, and inhibitory interneurons) in the process of ERP production. As reported earlier, cortical cells respond to external stimulation by modulating firing rates and thereby generating the event-related response (Brosch and Schreiner, 1997, 2000). On the contrary, neural oscillatory patterns identified in our study support the phase-reset model, suggesting that the P50 response is characterised by a complex event-related spectral perturbation, with alpha and beta desynchronisation, and gamma synchronisation. This notion about alpha-beta desynchronisation and gamma synchronisation has been previously reported for visual and somatosensory systems (Gaetz and Cheyne, 2003; Stevenson et al., 2011; Pammer et al., 2004). Models of ERP generation have been conflicting: some studies have suggested that sensory processing is strongly reliant on changes in cortical oscillatory activity (Fiser et al., 2004; Jansen & Brandt, 1991; Kisley & Gerstein, 1994), while others have proposed that ERP generation is independent of on-going brain activity (Makinen et al., 2005). Considering the potential phase shift in neural oscillatory pattern during P50 ASG and evidence of cortical neuronal activity from DCM connectivity model, findings from this study support the fire-fly model proposed by Burgess (2012), according to which ERP generation is a result of both evoked changes in spectral power and progressive shifts of phase during the post-stimulus period. A further result of the present study is the confirmation that activity during S2 (suppression phase) of the paired-click paradigm is characterised by higher gamma band power in the prefrontal cortex. This is a novel finding since previous studies on P50 ASG have not investigated oscillatory pattern in the source-space. However, a number of studies have reported atypical neural oscillations in the gamma band in patients with Schizophrenia, (Farzan et al., 2010; Gandal et al., 2012; Uhlhaas and Singer, 2006) and this aberrant spectral pattern could possibly be a distinctive pattern in this clinical group.

On the basis of our findings and the existing body of literature, we could attempt an integrated explanation of the neural mechanism underlying P50ASG. The activity of inhibitory GABAergic interneurons in the prefrontal cortex appears to be

central to the P50 suppression phenomenon as confirmed by connectivity findings (refer to chapter 4) and its spectral signature is a gamma-band neural synchronisation in the prefrontal cortex. Previous studies based on animal models using electrophysiology and optogenetics (Gonzalez-Burgos et al., 2011; Sohal et al., 2009) reported a key role for fast-spiking parvalbumin-positive interneurons in generating synchronous neural oscillations in the gamma frequency band (see Chen et al., 2014 for review), suggesting strong link between GABA function and gamma-band neural synchrony; this association was also observed in healthy individuals during visual tasks (Muthukumaraswamy et al., 2009). As described by Gonzalez-Burgos et al (2011), precise circuit mechanisms of synchronized oscillations via GABA-A receptor-mediated inhibition may involve rhythmic interneuron firing with trains of inhibitory postsynaptic currents, emphasising the need for adequate GABAergic transmission for the generation of synchronous gamma neural oscillations. GABA levels were found to be significantly low in the prefrontal cortex in schizophrenia patients as compared to healthy adults (Marsman et al., 2014). This evidence indirectly supports our findings; low GABA levels in patients with schizophrenia could result in reduced excitation of inhibitory inter-neurons in the frontal cortex; and it could be associated with aberrant neural oscillations in gamma frequency band in the same region.

Further evidence from behavioural measures (from ASEBA and SIAS), indirectly support the crucial role that GABA level might play in P50 suppression. High scores on anxiety/depression, ADHD, and social anxiety are positively correlated to P50 ASG ratio. Previous pharmacological and neuroimaging studies (Krystal et al., 2002; Nutt et al., 2002; Kalueff and Nutt, 2007; Edden et al., 2012) have shown that adults with anxiety/depression and ADHD show low GABA levels in the frontal cortex, in line with the reported P50 ASG deficit in these patients.

To conclude it can be suggested that top-down processes (fronto-temporal), gamma-band neural synchrony, and GABA levels in the prefrontal cortex play a crucial role in understanding the underlying mechanism of P50ASG. Considering the association of P50 with behavioural measures and other clinical deficits its role as candidate endophenotype for schizophrenia is certainly debatable. It is more plausible to consider the P50 ASG as an informative probe of the functioning of temporo-fronto-temporal networks, highly dependent on GABA-ergic function, hence potentially aberrant in a number of diagnostic categories the include disrupted fronto-temporal connectivity.

7.2 Limitations and Future Recommendations

Considering this is the first study to investigate non-invasively connectivity patterns during P50ASG, I found it challenging to formulate conclusive statements based on the relatively small sample size, particularly when investigating the relationship between P50 ASG and behavioural measures. Some of these measures (ASG) have shown very limited variability in healthy participants, making the correlation study with ASG statistically not meaningful. It is therefore essential to consider the results in Chapter 5 as preliminary. It might be beneficial to collect systematically behavioural measure of sensory processing when performing P50 ASG study, as it could possibly shed light on the dimensionality of this phenomenon.

In relation to the current findings there are a number of future avenues that could be explored. It might be useful to perform a comprehensive comparative sensory gating study understanding its development in infants, young children, adolescents, adults and older adults. Such study can provide with a better understanding about sensory gating in children as this area is still controversial.

The P50 ASG abnormalities are increasingly appearing as not schizophrenia-specific. It might therefore be enlightening to perform a study with a similar methodology as the current one to investigate whether disorders characterised by fronto-temporal aberrant neural oscillatory and connectivity patterns share similar profiles. As far as schizophrenia, given the evidence of low GABA levels in prefrontal cortex, combined GABA spectroscopy using MEGA-PRESS sequences and MEG-based measures of oscillatory behaviour in the gamma band and connectivity measures could provide further insight and inform further development of pharmacological interventions for these patients. Possible disruption in top down processes in schizophrenia can help understand the motivational impairment in this group which is a critical factor that contributes to their functional disability. Previous evidence (Strauss et al., 2013 & Millan et al., 2012) suggests that motivational impairment is not present due to loss of hedonic state and reward appreciation, but rather in terms of defective cortico-striatal integrated processes essential for reward acquisition and anticipatory pleasure (Millan et al., 2014). With pharmacological interventions it might be possible to overcome motivational

impairment which can further help adhere better to the treatment, and improve quality of life.

It will be stimulating to extend the study with modified paradigms to investigate the effect of visual emotional stimuli on P50ASG in healthy adults. Altered processing of fearful faces has been reported in patients with schizophrenia, who are also impaired in recognizing negative emotions (Strauss et al., 2011) specifically fear (Morris et al., 2009). A study that uses the methodology described in this study in patients with schizophrenia could also provide an insight into multimodal processing in this group, and examine any fundamental pre-attentive disturbances in the context of emotional processing.

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Appendix 1

WSQ Screening Form

Web Screening Questionnaire for Common Mental Disorders (WSQ)

Q	Web Screening Questionnaire for common mental disorders (WSQ)	Sub-scale	From
1	Circle a number from the scale below to show how much you are troubled by feeling miserable or depressed: Hardly at all (0) (1) Slightly disturbing/ not really disabling (2) (3) Definitely disturbing/ disabling (4) (5) Markedly disturbing/ disabling (6) (7) Very severely disturbing/ disabling (8)	Depres.	SQ
2	Do you experience a loss of interest and/or pleasure in most things, like work, hobbies and other things you usually enjoy? Yes (1) No (0)	Depres.	CIDI
3	During the past two weeks, how often have you been bothered by the following problem: Having trouble relaxing? Not at all (0) Several days (1) More than half the days (2) Nearly every day (3)	GAD	GAD-7
4	A panic attack is a sudden rush of fear or discomfort accompanied by at least 4 of the symptoms listed below. In order to qualify as a sudden rush, the symptoms must peak within 10 minutes. Symptoms are: rapid or pounding heartbeat, sweating, trembling/shaking, breathlessness, feeling of choking, chest pain/discomfort, nausea, dizziness/faintness, feelings or unreality, numbness/tingling, chills or hot flashes, fear of losing control or going crazy, fear of dying. If you have had any panic attacks during the past week, how distressing (uncomfortable, frightening) were they while they were happening? If you did not have any panic attacks but did have limited symptoms attacks, answer for the limited symptom attacks. Not at all distressing, or no panic or limited symptom attacks during the past week (0) Mildly distressing (not too intense) (1) Moderately distressing (intense, but still manageable) (2) Severely distressing (very intense) (3) Extremely distressing (extreme distress during all attacks) (4)	Panic	PDSS-SR
5	Do you avoid public places from which a quick escape may be difficult or do you endure this with clear suffering or anxiety? (e.g. public transport, shops/town centers, queues, cinema, unfamiliar buildings, distance from home). Yes (1) No (0)	AGO	SQ
6	Are you either extremely anxious or do you avoid specific objects or situations? Yes (1) No (0)	Specific Phobia	SQ
7	Are you scared of: animals (e.g. dogs, spiders, snakes, cats, birds, mice, insects) or medical issues (e.g. blood, dentist, injection, surgery, hospital, doctor) or specific situations (e.g. bus, crowded shop, tunnel elevator, airplane, bridge or car driving) Yes (1) No (0)	Specific Phobia	VU
8	Have you avoided social situations for fear that attention might be on you? Yes (1) No (0)	Social Phobia	MINI
9	Are you fearful or embarrassed being watched, being the focus of attention, or fearful of being humiliated? (This includes situations like speaking in public, eating in public with others, writing while someone watches, or being in social situations). Yes (1) No (0)	Social Phobia	MINI
10	Did your symptoms start after having experienced, witnessed or had to deal with an extremely traumatic event that included actual or threatened death or serious injury to you or someone else? (e.g. serious accident, sexual or physical assault, a terrorist attack, being held hostage, kidnapping, hold-up, fire, discovering a body, unexpected death, war, natural disaster…) Yes (1) No (0)	PTSD	MINI
11	Have you ever experienced a traumatic event? Yes (1) No (0)	PTSD	SQ
12	Obsessions are recurrent thoughts, impulses or images that are unwanted, distasteful, inappropriate, intrusive or distressing (e.g. the idea of hurting your children although you know you never want to do that). How much time did you spend on obsessions in the past week? 0 hr/day or no obsessions (0) 0-1 hr/day (1) 1-3 hr/day (2) 3-8 hr/day (3) >8 hr/day (4)	OCD	ybocs
13	How many drinks containing alcohol do you have on a typical day when you are drinking? None (0) 1-2 (1) 3-4 (2) 5-6 (3) 7-9 (4) 10 or more (5)	Alcohol	audit
14	How often do you have six or more drinks on one occasion? Never (0) Less than monthly (1) Monthly (2) Weekly (3) Daily or nearly daily (4)	Alcohol	audit
15	Has the idea of harming yourself or taking your own life, recently come into your mind? Definitely not (0) Has crossed my mind but I would not do it (1) I seriously considered it but I stopped myself (2) I would do it given the opportunity (3)	Suicide	SQ

*WSQ cut-off scores: Depression: Q1≥ 5 & Q2=1; GAD: Q3≥2; Panic: Q4 ≥1; Panic with Ago Q4 ≥1 & Q5=1; Ago: Q5=1; Specific phobia: Q6 or Q7=1; Social phobia: Q8=1 & Q9=1; PTSD: Q10=1 or Q11=1; OCD: Q12≥1; Alcohol Abuse/Dependence : Q13≥2 & Q14≥3 ; Suicide : Q15=3 (exclusion)

Appendix 2

SIAS form

Social Interaction Anxiety Scale (SIAS)

Page 1 of 1

Patient Name: _____ **Date:** _____

Instructions: For each item, please circle the number to indicate the degree to which you feel the statement is characteristic or true for you. The rating scale is as follows:

0 = **Not at all** characteristic or true of me.
1 = **Slightly** characteristic or true of me.
2 = **Moderately** characteristic or true of me.
3 = **Very** characteristic or true of me.
4 = **Extremely** characteristic or true of me.

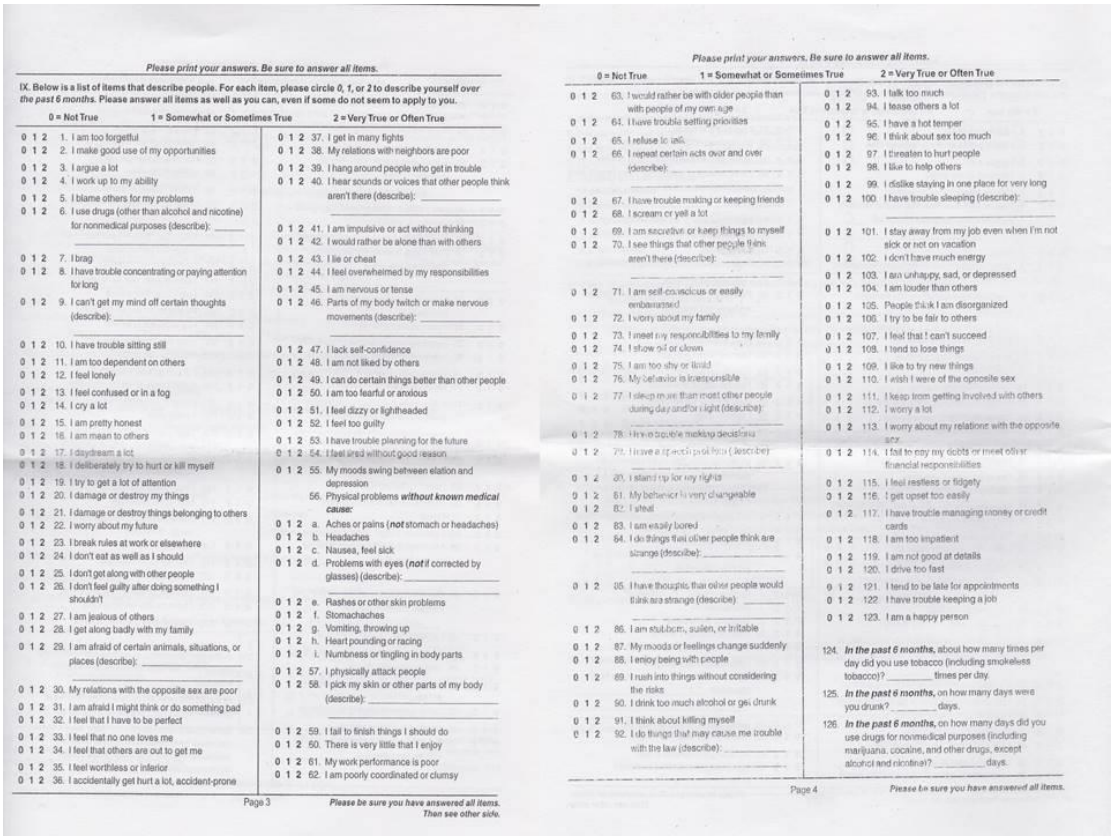
CHARACTERISTIC	NOT AT ALL	SLIGHTLY	MODERATELY	VERY	EXTREMELY
1. I get nervous if I have to speak with someone in authority (teacher, boss, etc.).	0	1	2	3	4
2. I have difficulty making eye contact with others.	0	1	2	3	4
3. I become tense if I have to talk about myself or my feelings.	0	1	2	3	4
4. I find it difficult to mix comfortably with the people I work with.	0	1	2	3	4
5. I find it easy to make friends my own age.	0	1	2	3	4
6. I tense up if I meet an acquaintance in the street.	0	1	2	3	4
7. When mixing socially, I am uncomfortable.	0	1	2	3	4
8. I feel tense if I am alone with just one other person.	0	1	2	3	4
9. I am at ease meeting people at parties, etc.	0	1	2	3	4
10. I have difficulty talking with other people.	0	1	2	3	4
11. I find it easy to think of things to talk about.	0	1	2	3	4
12. I worry about expressing myself in case I appear awkward.	0	1	2	3	4
13. I find it difficult to disagree with another's point of view.	0	1	2	3	4
14. I have difficulty talking to attractive persons of the opposite sex.	0	1	2	3	4
15. I find myself worrying that I won't know what to say in social situations.	0	1	2	3	4
16. I am nervous mixing with people I don't know well.	0	1	2	3	4
17. I feel I'll say something embarrassing when talking.	0	1	2	3	4
18. When mixing in a group, I find myself worrying I will be ignored.	0	1	2	3	4
19. I am tense mixing in a group.	0	1	2	3	4
20. I am unsure whether to greet someone I know only slightly.	0	1	2	3	4

CO-OCCURRING DISORDERS PROGRAM: SCREENING AND ASSESSMENT

19

Appendix 3

ASEBA Questionnaire



Please print your answers. Be sure to answer all items.

IX. Below is a list of items that describe people. For each item, please circle *0, 1,* or *2* to describe yourself *over the past 6 months*. Please answer all items as well as you can, even if some do not seem to apply to you.

0 = Not True 1 = Somewhat or Sometimes True 2 = Very True or Often True

0 1 2 1. I am too forgetful
0 1 2 2. I make good use of my opportunities
0 1 2 3. I argue a lot
0 1 2 4. I work up to my ability
0 1 2 5. I blame others for my problems
0 1 2 6. I use drugs (other than alcohol and nicotine) for nonmedical purposes (describe): _____
0 1 2 7. I brag
0 1 2 8. I have trouble concentrating or paying attention for long
0 1 2 9. I can't get my mind off certain thoughts (describe): _____
0 1 2 10. I have trouble sitting still
0 1 2 11. I am too dependent on others
0 1 2 12. I feel lonely
0 1 2 13. I feel confused or in a fog
0 1 2 14. I cry a lot
0 1 2 15. I am pretty honest
0 1 2 16. I am mean to others
0 1 2 17. I daydream a lot
0 1 2 18. I deliberately try to hurt or kill myself
0 1 2 19. I try to get a lot of attention
0 1 2 20. I damage or destroy my things
0 1 2 21. I damage or destroy things belonging to others
0 1 2 22. I worry about my future
0 1 2 23. I break rules at work or elsewhere
0 1 2 24. I don't eat as well as I should
0 1 2 25. I don't get along with other people
0 1 2 26. I don't feel guilty after doing something I shouldn't
0 1 2 27. I am jealous of others
0 1 2 28. I get along badly with my family
0 1 2 29. I am afraid of certain animals, situations, or places (describe): _____
0 1 2 30. My relations with the opposite sex are poor
0 1 2 31. I am afraid I might think or do something bad
0 1 2 32. I feel that I have to be perfect
0 1 2 33. I feel that no one loves me
0 1 2 34. I feel that others are out to get me
0 1 2 35. I feel worthless or inferior
0 1 2 36. I accidentally get hurt a lot, accident-prone
0 1 2 37. I get in many fights
0 1 2 38. My relations with neighbors are poor
0 1 2 39. I hang around people who get in trouble
0 1 2 40. I hear sounds or voices that other people think aren't there (describe): _____
0 1 2 41. I am impulsive or act without thinking
0 1 2 42. I would rather be alone than with others
0 1 2 43. I lie or cheat
0 1 2 44. I feel overwhelmed by my responsibilities
0 1 2 45. I am nervous or tense
0 1 2 46. Parts of my body twitch or make nervous movements (describe): _____
0 1 2 47. I lack self-confidence
0 1 2 48. I am not liked by others
0 1 2 49. I can do certain things better than other people
0 1 2 50. I am too fearful or anxious
0 1 2 51. I feel dizzy or lightheaded
0 1 2 52. I feel too guilty
0 1 2 53. I have trouble planning for the future
0 1 2 54. I feel tired without good reason
0 1 2 55. My moods swing between elation and depression
56. Physical problems ***without known medical cause:***
0 1 2 a. Aches or pains (***not*** stomach or headaches)
0 1 2 b. Headaches
0 1 2 c. Nausea, feel sick
0 1 2 d. Problems with eyes (***not*** if corrected by glasses) (describe): _____
0 1 2 e. Rashes or other skin problems
0 1 2 f. Stomachaches
0 1 2 g. Vomiting, throwing up
0 1 2 h. Heart pounding or racing
0 1 2 i. Numbness or tingling in body parts
0 1 2 57. I physically attack people
0 1 2 58. I pick my skin or other parts of my body (describe): _____
0 1 2 59. I fail to finish things I should do
0 1 2 60. There is very little that I enjoy
0 1 2 61. My work performance is poor
0 1 2 62. I am poorly coordinated or clumsy

Page 3

Please be sure you have answered all items. Then see other side.

Please print your answers. Be sure to answer all items.

0 = Not True 1 = Somewhat or Sometimes True 2 = Very True or Often True

0 1 2 63. I would rather be with older people than with people of my own age
0 1 2 64. I have trouble setting priorities
0 1 2 65. I refuse to talk
0 1 2 66. I repeat certain acts over and over (describe): _____
0 1 2 67. I have trouble making or keeping friends
0 1 2 68. I scream or yell a lot
0 1 2 69. I am secretive or keep things to myself
0 1 2 70. I see things that other people think aren't there (describe): _____
0 1 2 71. I am self-conscious or easily embarrassed
0 1 2 72. I worry about my family
0 1 2 73. I meet my responsibilities to my family
0 1 2 74. I show off or clown
0 1 2 75. I am too shy or timid
0 1 2 76. My behavior is irresponsible
0 1 2 77. I sleep more than most other people during day and/or night (describe): _____
0 1 2 78. I have trouble making decisions
0 1 2 79. I have a speech problem (describe): _____
0 1 2 80. I stand up for my rights
0 1 2 81. My behavior is very changeable
0 1 2 82. I steal
0 1 2 83. I am easily bored
0 1 2 84. I do things that other people think are strange (describe): _____
0 1 2 85. I have thoughts that other people would think are strange (describe): _____
0 1 2 86. I am stubborn, sullen, or irritable
0 1 2 87. My moods or feelings change suddenly
0 1 2 88. I enjoy being with people
0 1 2 89. I rush into things without considering the risks
0 1 2 90. I drink too much alcohol or get drunk
0 1 2 91. I think about killing myself
0 1 2 92. I do things that may cause me trouble with the law (describe): _____
0 1 2 93. I talk too much
0 1 2 94. I tease others a lot
0 1 2 95. I have a hot temper
0 1 2 96. I think about sex too much
0 1 2 97. I threaten to hurt people
0 1 2 98. I like to help others
0 1 2 99. I dislike staying in one place for very long
0 1 2 100. I have trouble sleeping (describe): _____
0 1 2 101. I stay away from my job even when I'm not sick or not on vacation
0 1 2 102. I don't have much energy
0 1 2 103. I am unhappy, sad, or depressed
0 1 2 104. I am louder than others
0 1 2 105. People think I am disorganized
0 1 2 106. I try to be fair to others
0 1 2 107. I feel that I can't succeed
0 1 2 108. I tend to lose things
0 1 2 109. I like to try new things
0 1 2 110. I wish I were of the opposite sex
0 1 2 111. I keep from getting involved with others
0 1 2 112. I worry a lot
0 1 2 113. I worry about my relations with the opposite sex
0 1 2 114. I fail to pay my debts or meet other financial responsibilities
0 1 2 115. I feel restless or fidgety
0 1 2 116. I get upset too easily
0 1 2 117. I have trouble managing money or credit cards
0 1 2 118. I am too impatient
0 1 2 119. I am not good at details
0 1 2 120. I drive too fast
0 1 2 121. I tend to be late for appointments
0 1 2 122. I have trouble keeping a job
0 1 2 123. I am a happy person

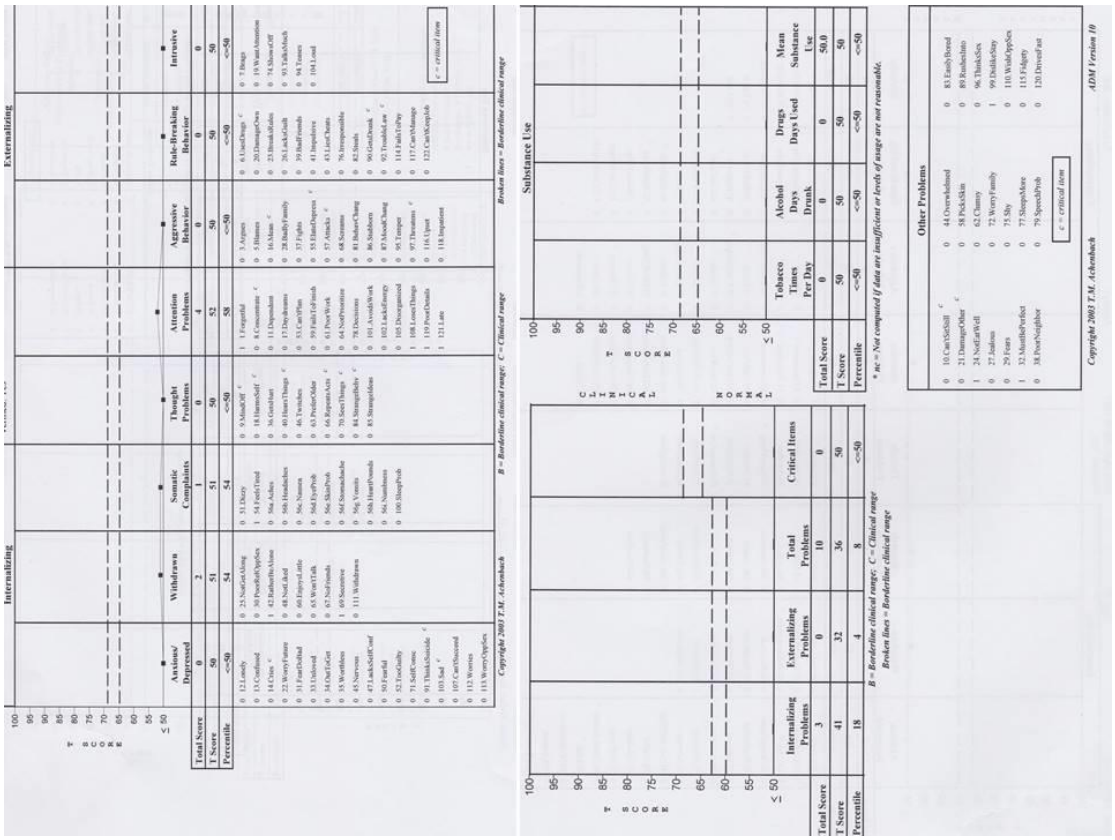
124. ***In the past 6 months,*** about how many times per day did you use tobacco (including smokeless tobacco)? _____ times per day.
125. ***In the past 6 months,*** on how many days were you drunk? _____ days.
126. ***In the past 6 months,*** on how many days did you use drugs for nonmedical purposes (including marijuana, cocaine, and other drugs, except alcohol and nicotine)? _____ days.

Page 4

Please be sure you have answered all items.

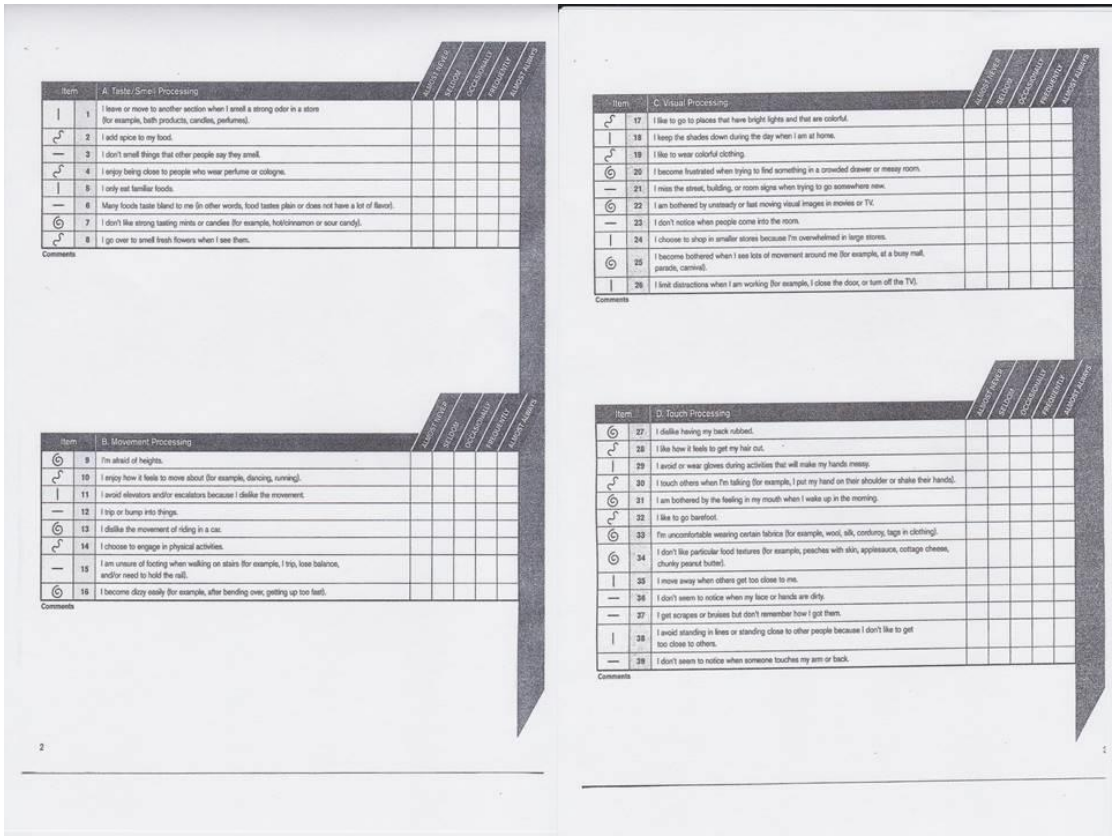
Appendix 4

ASEBA Output



Appendix 5

Adult Sensory Profile



Item		A. Taste/Smell Processing	ALMOST NEVER	SELDOM	OCCASIONALLY	FREQUENTLY	ALMOST ALWAYS
	1	I leave or move to another section when I smell a strong odor in a store (for example, bath products, candles, perfumes).					
	2	I add spice to my food.					
—	3	I don't smell things that other people say they smell.					
	4	I enjoy being close to people who wear perfume or cologne.					
	5	I only eat familiar foods.					
—	6	Many foods taste bland to me (in other words, food tastes plain or does not have a lot of flavor).					
	7	I don't like strong tasting mints or candies (for example, hot/cinnamon or sour candy).					
	8	I go over to smell fresh flowers when I see them.					

Comments

Item		B. Movement Processing	ALMOST NEVER	SELDOM	OCCASIONALLY	FREQUENTLY	ALMOST ALWAYS
	9	I'm afraid of heights.					
	10	I enjoy how it feels to move about (for example, dancing, running).					
	11	I avoid elevators and/or escalators because I dislike the movement.					
—	12	I trip or bump into things.					
	13	I dislike the movement of riding in a car.					
	14	I choose to engage in physical activities.					
—	15	I am unsure of footing when walking on stairs (for example, I trip, lose balance, and/or need to hold the rail).					
	16	I become dizzy easily (for example, after bending over, getting up too fast).					

Comments

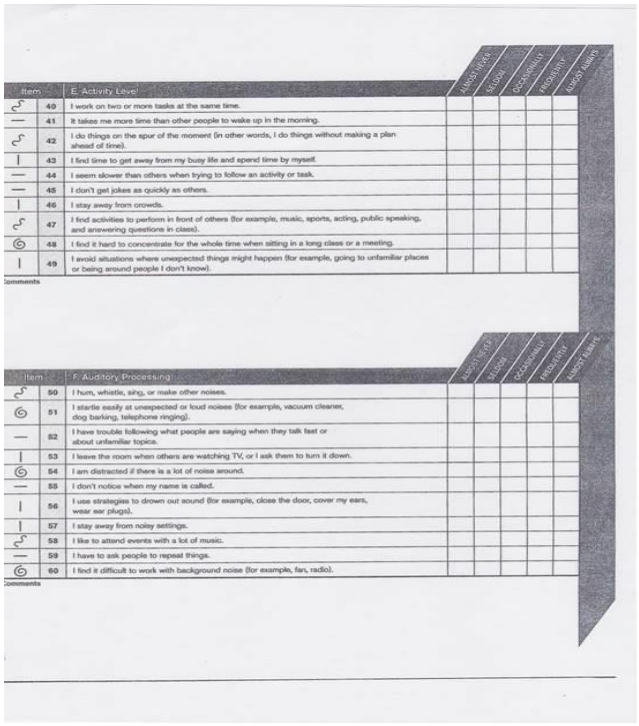
2

Item		C. Visual Processing	ALMOST NEVER	SELDOM	OCCASIONALLY	FREQUENTLY	ALMOST ALWAYS
	17	I like to go to places that have bright lights and that are colorful.					
	18	I keep the shades down during the day when I am at home.					
	19	I like to wear colorful clothing.					
	20	I become frustrated when trying to find something in a crowded drawer or messy room.					
—	21	I miss the street, building, or room signs when trying to go somewhere new.					
	22	I am bothered by unsteady or fast moving visual images in movies or TV.					
—	23	I don't notice when people come into the room.					
	24	I choose to shop in smaller stores because I'm overwhelmed in large stores.					
	25	I become bothered when I see lots of movement around me (for example, at a busy mall, parade, carnival).					
	26	I limit distractions when I am working (for example, I close the door, or turn off the TV).					

Comments

Item		D. Touch Processing	ALMOST NEVER	SELDOM	OCCASIONALLY	FREQUENTLY	ALMOST ALWAYS
	27	I dislike having my back rubbed.					
	28	I like how it feels to get my hair cut.					
	29	I avoid or wear gloves during activities that will make my hands messy.					
	30	I touch others when I'm talking (for example, I put my hand on their shoulder or shake their hands).					
	31	I am bothered by the feeling in my mouth when I wake up in the morning.					
	32	I like to go barefoot.					
	33	I'm uncomfortable wearing certain fabrics (for example, wool, silk, corduroy, tags in clothing).					
	34	I don't like particular food textures (for example, peaches with skin, applesauce, cottage cheese, chunky peanut butter).					
	35	I move away when others get too close to me.					
—	36	I don't seem to notice when my face or hands are dirty.					
—	37	I get scrapes or bruises but don't remember how I got them.					
	38	I avoid standing in lines or standing close to other people because I don't like to get too close to others.					
—	39	I don't seem to notice when someone touches my arm or back.					

Comments



Item		E. Activity Level	ALMOST NEVER	SELDOM	OCCASIONALLY	FREQUENTLY	ALMOST ALWAYS
	40	I work on two or more tasks at the same time.					
—	41	It takes me more time than other people to wake up in the morning.					
	42	I do things on the spur of the moment (in other words, I do things without making a plan ahead of time).					
	43	I find time to get away from my busy life and spend time by myself.					
—	44	I seem slower than others when trying to follow an activity or task.					
—	45	I don't get jokes as quickly as others.					
	46	I stay away from crowds.					
	47	I find activities to perform in front of others (for example, music, sports, acting, public speaking, and answering questions in class).					
	48	I find it hard to concentrate for the whole time when sitting in a long class or a meeting.					
	49	I avoid situations where unexpected things might happen (for example, going to unfamiliar places or being around people I don't know).					

Comments

Item		F. Auditory Processing	ALMOST NEVER	SELDOM	OCCASIONALLY	FREQUENTLY	ALMOST ALWAYS
	50	I hum, whistle, sing, or make other noises.					
	51	I startle easily at unexpected or loud noises (for example, vacuum cleaner, dog barking, telephone ringing).					
—	52	I have trouble following what people are saying when they talk fast or about unfamiliar topics.					
	53	I leave the room when others are watching TV, or I ask them to turn it down.					
	54	I am distracted if there is a lot of noise around.					
—	55	I don't notice when my name is called.					
	56	I use strategies to drown out sound (for example, close the door, cover my ears, wear ear plugs).					
	57	I stay away from noisy settings.					
	58	I like to attend events with a lot of music.					
—	59	I have to ask people to repeat things.					
	60	I find it difficult to work with background noise (for example, fan, radio).					

Comments