Differential expressions of task responsive neural inhibition and regulation across competing sensory and cognitive systems

by

Wilf Nelson

A thesis submitted to the University of Birmingham for the degree of

DOCTOR OF PHILOSOPHY

Centre for Human Brain Health

School of Psychology

College of Life and Environmental Sciences

University of Birmingham

September 2021

Word count: 46640

Abstract

Inhibition is a fundamental property of neural communication with widespread, uncontrolled activity being one of the defining features of an epileptic seizure. Healthy brain function requires a constant interplay between activity, of many different sorts, rest, and at times inhibition. Two major methods of measuring inhibition through modern-day neuroscience are Negative BOLD Responses (NBR) for fMRI experiments and the alpha oscillation in EEG/MEG experiments. In this thesis, the aim is to explore current theories regarding how different sensory and cognitive modalities interact with non-task-relevant regions (NTRRs) during tasks and measure inhibition. In the Introduction a review of the current literature and its gaps will be provided as well as a discussion on how similar NBRs and alpha oscillations are in representing a common neural signal. Chapter 2 will focus on studying multiple stimulated modalities at once and measuring inhibitory responses across the whole brain using fMRI. In Chapter 3 the same experimental paradigm is used as in Chapter 2 but with EEG to instead measure how sustained alpha synchronisation does and does not occur during trials which require inhibition for periods of 4 seconds and larger instead of the current focus on time periods only a few hundred milliseconds long. Chapter 4 uses MEG to explore the expression of posterior alpha power synchronisation during stimulation as a marker of two different inhibitory scenarios; comparing between proactive inhibition of a distracting, non-task-relevant sensory modality and more reactive inhibition of unexpected distraction. The final experiment of Chapter 5 studies positive and negative BOLD responses during a large sample of cognitive tests in the Human Connectome Project dataset. This experiment studies whether the inhibitory NBRs in NTRRs are a function of the cognitive systems being used or instead are just a function of the sensory modalities being stimulated. The thesis concludes with a discussion that highlights the key findings as they pertain to multiple chapters and also

areas for future studies including higher levels of alpha power variability across the population than was reported in the literature review in the Introduction.

Table of Contents

A thought experiment

At the start of this thesis please consider two different scenes. The same person is part of both scenes, but in each instance, they are new versions of themselves with no experience of the prior scene (this is a thought experiment after all).

In the first scene, our human subject will be viewing a film, theatre, or live performance. Others are present as this is a public showing, and the venue is running as normal. The complexity of this scene is of paramount importance and as such its elements are listed below:

The visual elements: There will be many colours, shapes, and items throughout the performance with a great deal of movement and also the features of other humans to perceive. From this, we can surmise that almost all the visual cortices will be activated throughout the performance along with the fusiform facial regions and areas that process biomechanical movement.

The auditory elements: whichever of these performances we choose we can also surmise that sound either in speech, music, or practical sounds resulting from the performers' actions, will be omnipresent. These sounds will carry with them semantic information about the events of the story and provide a potential to predict future events i.e., hearing footsteps outside the door which predicts the entry of a new character to the scene), and any emotional consequences that would cause.

The narrative: while this is not an area that has had a great amount of study it can be stated without dispute that following the narrative of a story is a very complex cognitive process. The subject is required to understand the actions of multiple characters, their social interactions, and the usually fanciful events the characters find themselves in.

This performance is not just limited in its experience to the stage/screen. There are also the smells and tastes which are associated with these locations, the interrupting sounds of others at the performance, the temperature, and climate of the location, etc., etc. Truthfully the remaining details could be listed for far too long, but the main point is they can all be operationalised as either sensory or cognitive stimuli which detract from a pure unadulterated and uninterrupted viewing of the performance. The inclusion of these elements is deliberate and again of great importance.

The second scene for comparison is a room with no furniture except for a desk, chair, and computer. The decoration is the same as the rest of the building and the room is cleaned at regular intervals. In this scene the subject must track the 'behaviour' of a series of checkerboards or small squares over a few seconds, this may also apply to some artificially generated sounds such as beeps or tones. This behaviour may be a change in tone, a rotation of the stimuli, or a change in colour/contrast to name a few possibilities. There is no social information in these presentations and the trial structure requires that these presentations are a few seconds long, the participant then describes the behaviour they experienced in a way that can be conveyed with a button press, there is a brief rest, and then the trial restarts.

The first vignette describes the sensory and cognitive richness of a performance that most people around the world view daily in one form or another. The first scene does not even require a theatre but simply a campsite with a couple of other members and imagination as the stage for an oral story would suffice. The other is a functional but bleak description of a normal psychophysics experiment conducted in a university or research institute. These experiments require control of a great number of variables and as such their limited facets and use of simplistic stimuli in controlled environments reflect a focus on the truly important elements being studied but bring a compromise that the more complex elements discussed above are also left either unstudied or unmentioned.

To date there is a strong body of research which throughout the introduction I will elucidate; the field of neuroscience has ample research describing many elements of how the second scene is processed by the brain. Of interest to this thesis is how the brain regulates the activations and flow of information in comparison to the deactivations, inhibition, and downregulation of the flow of information. It is however obvious that people very rarely encounter events like that of the second scene in their daily lives. Even if someone was to listen to a series of beeps in the form of Morse code in the same room as the second scene, which is the closest comparison that comes to mind while remaining ecologically valid, there is still the element of language processing and the social information the message intends to convey which quickly separates the Morse code scene from the experiment scene in irreconcilable ways.

Now we must imagine what we would need to understand in the field of inhibitory and regulatory neuroscience so that the first scene can be understood and processed as though it was routine for research scientists. Unfortunately, the sensory stimuli of the first scene are far more complex than what is currently studied and understood. The knowledge of how social information being processed creates inhibition and regulation is poorly understood and the same can be said for processing a narrative. The rest of the distracting influences described in the first scene which could not be predicted ahead of time to the exact instant at which they occur are also not understood. As such with these central problems having been identified as the most crucial areas to study the following chapters will approach each of them from different methodologies and imaging modalities.

Chapter 1 - Introduction

The brain is the seat of cognition (Storm et al, 2017). The full scope of mental activity however is not yet mapped out; there is no accepted theory of consciousness or any answer on how organic chemistry gives rise to epiphemonology (Corr and Mobbs, 2018). It is generally accepted that the neurons of the brain are responsible for conscious thought and behaviour (Vernet, Quentin, Japee, and Ungerleider, 2020; Doty, 1975; Rossi and Rossi, 2006). In the brain, there are 100 billion neurons, and they make up approximately 10% of our brain's total cell count (Herculano-Houzel, 2009). The rest of the brain is composed of glial cells whose function is to keep the neurons alive and functioning within parameters that allow cognition to continue (Herculano-Houzel, 2009).

Neurophysiology

The basics of a neuron are: the neuron has a soma which is the cell body. This cell body is surrounded by a cell wall with a series of ion channel pumps covering the surface. Action potentials occur when the neuron's cell membrane is depolarised from -70mV to -55mV which results in voltage-gated ion channels opening allowing for the flow of positively charged sodium ions into the cell. This results in an action potential, creating a chain reaction along the length of the axon triggering many ion channels in turn, which is measured as the firing of an electrical discharge from the soma, to the axon, resulting in the release of neurochemical transmitters. The signal is then propagated to thousands of other dendrites (Carlson, 2013, p. 30). Those dendrites, being the part of the cell that input to the soma, will transmit multiple electrical signals to the cell body which are integrated to create its own membrane potential (Carlson, 2013, p. 29). While there is a complex world of biochemistry occurring during these signalling processes this body of work will again only focus on the

electromagnetic component of neuronal communication, particularly that of the dendrite as will be covered in more detail in the EEG subsection of this chapter.

Communication via electrical means in the brain was first recorded by Berger in the 1929s (Berger, 1929). These signals were categorised into bands of oscillations based on their frequency, with alpha being studied by Adrian and Matthews in their seminal paper in 1934 (Adrian and Matthews, 1934). The neuronal firing causes extra-cellular current flow, known as local-field potentials (LFP) which primarily originates around the dendrites of pyramidal cells (Kirschstein and Kohling, 2009). The electric field component if this activity is measurable using electroencephalography (EEG) electrodes on the scalp and the magnetic component of the electromagnetic signal is measurable by magnetoencephalography (MEG). While neurons can fire anywhere from once to below once a second in what is called slow-wave communication (Csersca et al, 2010) neurons can also fire over a hundred times a second (Wang et al, 2016). Neurologists and neuroscientists have classified different speeds of oscillations which have been correlated to different cognitive and neuronal behaviour. Oscillations that occur between 8-13Hz have been linked to both cognitive resting states but also functional inhibition (Klimesch, Hanslmayr and Sauseng 2007). Inhibition for this thesis is defined as 'the reduction of the transmission of information or the suppression of a region in order that it cannot interfere with task-relevant processing of information". In this thesis, inhibition will be considered both in terms of the negative BOLD signal discussed more below as the reduction of metabolic processing in a given region implied reduced neural functioning and in terms of the alpha band. The alpha frequency, also discussed in greater detail below, is a signal strongly implicated in inhibitory functions (Klimesch, Sauseng, and Hanslymar, 2007) but instead of a reduced neuronal firing is related to increased synchrony of pyramidal neurons firing in a given region. This thesis will focus heavily on studying the alpha frequency band and how it is currently viewed to have a dominant role in managing

cortical inhibition and the regulation of information flow around the cortex but firstly I will discuss more of the basics of how alpha oscillations are measured using current neuroimaging techniques.

EEG/MEG signals

The study of these electrical (and by extension the magnetic) fields is performed through electroencephalography (EEG) and magnetoencephalography (MEG) which respectively record the electrical and magnetic components of the extracellular currents which occur around the dendrites. The generation of signals large enough to register in EEG/MEG sensors requires the coherent activity of large neuronal populations, all discharging at once which generates sufficient local field potential (LFP) (Teplan, 2002). In the top layers of the cortex the most populous neurons are pyramidal cells (see figure 1.1, image from da Silva) (da Silva, 2013) and their dendrites are arranged in parallel structures while the axons are not (Babiloni et al, 2009), which enables dendritic signals to summate across the neural population in a way that axonal signals do not. This means EEG signals measure dendritic currents, not the axonal firing. The dendritic electrical signals summate when a group of neurons is synchronised in their firing pattern. This synchronised and summated signal then propagates through the brain, skull, and skin (Teplan, 2002). This firing is only measurable with a minimum level of synchrony which effectively creates a dipole (da Silva, 2013) in the layers of the cortex that is believed to result from an approximate minimum of 10,000 neurons firing together. The electrical firing which forms the signal measured by EEG comes from the perpendicular and parallel parts of the cortical structure while the magnetic components only come from the perpendicular orientation (da Silva, 2013). In 1977 da Silva and van Leeuwen (Da Silva and Van Leeuwen, 1977) were able to show that dipole layers were specifically found in the fourth and fifth layers of the visual cortex in dogs. This was

one of the first papers which showed that set layers and regions within parts of the cortex were involved in creating the signals EEG and MEG measure.

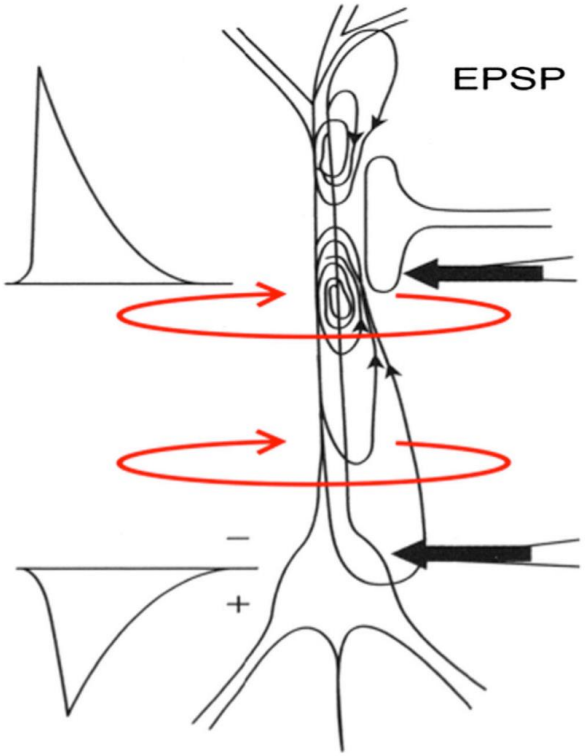

Figure 1.1. *A rendering of a pyramidal neuron showing the intra and extracellular current flow taken from da Silva, 2013.*

The value of MEG is that magnetic signals do not interact with the skull (da Silva, 2013). The magnetic signal does not travel through any organic medium (brain cells, cerebral spinal fluid, bone, muscle, or skin), and as such, there is no conduction loss between source and sensor. Electrical signals in comparison do interact with organic tissue, particularly facing resistance when passing through the bone of the skull and undergoing spatial smearing as they face impedance from the brain, CSF, skull, and skin tissues and the boundaries between them (da Silva, 2013). The preservation of the MEG signal, in combination with a greater number of sensors in that instrument, allows for greater spatial resolution compared to EEG. It also allows improved disentanglement between the sources of two concurrent signals which

may be combined across the scalp during EEG recordings as opposed to reasonable spatial filtering that can be done through a MEG recording (da Silva, 2013). With the use of nonferrous EEG caps concurrent EEG/MEG recordings can be done (Ritter and Villringer, 2006) but they will not be focused on in this or subsequent chapters.

Oscillations

The activity of neuronal populations gives rise to electromagnetic waves oscillating at a range of frequencies, for instance, 10 Hz oscillations are called the 'alpha band'. As long as a sufficient proportion of a neural population fires together then that region's activity is deemed to be synchronised within that frequency band. The range of neuronal oscillations has been divided into:

- Delta – 0.5 Hz to 3Hz. This band is found across the neocortex and is mostly associated with non-REM sleep (Steriade, 2003).
- Theta – 4 Hz to 7Hz. Activity in this band is often observed over the frontal cortex during e.g. social navigation, and memory processing (Karakas, 2020).
- Alpha – 8 Hz to 13 Hz. This band is primarily seen in the occipital cortex but has also been measured across the cortex and this chapter will go into depth on its functions and behaviour across the cortex (Klimesch, Sauseng, and Hanslmayr, 2007).
- Beta – 13 Hz to 30 Hz. Beta oscillations are heavily associated with motor preparation and execution across the sensorimotor cortex and are part of the defining neural behaviour when assessed sleep (Heinrichs-Graham, Arpin, and Wilson, 2016).
- Gamma – 30 Hz to 120 Hz. This band is understood to be involved in directed attention and information processing in the brain and has a direct relationship with how our brain gates attention when used in a phasic relationship with alpha (Jensen and Mazaheri, 2010). This will also be discussed in detail further in this chapter.

Finally, there are neural firing patterns that are higher than 120 Hz but are rarely studied in human non-invasive imaging and are not within the scope of this thesis (Wang et al, 2016). For this thesis, the focus is on firing in the alpha band and the lower gamma range, while ultra-high gamma firing may include crucial signals previous literature (Klimesch, Sauseng, and Hanslmayr, 2007; Jensen and Mazaheri, 2010) have highlighted the main functional relationship between alpha and lower gamma and as such we do not see any critical data will be lost in not analysing ultra-high gamma waveforms.

Of particular interest in this thesis is the alpha band; the physiological correlates of neuronal firing in the alpha band are discussed in more detail below. Neuronal oscillations form the framework for cognitive communication (Donner and Siegel, 2011) whereby local exhibition/inhibitory patterns shape how sensory and motor information is processed inside a respective region i.e., primary visual cortex (V1), the primary somatosensory cortex (S1), the primary motor cortex (M1) and which regions are inhibited to prevent them from interfering with a given task. Under Donner and Siegel's model longer-range communication across regions of the cortex allows for large-scale integration primarily through slow-range neuronal oscillations (<8) and the beta band. In their model Donner and Siegel propose a framework with two different classes of cognitive firing or cognitive functions. There is local exhibitory and inhibitory firing which shapes the majority of the sensory, cognitive, and motor functioning and this is controlled by local gamma-band oscillations transmitting parcel of information at high speed. The other element is long-range communication between cortical regions and this is better represented by alpha and beta range oscillations which over large distances (for the cortex) control the more local gamma-band oscillations and organise neural communication.

In addition to the interplay between alpha, beta, and gamma, for cortical neuronal frameworks to function neuronal synchrony is an important component (Uhlhaas et al, 2009). In a given population of neurons, not all of the neurons will be firing at the same rate, this means excitatory and inhibitory, high, and low-frequency neuronal communication will interfere with each other. To ensure effective neuronal communication synchrony is required with a sufficiently large population of neurons firing together i.e., gamma to allow for information processing and parcellation (Proix et al, 2016).

Event-related synchronisation and desynchronisation

With the basics of the EEG signal discussed the chapter will now turn to the main types of activity which are seen in EEG/MEG recordings. Firstly, for reference are event-related potentials (ERP) which show a large, transient spike in the amplitude of the electromagnetic field (Buzsaki, Anastassiou, and Kock, 2016). This, for example, can occur in the occipital regions (Luck, 2012) when a stimulating image is presented in the visual field. This ERP is taken to reflect the sudden bottom-up requirement to process the visual item and the recruitment of neurons accordingly. This thesis will not study ERPs and therefore they will not be discussed hereafter, but instead will focus on event-related changes in oscillatory power, which occurs when neurons respond to events by synchronising/desynchronising their oscillatory activity in certain frequency bands, leading to event-related synchronisation/desynchronisation, ERS/ERD.

As far back as Adrian and Matthew's work in 1934, it has been known that the alpha oscillation (then thought to just reflect an idling or resting signal) would synchronise, increase in power, and be easily detectable during a period of resting wakefulness or closure of the eyes (Adrian and Matthews, 1934). Any stimulus would immediately desynchronise the alpha oscillation as the neurons could no longer be in a resting state but instead had to

function to process the stimulus. In recent years it has been discovered that alpha plays a much more active role in brain processing and this will be discussed in greater detail in later parts of the introduction and all future experimental chapters.

Source estimation for EEG and MEG through beamforming

Neuronal signals are regularly subject to interference and distortion from the tissue and the structure of the brain and skull. To better identify how different neuronal signals correlate to cognitive functions accurately identifying their spatial location is important, this has helped to show visual and parietal lobe intercommunication which would not be possible without accurate spatial filtering (McFarland, McCane, David, Wolpaw, 1997). However, the neural signals which are measured from the brain do not propagate outwards in a straight line with no disruption (Jackson and Bolger, 2014) but instead propagate out approximately in a spherical pattern and are distorted in each direction by other activity and the mediums they come into contact with (figure 1.1. from da Silva, 2013). This is classically known as the volume conduction of the signal through the brain and skull (da Silva, 2013). To correctly model the spatial location of the source a series of dipoles (Fuchs, Wagner and Kastner, 2001) are placed in a model of the brain which can explain the electromagnetic fields measured at the sensors, this is called the forward model (Fuchs, Wagner and Kastner, 2001). The primary difficulty with obtaining source estimates is that a theoretically infinite number of solutions exist that can explain the sensor data and as such algorithms are used to propose constraints on the solution.

In this example, only one dipole will be used for the sake of simplicity. In computing the signals from any region of the brain the signals of any given period will have also undergone a level of spatial smearing because of the resistance the bone in the skull causes or could have been generated by an infinite potential set of combinations of sources (von Helmholtz, 2004).

To reduce the number of possible configurations to a computable size assumptions are required about the sources themselves (Hallez et al, 2007). The first is that a given source can be represented as a current dipole which is characterised through the higher and lower layers of the cortex having differing electrical potentials (Hallez et al, 2007). Next limiting the number of dipoles is very useful and even placing them in locations that match the theory being tested i.e., placing a dipole in the contralateral visual cortex to where a visual stimulus was presented. This provides a location for a researcher to test whether a given neural signal is originating from that location in the brain and match it to known anatomical structures. Once a dipole has been placed in a head model the question of what head model is used is also important. The creation of various head models can be used to model the conductivity of each layer of tissue on a unique map per participant to provide the best possible attempt at modelling the idiosyncratic path a given signal would have to take on any modelled trial (Vorwerk et al 2014). A boundary element model, through modelling the location and thickness of different tissue types, is used repeatedly throughout this thesis (Vorwerk et al 2014; Oostenveld, Fries, Maris, Schoffelen, 2011).

This whole process of understanding how the signal is affected by volume conduction and spatially filtering out where signals originate in the cortex can be done with a process called beamforming (Van Hoey et al, 1999). Linearly constrained minimum variance (LCMV) beamforming will be the main method of modelling volume conduction in this thesis (Van Hoey et al, 1999). To explain beamforming is a method of spatial filtering where you choose to enhance signals from certain locations and filter our signals from others, in the case of neuroimaging the signals from a stimulated region are enhanced, and non-task-relevant regions are reduced. LCMV beamformers choose the weights of different source locations to create an output with the variance minimized while allowing the signal from the desired location to not be filtered out. Once the beamformer is run the sourcemaps produced the

regions with the highest variance are assumed to be the most active while areas with small variance are assumed to be least active (Brookes et al, 2007).

This means not only does interference need to be accounted for when understanding the source and original pattern of a signal but also that the signal at any scalp sensor will reflect some component of every signal generated across the cortex (da Silva, 2013) (figure 1.1). Sensors placed over the occipital lobe of a participant will contain a strong component of the signals emanating from the visual cortex but in addition, contributing and even confounding signals from the frontal and parietal lobes will also be measured. Equivalent effects are also observed at any other sensor on the subject's scalp (Jackson and Bolger 2014).

Of course, modelling only one dipole using a custom head model during certain stimulation protocols is infeasible/illogical i.e., during multimodal stimulation. In visual and somatosensory stimulation dipoles would be expected in the visual system, somatosensory system, and parietal cortex. The simplest way to model this would then be with three dipoles, but this increases the number of potential solutions (Vorwerk et al 2014; Oostenveld, Fries, Maris, Schoffelen, 2011) again. Finally, with MEG the conduction of magnetic signals is not disrupted by tissue. As such the modelling of the neuronal sources with only a dipole source algorithm modelling the magnetic signal as a sphere or spheres is sufficient (da silva 2010). In this thesis, the merits of using a single brain model where only the brain tissue is modelled to better model the shape of the brain are compared to using a spherical model (chapter 3 and 4)

Alpha inhibition

The alpha oscillation (also hereafter called the alpha band, alpha signal, or simply alpha) was initially discussed by Adrian and Matthews as reflecting a resting or idling state of the brain (Adrians and Matthews, 1934). When participants were not conducting a task and in a state of

resting wakefulness the brain would show an increase in the power of the alpha band, leading to alpha being described as a marker of the subject's arousal. This was also the case when participants were asked to close their eyes and it was found that when visual stimuli were not present alpha power increased. Alpha was deemed to be a 'resting signal' or a signal which occurred while a participant was not actively engaged in a task however more recently it has been shown that while a participant performs a task a non-task relevant region shows an increase in alpha power (Klimesch, Sauseng, and Hanslmayr, 2007). The participant wasn't resting but alpha power was increased and as such these findings discussed 'paradoxical alpha' (Klimesch et al, 1999). In the 1999 study on the interaction between alpha and memory, the participant would be presented with information visually during an encoding period, then they must maintain the information and finally retrieve and report a response following a memory probe presentation. During the encoding period, alpha would desynchronise (ERD) in the visual cortex but during maintenance when new visual information would interfere with the attempt to maintain the information, the visual cortex showed a synchronisation (ERS) of alpha, but the participant was still using their visual cortex, so they were not at rest. The findings proposed that alpha could be used by the cortex not only for rest but to effectively create a 'forced rest' in a region that did not need to process information because it would be counterproductive to the task at hand. This "forced rest" is now viewed as the active inhibition of information (Klimesch et al, 2007) and it is unclear if alpha synchronisation in non-task relevant regions reflects inhibition by forcing that area into a resting state as seen during resting wakefulness. This will be discussed in chapter 3.

Research around the alpha oscillation has focused heavily on the now well-documented effect that alpha power lateralizes across the cortex in conditions requiring the lateralised allocation of attention, such as in the famous Posner experiment (Posner, 1980). When a pre-stimulus

cue indicates that a given location or modality will subsequently have a stimulus presented in it, the subject's spatial attention is allocated in the cued direction and alpha is desynchronised in the contralateral sensory cortex region i.e., left visual cortex required to process the upcoming stimulus. Therefore, other locations and modalities are distractors in the task and show an alpha synchronisation in the ipsilateral sensory cortex that is not task-relevant i.e., the right visual cortex. This has been widely studied and is a replicable effect that forms the foundation of the alpha inhibitory field (Kelly, Lalor, Reilly, Foxe, 2006; Romei, Brodbeck, et al 2008; Sauseng et al 2005a, b +c; Thut, Nietzel, Brandt, Pascual-Leone 2006; Worden, Foxe, Wang, and Simpson 2006). Alpha has also been shown to not just be a passing irrelevant neural signal but to be correlated to task performance; regions that have higher alpha synchronisation perform worse in tasks with slower reaction times and a poorer perceptual threshold (Handel, Haarmeier, Jensen 2011; Thut, Nietzel, Brandt, Pascual-Leone 2006; Bengson, Mangun and Mazaheri 2012). The replicability of the alpha lateralisation and synchronisation effects has been so successful it has been claimed as a way of directly measuring the attentional state of a person (Trachel, Clerc, and Brochier 2015).

While the first collection of evidence on alpha inhibition was in the visual cortex (Klimesch et al, 1999) alpha is generated in all cortical areas propagating from the higher-order to lower-order areas i.e., in parietal cortex and associative somatosensory regions through to the primary S1 region (Halgreen et al, 2019). Alpha can be measured in the visual cortex (Worden, Foxe, Wang and Simpson 2000; Foster, Sutterer, Serence, Vogel and Awh 2017; Ikkai, Dandekar and Curtis 2016), in the auditory domain (Frey et al 2014; Muller and Weisz 2012; Weisz et al 2014; Klatt, Getzmann, Wascher and Schneider 2018), alpha plays a role in how tactile responses are processed (Haegens, Luther and Jensen 2012; Haegens, Handel and Jensen, 2011) and is highly correlated with the activity of the default mode network during

rest which spans multiple brain regions (Knyazev, Slobodskoj-Plusnin, Bocharov and Pylkova 2011).

Visual attention is a primary area of study when looking at alpha inhibition given that alpha is mostly strongly measured in the visual regions (Klimesch, Sauseng, and Hanslmayr, 2007 for a review on visual alpha). The alpha inhibition model argues that alpha is used to guide or direct attention to both important areas and reduce interference from non-task-relevant regions. Visual attention is controlled by the dorsal attention network (Capotosto et al 2009; Corbetta 1998; He et al 2007 and Shulman et al 2010) whereby the frontal eye fields relay information through to the intraparietal sulcus which determines whether a region is required to process information (Marshall, O'Shea, Jensen, Bergmann 2015). The dorsal attention network (particularly including the frontal eye fields and intraparietal sulcus) has also been argued to show evidence for exerting top-down control and driving alpha synchronisation in auditory and somatosensory regions (Michalka et al 2016; Noyce et al 2017). The generation of alpha by the parietal networks then shifts attention to the desired location (Foster et al 2016; Rihs et al 2007; Samaha et al 2016; Worden et al 2000).

The dorsal attention network is specifically implicated in a person's ability to identify the spatial location of a stimulus and plan motor actions to engage with an object (Spreng et al, 2013). The dorsal attention network's primary role of focusing attention to external objects in space and orientating behaviour towards those items is directly in contrast to the default mode network, a network primarily involved in introspection and mind wandering (Spreng et al, 2013). In a review by Spreng et al in 2013, he discussed that the frontoparietal attention network was responsible for shifting between the dorsal attention network and default mode network or in cognitive terms between external and internal focus. The dorsal attention network uses alpha to regulate non-task relevant regions when conducting tasks involving controlling how the spatial attention of the visual system orientates for a task (Hopfinger et al

2000; Buschman and Kastner, 2015; Liu et al 2017; Marshall, Bergmann, and Jensen 2015; Marshall, O'Shea, Jensen, and Bergmann 2015; Popov, Kastner and Jensen 2017).

Whether the dorsal attention network and its relationship with visual cortex alpha has an equivalent for the auditory cortex is questionable as Wilsch et al in 2020 showed the visual system is very dependent on spatial cues but the auditory system is more reliant on temporal expectation. However, as listed above both the visual and auditory systems show remarkable similarities in their use of alpha and how the dorsal attention network regulates the use of alpha in both auditory and visual regions.

On a final note, it is not only the frontoparietal and dorsal attention networks that are believed to control the functional use of alpha across the cortex. Mazzetti et al (2019) found using an analysis of MEG and MRI data in combination that when presented with a stimulus that generates alpha lateralisation across the hemispheres the globus pallidus and thalamus presented patterns of activation which explained individual differences seen in the ability to modulate posterior alpha power. The authors argue that a subcortical attention network is used for the regulation of alpha but due to EEG and MEG's poor ability to measure subcortical signals further study is needed to better understand how cortical and subcortical regions both regulate the use of posterior alpha. More generally the thalamus has been implicated as the 'alpha pacemaker' (Halgren et al 2019) but the precise contribution of the thalamus to the generation or regulation of alpha oscillations is still a topic of debate. Halgren in 2019 used Granger causality analysis of simultaneous recordings from the cortex and subcortex to highlight that discrete bursts of alpha in the cortex drove thalamic alpha. Hughes and Crunelli (2005) showed that thalamic firing, especially a form of rhythmic burst firing which occurs in thalamocortical neurons and the interconnection of those neurons to the rest of the cortex via gap junctions resulted in alpha generation across the rest of the cortex. Liu, Zwart, Yao, Gelderen, Kuo, and Duyn in 2012 further specified the relationship the thalamus

has with cortical alpha generation by presenting that spontaneous alpha activity during an "eyes-closed" resting period was positively correlated with the activity of the anterior and medial dorsal nuclei of the thalamus but negatively correlated with the activity of the visual thalamus, specifically the pulvinar, however, the authors argue that this shows the visual thalamus and pulvinar are involved in the modulation of posterior alpha.

To provide some synthesis between the many studies an alpha inhibition theory has been provided. In 2007 Klimesch, Sauseng and Hanslmayr proposed the alpha inhibition hypothesis which formalised the body of evidence that alpha was not merely a resting signal in the brain but played an important role in inhibiting non-relevant information, suppressing distraction and therefore allowing for the effective processing of the world around us. Of course, when saying alpha inhibits information ultimately means the result is a vague understanding of what 'information' is and how it is being inhibited. To briefly provide some clarity, in 1999 Tallon-Baudry and Betraud showed that increased synchronization and power in the alpha band effectively inhibited the gamma band (Tallon-Baudry and Betraud, 1999). Similar evidence was provided in the visual field by Osipova et al in 2008 and in the motor cortex by Yanagisawa et al 2012. In 2010 Jensen and Mazaheri proposed the gating by inhibition hypothesis whereby increased alpha power results in a greater restriction on the gamma signal. When alpha power is low or desynchronized parcels of information, presented in short bursts of gamma waves during a set period of the alpha oscillation's phase, could be transmitted see figure 1.2. below (Jensen and Mazaheri, 2010). If the alpha power was too high the gamma signal was too restricted, and information was not sent to the rest of the cortex and this provided a mechanism by which irrelevant or distracting information could be inhibited.

This theory is the one that will be used throughout this thesis when discussing electrophysiological neural transmissions.

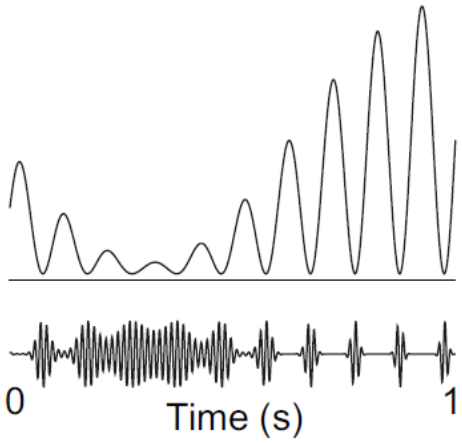

Figure 1.2. *A figure showing that as the slower alpha oscillations increase in power the transmission of gamma oscillations reduces as seen on the left and right of the figure. In the center where the alpha oscillation power is low, there is an increase in gamma oscillation firing representing a greater transmission of information. This interplay between alpha and gamma oscillations is also fundamental to the concept of alpha as a signal responsible for functional inhibition.*

Causal evidence for alpha causing functional inhibition

To provide causal evidence rTMS/TMS (repetitive transcranial magnetic stimulation) and tACS (transcranial alternating current stimulation) have been used to stimulate specific regions of the brain with electrical/magnetic fields exciting the neuronal population to fire at a specific frequency, which enables the study of the consequent effects upon subsequent behaviour. TMS of the visual cortex has been shown to induce visual phosphenes more reliably when stimulation was delivered during moments of low alpha power. This shows that induced activity in the neurons in the alpha frequency range is linked to cortical excitability (Thut et al, 2006; Romei et al 2008 a+b; van Djik et al 2008). Furthermore, the alpha phase was shown to be the most important factor in altering stimulus perception, and using precisely timed TMS pulses to disrupt alpha at set periods in the phase of the oscillation

resulted in participants not perceiving brief flashes of light at varying levels of luminance around the level of perception in Busch et al, 2009 (Busch et al, 2009; Mathewson et al, 2011; Dugue, Marque and van Rullen, 2011). Similar results have been achieved with tACS by Schuhman et al in 2019 stimulating the alpha band to alter the perception of a stimulus and by de Graaf et al in 2020 where 10Hz stimulation over the O2 electrode significantly decreased the reaction time of participants to notice changes in a grating on a visual stimulus. This provides evidence that increased alpha power in the visual region below the O2 electrode resulted in functional inhibition which caused a poor reaction time compared to sham stimulation.

By altering the alpha power in the visual region researchers have not only been able to alter the reaction time but effectively abolish the perceptual experience of stimuli, the participant does not get any conscious information the stimulus exists. By stimulating neurons at a frequency in the alpha band the alpha power in a region increases before the stimulus presentation resulting in the participants presenting with poor perceptual change detection (de Graaf, Duecker, Fernholz and Sack 2015; de Graaf, Koivisto, Jacobs, and Sack 2014; Jacobs, de Graaf and Sack 2014). Of course, this evidence is confined to the visual field but there is also research that shows the same causal link with alpha, and inhibition being generated by TMS in the motor cortex (Jin et al, 2017) and even in emotional processing (Lapate et al 2011).

While this research provides a strong case for the alpha oscillation having a direct causal role over inhibition it does currently hinge on the viability of TMS as a methodology. TMS however has been scrutinized in the past for failing to prove a causal link because studies have been unable to prove that region A directly influences region B and cannot rule out the effect of intervening regulatory regions or concurrent behaviour in other regions which isn't measured in a paradigm (Sack and Linden 2003; Paulus 2014). To further support the case for

alpha inhibition and its causal link to functional inhibition in the cortex other methods need to be used like tACS (Zaehle, Rach, and Herrmann, 2010) which can alter neural firing in a given region providing a causal, not correlational, experimental paradigm. A non-invasive method is the use of neural entrainment (Ding et al, 2017; Nozaradan, Zerouali, Peretz and Mouraux, 2015; Okawa, Suefusa and Tanaka, 2017). Neural entrainment is the phenomenon whereby presenting a participant, and more importantly, their brain, a set of stimuli at a set frequency the neurons in a region responsible for processing that information begin to fire at that rate i.e., a left hemifield visual checkerboard firing at 10Hz will result in the neurons firing at 10Hz and as such that region can be made to synchronize an alpha signal (Otero et al, 2020). This method has increased in popularity over the years given it removes much of the need for using TMS/rTMS to generate neural activity at set bands.

Entrainment with stimuli in the alpha band has been shown to disrupt the processing of information in the same causal way as TMS (Rohenkohl and Nobre 2011; Heinrichs-Grahams and Wilson 2012; de Graaf et al 2013; Gulbinaite et al 2017). This provides further causal evidence for alpha being an inhibitory control signal which can stop the processing of information and thereby direct attention to certain locations/modalities and reduce interference from other locations/modalities.

Finally, in chapter 4 this thesis will discuss the differences between proactive and reactive alpha processing. The studies discussed so far have all used cues to inform the participant of the temporal and spatial location of the impending relevant stimulus. This allows the participant to prepare and synchronise the alpha oscillation in the non-task relevant regions ahead of time but does not represent ecologically valid scenarios where stimuli must be reacted to spontaneously and cues can either be incorrect or simply not present. Study into reactive stimulus processing and the role of alpha has shown that alpha is limited in its applications in reactive processing with other waveforms such as theta and gamma being

suggested to be more instrumental in reducing interference from distractors (Kelly, Lalor, Reilly, and Foxe in 2006; Sauseng et al in 2009; Janssen et al 2017; Marini et al (2016); Vissers, van Driel and Slagter in 2016). This topic will be discussed in greater depth in chapter 4.

MRI, fMRI, and BOLD

MRI stands for magnetic resonance imaging and fMRI stands for functional magnetic resonance imaging. “Magnetic resonance measures how radiofrequency electromagnetic waves act upon dipoles in a magnetic field” (Logothetis and Wandell, 2004, pg. 2.). In the case of neuroimaging MRI applications, the dipoles are hydrogen protons found in the water molecules in the brain tissue and the magnetic field is a 1.5-or greater Tesla static field called the B0 field. The B0 field creates a small net magnetisation on the hydrogen atoms in the water molecules and then radiofrequency pulses applied at the magnetic resonance Larmor frequency (Seo et al 2012) excite the brain tissue sample. The hydrogen atoms absorb this energy and are put into a high-energy state but without a supply of further energy, the atoms decay from this energy state back to equilibrium. This loss of energy is detected by the scanner’s receive coils and used to create images of the tissue. The signal decay can occur in a variety of ways that can be used to create a range of MR contrasts, sensitive to different characteristics of the tissue. For example, the longitudinal loss of signal is called T1 relaxation (Logothetis and Wandell 2004). T1 is used to structurally differentiate different cell types that contain different levels of water i.e., neurons, blood vessels, ventricles, muscle, and bone. For fMRI, a temporally dynamic measure of the functional state of the tissue sample is needed which T1 cannot provide. T2, however, the transverse relaxation as the hydrogen atoms spin can have dynamic properties. If the local magnetic field is homogeneous then T2 is measured as a constant. However, if the field is inhomogeneous e.g., due to

boundaries between different tissues, tissue, and air, or differing tissue oxygen properties (see below) then the decay signal is altered (Pauling and Coryell 1936; Thulborn et al 1982; Logothetis and Wandell 2004). This is called T2* and is the fundamental signal that underlies fMRI.

During neuronal activity oxygenated blood feeds the brain with fresh oxygen extracted from the haemoglobin. Increases in neuronal activation increase the metabolic demand of the neural tissue, therefore more oxygen and other metabolites must be provided to the neurons to protect against neuronal death and ensure optimal firing (Logothetis, 2003). Increases in cerebral blood flow (CBF) occur to meet this metabolic demand but occur to a disproportionately large extent such that fresh oxygenated blood is oversupplied and the local ratio of oxyhaemoglobin to deoxyhaemoglobin in the blood increases. This functional hyperaemia is used by fMRI to imply increased neuronal activity (Logothetis and Wandell, 2004). When neuronal firing occurs astrocytes signal to the local blood vessels resulting in the dilation of blood vessels and increased CBF to the needed region (Iadecola, 2017). In terms of the T2* measurements, the increasing ratio of oxygenated to deoxygenated haemoglobin results in a change in the local magnetic field, due to the differing magnetic properties of oxygenated and deoxygenated haemoglobin (Iadecola, 2017) resulting in the blood oxygenation level-dependent BOLD signal (Ogawa et al 1990). The BOLD signal, therefore, reflects an indirect, haemodynamic correlate of increased neural firing allowing for a measure of implied neural activity.

In this thesis, the applications of the BOLD signal are focused on the ability to indirectly infer neuronal activity from haemodynamic responses. As neurons use more energy and local CBF and $CMRO_2$ increase, the changing ratio between oxyhaemoglobin and deoxyhaemoglobin can be measured in voxels representing a defined region of space i.e., 3mm isotropic. The great strength of BOLD fMRI is its ability to measure the activity of the

whole brain as temporal series of 3D maps of voxel activity. This can encompass as many as 100,000 voxels to give full coverage of the brain. Measurements of the BOLD signal can be taken during the resting spontaneous activity that the brain undergoes naturally and constantly. More importantly, for this thesis is the estimation of statistical contrasts between different brain states. The BOLD signal is only a relative measure of changes in brain activity because it only reflects changes in the ratio of oxyhaemoglobin and deoxyhaemoglobin, therefore statistical evaluation of a region's involvement in a task requires the comparison between a baseline period i.e., resting fixation, and a task period during which a stimulus e.g. a visual checkerboard, is delivered. The baseline period is chosen as the part of the experiment where task-relevant activity was minimal. The BOLD signal from the rest period is contrasted against that of the task period using a general linear model (GLM) to test if a regression model can show a statistically significant difference in signal between the two conditions. GLMs have the additional benefit of allowing modelling out of confounding signals such as movement, breathing rate, heart rate, and cognitive factors i.e., performance and attention. This general linear model uses the haemodynamic response function (HRF) to create regressors that model the expected BOLD signal arising in response to a given task period. The HRF is a standardised measure of the change in the BOLD signal as a response to a task and is used to create predictions of the BOLD signal timecourse from the known timings of the experimental stimuli.

Neuron firing is a complex event with post and presynaptic events, action potentials, the metabolic requirements of the cell membrane, and many other cellular events that occur constantly which aren't the topic of this thesis. What is of relevance is the correlation between the BOLD signal and region-wide neuronal firing and inhibition. Heeger et al in 2000 and Rees et al in 2000 both found the BOLD signal was proportional to the total aggregate neuronal signal. The BOLD signal is not singularly influenced by specific types of

neuronal activity but many different bands and patterns of excitatory neuronal firing are all expressed in fMRI simply as a positive BOLD signal reflecting the total metabolic demand of all signalling in a given region. However, it is Logothetis' paper in 2008 that shows both the pre and postsynaptic events influence the BOLD signal which is why the neuronal signal was termed to be "peri-synaptic" by Ekstrom in 2010.

It is worth mentioning there are many other cell types in the brain covered under the terms glial and microglial which also metabolise and use oxygen and have been discussed in how they impact the BOLD signal (Iadecola and Nedergaard, 2007) but that is not the focus of this thesis and for the remainder, the assumption will be that neuronal activity has a measurable impact on the BOLD signal.

Negative BOLD signals

In contrast to the BOLD signals discussed above which are called 'positive BOLD signals' (PBR) this section will cover 'negative BOLD signals' (NBR). A PBR occurs when a region shows an increased BOLD signal in response to a stimulus or task compared to a resting baseline period and is widely used to map neural recruitment. An NBR conversely is a reduction in BOLD signal compared to baseline. NBRs were first reported over two decades ago (Raichle, MacLeod 2001; Shulman 1997; Smith, Singh, Greenlee 2000; Smith, Williams, and Singh 2004) and are widely observed in unstimulated or non-task relevant regions but to-date are not commonly used for functional brain mapping.

NBRs have been discussed as representing neural suppression (Sten, Lundengard, Witt, Cedersund, Elinder and Engstrom, 2017); the logic is quite simple that if a region requires more oxygen and metabolites to process information then a suppressed/inhibited region would show the opposite. However, NBRs were first measured in the primary visual cortex, in response to visual stimuli such as flicking grating patterns and were measured adjacent to

the PBRs that the stimuli had generated (Harel et al 2002 and Bressler, Spotswood and Whitney 2007) Harel et al 2002 argued that this NBR was a function of 'blood stealing' the metabolic demands of PBR regions were supported by stealing blood from a nearby region, creating an NBR, rather than require the vascular system to provide new resources. Smith, Williams, and Singh (2004) presented the argument that since visual stimulation in one hemisphere can result not just in NBRs adjacent to that region but also in the opposing hemisphere that blood stealing was not a feasible solution. Bressler, Spotswood, and Whitney showed that the movement of gabors images (grated flickering circles) resulted in a corresponding PBR in the visual cortex but also an adjacent NBR which matched the retinotopic architecture of the visual cortex. As the gabors moved across the screen both the PBR and adjacent NBR followed the movement of the Gabor across the retinotopic mapping of the visual cortex. The authors concluded that the movement of the PBR/NBR more closely fit the neural architecture instead of the known vasculature layout in the stimulated visual regions and therefore it was more likely the NBR represented neuronal inhibition over blood stealing. This was proposed as inhibition and a form of attention where the area being attended to was being processed but that the surrounding area was being inhibited to reduce distraction and effectively form the attentional spotlight.

Negative BOLD effects have also been found to not just occur adjacent to responses showing a PBR. Mozolic et al 2008 and Hairston et al 2008 found evidence for cross-region inhibition, where attending to a cued auditory stimulus resulted in NBR in the visual cortex. In Hairston et al 2008 the magnitude of this deactivation increased as the task difficulty increased suggesting functional inhibition to support task performance. Liu et al in 2011 showed that sustained NBRs to a finger tapping task occurred in the frontal, somatosensory, and occipital regions. Both the authors and the field at large have concluded the NBRs and PBRs were too far apart and involving different vascular territories for blood stealing to be the sole

explanation and that a contribution from neuronal inhibition was most likely. NBRs have since been linked more readily to neuronal inhibition (Boorman et al 2010; Devor et al 2007; Shmuel et al, 2002 and 2006) along with evidence of NBRs occurring on the ipsilateral side to unilaterally presented stimulation with the PBRs appearing contralaterally (Allison et al 2000; Hlushcuck and Hari 2006; Schafer et al 2012; Smith et al 2004; Stefanovic et al 2004; Kevin et al 2008).

In 2002 Shmuel et al showed that stimulating the visual field in humans with a ring of high contrast checkers induced a PBR in the retinotopic representation of the ring and a separate NBR in surrounding visual regions. The analysis showed that the PBR and NBR amplitude covaried both with increasing stimulus duration and intensity showing the NBR was being driven (at least through correlational evidence) by the stimulus. In 2006 Shmuel showed that stimulation of primate visual cortex induced NBRs adjacent regions to PBRs resulting from visual stimulation. Outside of the visual system Devor et al 2007 found evidence of cross hemisphere positive and negative blood oxygenation response relationships in rodents. Using unilateral forepaw stimulation, the contralateral S1 region presented an increase in blood oxygenation and flow while the ipsilateral region presented a decrease in blood oxygenation and flow which can be extrapolated to traditional PBR/NBRs in humans. This effect of increased and decreased blood flow corresponded to predominant depolarisation of the neuronal populations when increases in oxygen occurred and hyperpolarisation when oxygenation decreased (Devor et al, 2007). Finally, Boorman et al 2010 showed that by stimulating the whisker pads in mice NBRs were measured adjacent to PBRs and in deeper cortical layers. These NBRs were measured in real-time using two-dimensional optical imaging spectroscopy and laser Doppler Flowmetry. They correlated reductions in blood oxygenation and flow to decreases in gamma frequency neuronal activity measured with multichannel electrodes implanted at varying cortical depths. Boorman, Devor, and Shmuel's

work provides strong evidence for NBRs being linked to altered neuronal firing states which further on in this chapter will be linked to functional inhibition. It also provides evidence that NBRs are seen both in regions adjacent to PBR, which are later discussed to be involved in the suppression of adjacent stimulus which could be distracting i.e., the region directly next to a visual stimulus; and also, in the form of cross-hemisphere suppression when a hand or paw is not required for a task and suppression improves attention in the stimulated paw/hand.

Additionally, before the 2008 paper, Logothetis, Pauls, Augath, Trinath, and Oeltermann in 2001 had shown coupling between EEG and fMRI with increases in LFP directly correlating to increases in the BOLD signal. In this experiment, the LFP response was sustained throughout the stimulus period, similar to the BOLD signal, but multi-unit activity was not sustained. This shows a separation in neuronal firing as measured by the multi-unit activity and the LFP and BOLD signal and presents a common origin for NBR and alpha synchronisation reflected in the dendritic activity instead of on the axonal side. Evidence of a common neural origin between NBRs and alpha synchronisation has been shown in animals (Ogawa et al 2000; Tsubokawa et al 1980; Ngai et al 1999; Mathiesen et al 1998; Brinker et al 1999; Nielsen and Lauritzen 2001) as well as in humans (Arthurs et al 2000; Arthurs and Boniface 2002). This correlation was even found to be linear allowing for an interpretation of direct increases in BOLD signal to also mean direct increases in neuronal recruitment (Logothetis et al 2001; Arthurs et al 2000).

It is not only non-task relevant regions that show an NBR. The default mode network is considered a task anti-correlated network (Raichle, MacLeod, Synder, Powers, Gusnard and Shulman, 2001; Gusnard and Raichle, 2001; Greicius, Supekar, Menon and Dougherty, 2009; Raichle, 2015) which presents an NBR during any externally engaging task. This is in contrast to the frontoparietal network which presents a PBR during any attention engaging task. The DMN has been related to several functions but since it presents a PBR when a

participant is internally reflecting or "mind-wandering" the DMN is thought to have a role in introspection (Gilbert, Dumontheil, Simons, Frith, & Burgess, (2007; Poerio, Sormaz, Wang, Margulies, Jefferies, & Smallwood, (2017). Throughout this thesis, the NBRs in the DMN are expected but given the DMN's task anti-correlated behaviour the DMN's relationship with neuronal inhibition will be discussed in the introduction for each experiment on a chapter-by-chapter basis.

With this evidence covered in this chapter in mind, NBRs provides an interesting opportunity to study how inhibition occurs across the sensory regions of the cortex (Klimesch et al 2007, Jensen and Mazaheri 2010, Mullinger, Mayhew, Bagshaw, Bowtell and Francis (2012); Mayhew, Ostwald, Porcaro, and Bagshaw (2013); Mullinger, Mayhew, Bagshaw, Bowtell, and Francis (2014)). fMRI has better spatial resolution than EEG being able to measure voxels as small as 1mm cubed whereas EEG only has a spatial resolution of ~cms at best (da Silva, 2013) and through MRI structural scans we can see the subcortical structure and implied neuronal responses in the auditory cortex which is not possible through EEG or MEG. Alongside this, if fMRI NBRs and EEG/MEG's alpha oscillations are representing a marker of the same underlying inhibition of non-task relevant activity then this allows for a comparison of the effect using two different modalities. This is important as fMRI gives us a greater spatial resolution across the whole brain but is only an implied measure of neuronal activity through the BOLD signal whereas EEG/MEG is a true measure of the neuronal signal through the electrical/magnetic signal generated by pyramidal dendrites (da Silva, 2013).

Alpha, NBR, and GABA

EEG and MEG are incredibly useful techniques as their high temporal resolution allows the measurement of neural signals on a millisecond basis, however, the signals measured by these methods only represent large scale synchronization of activity over large populations of

neurons (Lowet, Roberts, Bonizzi, Karel and De Weerd, 2016). With the evidence provided that alpha at its most summary level is an inhibitory signal and gamma is an information processing signal, gated by alpha, then we would expect to see some biochemical evidence to support increased inhibitory neurotransmitter activity while alpha power is high and vice versa. One of the main inhibitory neurotransmitters across the cortex is GABA (gamma-aminobutyric acid) (McCormick, 1989) and is a key candidate for being a neurotransmitter that gives the alpha band its inhibitory/regulatory properties.

Rowlands et al in 2013 using magnetic resonance spectroscopy (MRS) found that GABA levels in schizophrenia patients did correlate with the 3-13Hz oscillations accounting for 47% of the variance in the gating of the theta-alpha activities during a paired click paradigm. The paradigm involved a 1-millisecond duration click at 72 decibels then a 500-millisecond duration interclick internal and finally a 10-second intertrial interval. Higher GABA levels in the medial prefrontal cortex were associated with stronger inhibitory responses, measured as greater theta-alpha power at the Cz electrode site 25-150ms post-stimulus, compared to lower GABA levels in neurotypical populations. GABAergic modulation in the visual cortex has been implicated with altering the power of visual gamma as the consumption of Lorazepam, a benzodiazepine upregulating GABAergic compound, increased stimulus-induced gamma power and reduced occipital alpha power modulations during a working memory task (Lozano-Soldevilla, Huurne, Cools and Jensen, 2014). These findings were limited only to the visual cortex which is interesting given that alpha is seen across the cortex and in different sensory modalities (Klimesch et al, 1999; Frey et al, 2014; Haegens, Luther and Jensen, 2012; Knyazev, Slobodikoj-Plusnin, Bocharov and Pylkova, 2011). During a working memory task, where participants had to identify if a sample array of six coloured squares matched a probe array of coloured squares, consumption of Lorazepamresulted in decreased alpha power modulation which worsened task performance (Lozano-Soldevilla, Huurne,

Cools and Jensen, 2014) as other evidence of alpha power modulation has been shown to do. Specifically, the alpha power was reduced contralateral to the direction of attention and increased relatively over the ipsilateral hemisphere compared to placebo. This was limited to the non-task relevant regions suggesting a regionally specific effect instead of a general cortical effect which would be expected given its cortex-wide administration through the bloodstream (Lozano-Soldevilla, Huurne, Cools, and Jensen 2014).

As this thesis does not collect any measures of neurotransmitters through the experimental chapters the discussion of GABAergic upregulating compounds and their effects on the alpha band will be concluded here.

The link between fMRI and EEG in inhibition

Throughout this chapter, while the alpha waveband and the NBR have been discussed as being neural mechanisms for inhibition they have been separately discussed. This leads to the question: are the two different mechanisms separate forms of neuronal inhibition which are also measured by two different imaging modalities or do they represent a common neuronal mechanism that is simply measured and recorded by fMRI and EEG/MEG in different ways while ultimately coming from the same root?

Multiple studies on this question have been provided by Mayhew and Mullinger who have used simultaneous EEG-fMRI recordings to see how the activity between the two concurrent measures correlates and if any causal link can be drawn. The first evidence for the link between the alpha band and the directionality of BOLD signals comes from Mullinger, Mayhew, Bagshaw, Bowtell, and Francis in 2012. In their paper, they showed that the concurrent BOLD and CBF responses in the sensorimotor cortex during unilateral median nerve stimulation (MNS) depended on the post-stimulus synchrony of the alpha band across

both the contralateral and ipsilateral somatosensory cortices. This provides evidence that there is a correlation between the alpha band and BOLD signal, but it is unclear if this is two separate correlated mechanisms or one inhibitory neural mechanism. Alpha is highly prominent in the visual field (Klimesch, Sauseng, and Hanslmayr, 2007), and work by Mayhew, Ostwald, Porcaro, and Bagshaw in 2013 studied the correlation between BOLD signals and the alpha band in the visual field. The author using left visual hemifield checkerboard stimulation for one second found that the PBR and NBR in the visual field were shaped by the amplitude of the pre-stimulus EEG recorded alpha power in the same regions. The authors also found a 'nonlinear reduction of visual PBR and enhancement of auditory NBR and default mode network NBR' in trials which presented high alpha power in the pre-stimulus period. This work shows not only that the post-stimulus alpha power affects the BOLD signal but also the variable brain state prior to the stimulus onset as defined by the alpha power in a given trial. Following this in 2014 Mullinger, Mayhew, Bagshaw, Bowtell, and Francis showed a negative correlation between the sensorimotor cortex BOLD signal and alpha power response to MNS, reflecting inhibitory control (Klimesch, Sauseng, and Hanslmayr, 2007). As alpha power increased through synchronisation of the neuronal population in the contralateral and ipsilateral somatosensory cortices the BOLD signal became a significant NBR. This presents evidence for neurovascular coupling and a direct link between the inhibitory alpha band signal and the inhibitory NBR.

More recently studies have been done on post-stimulus interactions with the BOLD signal and the alpha band. In 2017 Mullinger, Cherukara, Buxton, Francis, and Mayhew showed that BOLD and CBF signal amplitudes in the contralateral and ipsilateral visual cortex depended on post-stimulus occipital alpha power. This firstly implies there is a neuronal origin to the BOLD signal, a discussion that has been ongoing for decades (review on neurovascular coupling by Iadecola, 2017). In addition, the evidence for a link between alpha

ERS and NBR does not just come from intra/within modality stimulation and inhibition. In 2019 Wilson et al showed both motor stimulation and visual stimulation resulted in increased PBRs and reduction in alpha in the stimulated regions but an increase in the respective non-task-relevant regions in NBR and power in the alpha/beta band with the increase in the beta component of the signal primarily resulting from the motor cortex.

These studies particularly show the effect of inhibition on non-task relevant regions. By using EEG-fMRI studies it is possible to measure both the alpha synchronisation and NBR and they occur with a degree of temporal synchrony in regions that are not required for a task i.e., the auditory cortex during a visual task, the left visual hemifield when the right visual hemifield is being stimulated or the ipsilateral somatosensory cortex during unilateral somatosensory stimulation. We see both intra-modality inhibition where the inhibition occurs due to competition from within a modality i.e., inhibiting part of the visual field so the area with task-relevant information can be focused on better, and inter-modality inhibition where another modality i.e., the auditory cortex is inhibited during visual stimulation. To date, the evidence shows that both intra and inter-modality inhibition serves the same purpose of reducing distraction from non-task-relevant modalities and locations that could be attended to. The evidence also appears to suggest that both intra and inter modality inhibition use the same neural mechanism of alpha ERS and NBRs, but it is not as clear if the short vs long-range of communication needed in both respective forms of communication means differing neural organisations are used i.e., intra inhibition is handled entirely with the modality in question without needing parietal or frontal cortex coordination while inter modality inhibition does.

The need for inhibition

With the literature on alpha oscillations, NBRs, and the current theory that they represent inhibitory signals in the brain we are still presented with the question, why would the brain need inhibition? There is plentiful literature on response stop tasks or go/no-go tasks where a response, often a motor one needs to be inhibited to complete a task (see Simmonds, Pekar, and Mostofsky, 2008, for a meta-analysis on this subject) but why should a region that is not relevant in a task need to be inhibited (Klimesch, Sauseng, and Hanslmayr, 2007)? In many of the studies discussed above while there is a cued location for a presentation and then a stimulus in that location there is no conflicting stimulus in another location. Why would the brain need to inhibit a blank area of the screen or the auditory cortex when no sounds are being presented?

Potentially the solution is that the brain does not know that the other location/modality will be empty and remain irrelevant and therefore utilising proactive inhibition of those regions is the most practical solution. But here the use of the word 'know' is used due to a limitation of language and does suggest an anthropomorphised conscious control unit for each inhibitory neural action. This solution can be tested by presenting information in either single or multiple modalities and comparing the measured response. If a strong visual stimulus is the target (i.e., an item to be identified) then it would be behaviourally beneficial for the auditory systems to be inhibited to some extent during conditions with and without concurrent auditory stimulation which contains no task beneficial information. The use of unimodal and multisensory presentations would allow measurement of how non-task relevant regions are inhibited when a subject knows if that region's sensory field will have a stimulus in it or not, while that region is still non-task relevant. This will be studied in chapters 2 and 3.

This line of thinking however leads to a question regarding ecological validity. The experimental methods discussed above almost exclusively use proactive cues to inform participants where a stimulus will be and where non-task relevant information will come from, or if any will be present. In real life, this is a rare scenario, as even when cues are presented there are still plenty of unexpected distractors that can occur requiring immediate reactive inhibition. Due to the very small literature on this field (Kelly, Lalor, Reilly, and Foxe in 2006; Sauseng et al in 2009; Janssen et al 2017; Marini et al (2016); Vissers, van Driel and Slagter in 2016), there is a question if the robustness of the inhibition mechanisms is ultimately arising to the use of proactive cueing or whether they actually reflect a functional inhibition system that works with real-time reaction to distractors. This thesis aims to test this is by looking into how the brain processes reactive stimuli; I propose that regions that are cued as non-task relevant may be inhibited not because a region is currently processing a stimulus but because there might be a need in the future to inhibit a potential stimulus and it is best to prepare in case of a new stimulus appearing which would cause a distraction. In chapter 4 an experiment will train a participant that on the majority of trials the cues provided are truthful and the optimal strategy is to trust the cues but then on a minority of trials add in distractors at irregular intervals that require the subject's brain to react and filter out a distractor. The primary question of this chapter is studying if the inhibitory mechanisms, primarily in the alpha band, are equally as responsible for inhibiting non-task-relevant information in a more ecologically valid, reactive scenarios which contain non-cued distractors that require immediate reaction. We are not just interested in scenarios with proactive cues that have one hundred percent accurate information. If it is the case that trials involving reactive processing and proactive processing show the same pattern of alpha ERS in non-task relevant regions we can assume the literature for proactive processing is an adequate corollary for reactive distractor processing. If there is no clear similarity in the

behaviour of the alpha band and by extension assumed inhibitory response between the proactive trials and reactive trials this would suggest the uses of alpha in scenarios with reactive distractors and more generally non-perfectly controlled sensory presentations and cues is something, we cannot understand solely from proactive cue-based paradigms.

Finally, as discussed in the section above both intra and inter inhibition in the sensory cortices is the primary area in which alpha ERS/ NBR inhibition is seen (Mullinger et al, 2012 and 2014 and 2017). There is limited information that the memory and visual system can use proactive inhibition (Klimesch, 1999). This suggests that functional inhibition is not just a system used by sensory systems exclusively but that cognitive systems which can take inputs from multiple sensory domains and output to multiple sensory domains like the short-term and long-term memory systems can use functional inhibition as well. To date, there has not been an in-depth study of how different cognitive systems i.e., memory, language, social processing, relational processing, reward, or emotional processing, may use functional inhibition. It is reasonable to assume that in a task with only one network being required i.e., reading lines from a book to assess if they are grammatically correct, that other cognitive systems/networks would not be required i.e., the networks involved in spatial rotation or risk/reward monitoring.

In chapter 5 we will study how using a series of localisers to specifically activate different cognitive functions, with as much specificity and little cross-over as possible will help us to understand if cognitive functions show similar patterns of functional inhibition as sensory systems do. This experiment will be done using fMRI due to the need for full brain coverage and look to measure NBRs in the networks/regions the other localisers identify as the primary processing region for a given task. The methods for this experiment will be discussed in much greater detail in chapter 5.

The main rationale behind this experiment is to isolate if the current inhibitory model of inhibition being seen in non-task relevant regions is ultimately only a behaviour belong to the sensory cortices and the hippocampus (Klimesch, 1999) which is the conclusion the current evidence can provide or if other cognitive systems can also use functional inhibition when necessary. In combination with the findings of chapters 2, 3, and 4 this will allow us to better understand how well the current literature on inhibition which informs us in great detail on the use of proactive cueing paradigms involving exclusively sensory stimulation relates to more ecologically valid scenarios involving multi-sensory stimulation, reactively processing of distractors and using sensory input for cognitively engaging tasks and not abstract experimental paradigms with checkerboards, beeps or basic geometric shapes.

Chapter 2 - The effect of NBRs as a sign of inhibition in non-task relevant sensory regions during single and multi-sensory stimulation across the visual, auditory, and somatosensory domains.

Introduction

fMRI positive and negative BOLD responses

The positive BOLD response (PBR) is commonly observed during the performance of a task in regions responsible for neural processing i.e., a PBR is observed in the retinotopic visual cortex representation of the stimulated visual field (Chen, Tyler, Liu, Wang, 2005). It is comprised of an increase in the oxyhaemoglobin content of the blood (changing the ratio with deoxyhaemoglobin) in that region which occurs from an increase in cerebral blood flow to compensate for increased metabolism of oxygen resulting from increased peri-synaptic neural activity (Logothetis et al, 2001; Logothetis et al 2008; Goense and Logothetis, 2008 Ekstrom, 2010).

Conversely, task-induced decreases in BOLD signals have been measured for over two decades called Negative BOLD Responses (NBR) (Raichle, MacLeod 2001; Shulman 1997; Smith, Singh, Greenlee 2000; Smith, Williams, and Singh 2004) which are correlated to reduced neuronal firing (Boorman et al 2010; Devor et al 2007; Shmuel et al, 2002 and 2006) and functional inhibition (Ferbert et al 1992; Klinger et al 2010; Shmuel et al 2006; Mayhew 2012, Mayhew et al 2013, Mullinger 2014 and 2017). Neural firing and increases in local

field potential activity in the gamma frequency range have been specifically linked to PBR (Niessing and Lauritzen, 2005; Scheeringa et al, 2011) while negative BOLD responses (NBR) have been associated with lower frequency activity in the alpha range (Scheeringa et al 2011; Mullinger et al 2014).

These NBRs reflect a decrease in the local cerebral blood flow and oxygen metabolism (Harel et al 2002, Shmuel et al 2002 and Shmuel et al 2006, Pasley et al 2007, Stefanovic 2004) and they have been argued to reflect a decrease in neural activity; more specifically in monkeys, Shmuel et al 2006, in rats Boorman et al 2010; 2015 and also in humans Mullinger et al 2014. It has also been argued to represent functional inhibition in the contralateral S1 regions (Schäfer et al, 2012). The NBR, which is linked with modulations of the power of the alpha oscillation, is described as reflecting 'inhibitory' neural activity (Boorman et al 2010, 2015, Shmuel et al 2006, Klimesch et al 2007, Mullinger et al 2014) and as such evidence of a causal relationship between alpha and NBR would reflect the measurement of a common neural mechanism (Mullinger et al, 2014). While this causal link has not yet been established this chapter will assume a common neural mechanism that is represented by alpha oscillations or NBRs. The NBR cannot only be seen in the light of its correlation to alpha power, NBRs are also correlated to reductions in gamma power. Shmuel et al 2002 and in 2006 as well as Boorman et al in 2010 found not only that NBRs were correlated to an increase in alpha power but additionally that there was a negative correlation between NBRs and gamma power. This presents an interaction whereby neuronal processing ability through the gamma band (Miltner et al, 1999) is decreased as inhibitory power is increased through a rise of power in the alpha band (Klimesch, Sauseng, Hanslmayr, 2007). Conversely, PBRs are seen to decrease alpha power and increase gamma-band power which suggests a balance of neuronal systems between the inhibitory and the excitatory which can be measure through the BOLD response.

Within/Intra Modal Inhibition

NBRs can also arise from within the same sensory modality, e.g., when only part of one sensory field is stimulated or attended. The requirement for within modality interference and its control via inhibition comes down to attentional demands that are competing in space. If an attended object is on the left side of a subject, then any sensory information originating from the right side is potentially distracting, and suppressing such distraction is beneficial for performance. In this section, we will discuss the use of within modality inhibition to improve attentional control and reduce interference even when other modalities do not need inhibitory control.

Studies of within modality inhibition have a longer history than cross-modal inhibition. The basic principle is that unilateral (single-sided) visual or somatosensory stimulation results in the contralateral primary sensory region presenting a PBR but conversely, an NBR is observed in the ipsilateral region, the cortical representation of the unstimulated, task-irrelevant, and potentially interfering sensory field. (Allison et al 2000; Bressler et al 2007; Hlushchuk and Hari 2006; Kastrup et al 2008; Newton et al 2005; Tootell 1998; Smith et al, 2000 and Smith et al 2004).

Of interest in understanding, within-modality inhibition is a paper by Bressler, Spotswood, and Whitney (2007). By using a series of flashing gabors that moved across the visual field and tracking the position of PBRs and NBRs in the visual cortex the authors found that the movement of the PBR and NBR locations matched the neural architecture and retinotopic mapping of the visual systems, but not the vasculature, presenting strong evidence for the NBR showing an effect of functional inhibition instead of blood stealing. Kastrup et al 2008 stimulated the somatosensory cortex with right median nerve stimulation (MNS) and found PBR in contralateral S1 (primary somatosensory cortex) and S2 (secondary somatosensory

cortex) but also an ipsilateral S1 NBR. This again suggests that the contralateral S1 was not stealing blood across the hemispheres but instead that the ipsilateral S1 could interfere with the task performance and needs to be inhibited. Additionally, the ipsi S1 NBR induced by MNS was associated with lower current perception thresholds in the task-relevant hand (compared to when no MNS was delivered), indicating a direct effect on perception and task performance (Kastrup 2008). However, evidence of relationships between NBR and task performance are rare and the importance of NBR to the functional operation of the brain remains one of several poorly understood properties of NBR that the current experiment aims to address.

fMRI NBR cross-modality inhibition

Cross-modal inhibition has been well established in the literature (Mayhew et al 2013a and 2013b, Wilson et al 2019) as a mechanism by which attention is used to prioritise processing on one location or in a given sensory modality over another and to improve task performance. In this section, I will discuss the history of how cross-modal inhibition was discovered and key findings which helped to conceptualise the use of cross-modal inhibition for supporting task-relevant processing.

Laurenti et al in 2002 first presented fMRI evidence for cross-modality inhibition. The authors found that auditory stimulation resulted in an NBR of the extrastriate visual cortex and conversely visual stimulation resulted in NBR of the auditory cortex. These findings showed that the sensory cortices did not operate independently but were capable of cross-region communication, leading to suppression of the BOLD signal in regions that were not relevant to the current task. This has been studied more fundamentally in animals where activation of the auditory cortex by a noise burst caused localised inhibition in supragranular pyramidal cells in the mouse visual cortex (Iurilli et al, 2012).

These findings of reciprocal, cross-modal deactivation of the visual and the auditory cortex were later replicated and extended by Mozolic et al, 2008. A cued detection task presented either visual or auditory targets to localise modality-specific attention effects. The primary finding was a difference in the non-attended cortical modality during stimulation, when a modality was not required it presented an NBR even if the stimulated modality did not present a significant PBR. This modulation as a function of attention was even observed in trials where no target stimulus was presented. This suggests that the NBR does not arise from stimulus input alone and raises the question of how much of NBR can be explained by shifts in attention. The authors present that the benefit in performance from attending to a location arises not only from an increase in PBR magnitude in the relevant cortical region but also from the NBR, and assumed consequent inhibition, in non-relevant regions. Hairston et al 2008 provided more evidence for visual-auditory cross-modal inhibition. Participants performed an auditory temporal-order judgment task and cross-regional deactivations were observed during both the moderate and high-level difficulties of the task. Specifically, NBRs were seen in the parietal, cingulate, and occipital cortices, and importantly they found that the NBR magnitude in the occipital cortex increased with task difficulty. Therefore, taken together the Mozolic paper presents evidence for NBRs being part of the mechanism where attention withdraws the focus and information processing away from a cortical location/ sensory field. Whereas the Hairston et al 2008 paper finding that NBRs increased with increasing difficulty suggests that the NBRs represent functional inhibition in non-task relevant regions to support task performance and reduce cross-region interference.

The need for inhibition or the use of inhibition across the cortex

As discussed in the introduction, sensory regions of the brain present reductions in BOLD signal, neural and metabolic activity through NBRs (Raichle, MacLeod 2001; Shulman 1997; Smith, Singh, Greenlee 2000; Smith, Williams and Singh 2004) or synchronisation of alpha

frequency oscillations (Klimesch et al 2007) which have been argued to present a functional inhibitory signal (Klimesch, Sauseng, and Hanslymayr, 2007; Jensen and Mazaheri, 2010; Klimesch, 2012; Slagter, Prinssen, Reteig, Mazaheri, 2016). For the remainder of this chapter and for most of the thesis the interest will be on NBRs, alpha synchronisation, and in general, inhibitory, or regulatory control of neuronal populations. To that effect, the current evidence suggests that this inhibition is used to reduce interference from non-task relevant regions and improve task performance (Hairston et al, 2008, Boorman et al 2010; Devor et al 2007; Shmuel et al, 2002 and 2006). It remains an open question concerning why a subject would need to inhibit a non-task-relevant region instead of simply ignoring it or just processing everything simultaneously? Furthermore, why the NBR is so readily observed during passive tasks, where the need for inhibition is minimal as there are no competing task demands. To begin to answer this question, I would argue that the use of alpha ERS/NBR effectively represents the same thing as ignoring or moving something out of our attention. For example, PBR and gamma ERS in the visual cortex while viewing a visual image will characteristically occur concurrently with alpha ERS/NBRs in the auditory cortex (Mozolic et al, 2008; Mayhew et al, 2010, Mayhew et al 2013). Behaviourally the subject will ignore the non-relevant modality and focus on the visual information, and the 'inhibitory' signals reported in the literature represent how this is achieved. By choosing to ignore a stimulus the brain inhibits a non-task relevant modality or spatial location, it is the method by which we narrow in our attentional spotlight. The reason a person does not process all information simultaneously is because they have a limited attentional spotlight (VanRullen, Carlson and Cavanagh, 2007) and by focusing on one location or modality you by definition are choosing to not focus on another. This results in a change in the balance of activity, between the areas displaying PBRs/gamma ERS and the areas whose activity needs to be dampened through NBR/alpha ERS. VanRullen, Carlson, and Cavanagh (2007) bring to light a flaw in the

strictest interpretation of a singular attention spotlight when evidence has been shown that multiple locations can be attended to concurrently. In this thesis, I propose that the alpha inhibitory system is still used when highlighting the physical space or sensory modality to be ignored, regardless of whether the attentional spotlight is a singular or plural neural construct.

Rationale

Due to the scarcity of research on how multisensory stimulation alters the NBR in non-task - relevant regions (NTRRs) we aim to study whether increasing from single to multiple sensory (visual, auditory, and somatosensory) stimulation and the increase in sensory interference that presents, changes the expression of NBRs in NTRRs. Firstly, this study aims to understand this by providing a battery of visual, auditory, and somatosensory stimulation, with modalities delivered either alone or paired with one other and measuring the BOLD responses of visual, auditory, and somatosensory cortex. The increased interference from the second active modality will allow us to measure how the shift in attention from the directed vs interfering modality alters the NBR in NTRRs.

Secondly, in this experiment we aim to understand better how each sensory modality is unique in its expression of NBRs in NTTRs; is there parity between different modalities in their expression of NBRs i.e., are NBRs in the auditory cortex comparable when the stimulation is either visual or somatosensory? Thirdly, we also want to understand if each stimulated sensory modality results in a comparable NBR across the cortex or if different modalities cause NBRs in unique areas. To date, there is no study comparing sensory modalities and the NBRs to their stimulation in this way. This experiment aims to present a novel paradigm of studying NBRs due to visual, somatosensory, and auditory stimulation all within the same experimental session.

Fourthly and finally, we also want to understand if NBRs are additive, for example, whether two stimuli (e.g., auditory, visual) that alone cause NBR in a single cortical location (somatosensory) create an even greater NBR when delivered concurrently. A paper by Wilson, Thomas, and Mayhew (2020) showed that visual cortex NBRs were not additive in response to stimuli combining foveal and middle-eccentricity checkerboards presented in the left visual field. To date, there are no other papers presenting replication, that study how NBRs interact with multiple stimuli or looking at NBRs to multisensory stimulation combining multiple different modalities. In response to this gap in the literature, our paradigm includes auditory, visual, and somatosensory stimuli; delivered alone as well as in concurrent but non-integrated combinations. This allows us to present two independent streams of sensory stimulation whilst maintaining the other modality as non-task relevant. Through this, we can measure if there is an additive effect on the NBRs when comparing single vs dual-modality stimulation as a function of increasing cognitive load. This will greatly elucidate the nature of NBRs both across and within the different sensory domains.

Hypotheses

The key research questions and hypotheses for this experiment are:

- H1: Do sensory NTRR consistently show an NBR both within and across a modality? E.g., we expect that visual stimulation induces NBR in auditory and sensorimotor regions, and is this reciprocated by sensorimotor stimuli inducing NBR in visual and auditory regions.
- H2: NBR behaviour is consistent across different stimulation modalities. E.g., We expect that for simple sensory tasks (e.g., sensorimotor stimuli) that two NTRRs (e.g., auditory and visual cortex) are equivalent and will, therefore, show comparable NBR amplitudes.

- H3: There are differences are observed in cross-modality NBRs compared to within modality. E.g., We expect the spatial extent and amplitude of cross and within modal NBRs to be comparable for conditions of comparable sensory input (e.g., ipsilateral visual NBR and auditory NBR to visual stimulation).
- H4: Increases in the amplitude of the NBR will be related to an increased need to suppress distraction and activity in NTTRs.
- H5: NBR amplitude/location is modulated differentially between single vs. dual stimuli conditions E.g., Non-relevant modalities will show a significantly greater NBR to dual stimulation conditions than single modality conditions.

Methods

19 participants (9 males, mean age was 23.2) were recruited from the University of Birmingham student population. All participants were in good health, did not need corrective lenses or a hearing aid, and had no contradictions for MRI. The study was conducted with the approval of the University of Birmingham Ethics Board and informed consent was obtained from all subjects before their participation.

fMRI was used to record BOLD responses to visual, auditory, and somatosensory stimulation. Sensory modalities were either stimulated separately (e.g., Visual), or in pairs (e.g., Visual and Auditory), see below for further details. Participants detected targets presented in a single, attended, sensory modality that was delivered either alone or whilst another sensory modality was stimulated. The visual stimulus was a lower left-hemifield, black/white checkerboard of 100% contrast with pattern reversal at 7Hz. The auditory cortex was stimulated with a train of pure tone (1kHz) beeps at 7Hz, and the somatosensory cortex was stimulated with electrical median nerve stimulation (MNS) at 7Hz via two electrodes placed on the right wrist. The MNS

was delivered using a Digitimer DS7A stimulator (0.5ms square wave pulses). The MNS current amplitude was set just above the individual's motor threshold as to cause a small, involuntary thumb distension.

The experiment featured six conditions, three of single modality stimulation: visual (V), auditory (A), and somatosensory (S); and three dual-modality conditions: visual and auditory (VA), auditory and somatosensory (AS), visual and somatosensory (VS). The paradigm ensured there was always a non-task relevant sensory region within which we could investigate the NBR, see Table 2.1.

Experimental condition	Stimulated and attended modality	Modality to be inhibited	Measured for PBR	Measured for NBR
1	Auditory (A)	Visual and Somatosensory	Auditory	Visual and Somatosensory
2	Somatosensory (S)	Visual and Auditory	Somatosensory	Visual and ipsilateral somatosensory cortex
3	Visual (V)	Auditory and Somatosensory	Visual	Somatosensory and ipsilateral visual cortex
4	Auditory and somatosensory (AS)	Visual	Auditory and somatosensory	Visual and ipsilateral somatosensory cortex
5	Visual and auditory (VA)	Somatosensory	Visual and auditory	Somatosensory and ipsilateral visual cortex

6.	Visual and somatosensory (VS)	Auditory	Visual and somatosensory	ipsilateral visual cortex

Table 2.1. *A table showing the conditions of the experiment and the areas that are to be attended to and inhibited as well as the expected NBR.*

Main Experimental Procedure

Paradigm

An experimental trial consisted of the following structure:

• A 1s cue period, where a centrally displayed capital letter indicated the modality of the subsequent stimulus to both attend to and detect targets in (V for visual, S for MNS, and A for auditory). This enabled the subject to prepare accordingly for the upcoming trial.

• A 1s fixation interval with a central cross

• A 6s period of stimulation. This period contained either 0,1 or 2 target stimuli. The targets were brief, deviant stimuli presented amongst the train of standard 7Hz stimuli, in the form of one of the following, either:

1. In attend to Auditory trials, the higher pitch (+20Hz) of an auditory tone,

2. In attend to Somatosensory trials, a larger temporal interval (+50ms) between MNS pulses

3. In attend to Visual trials, a deviant contrast of a single checkerboard reversal (grey instead of black/white) which covered the whole left hemifield

• A 3s fixation interval to separate the stimulus-response from the motor component of the target response

• A 1.5s response period (indicated by 'T?' displayed in the centre of the screen). Participant's responses were given on an MRI compatible button box detecting either 0, 1, or 2 targets.

• Finally, 12.5/13.5s of resting fixation to act as a baseline period. A one-second jitter was employed equally over trials to provide a better sampling of the BOLD signal.

A schematic of the stimulus paradigm is shown in Figure 2.1, below.

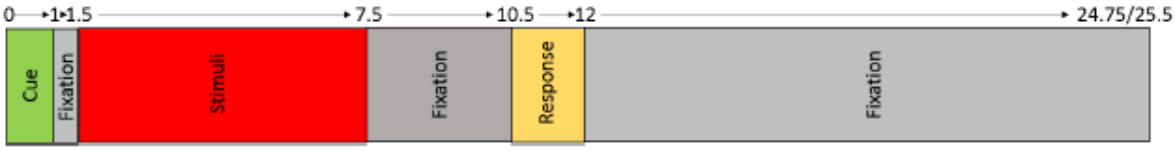

Figure 2.1. *Timeline of a typical experimental trial.*

During each trial, the subject's task was to attend to the cued modality and detect any targets presented, whilst ignoring any other modality that was stimulated. The subject only reported the number of detected targets during the T? response period after the stimulation had ceased. This temporally separated the response from the stimulation to minimise the contamination of somatosensory NBRs to stimuli by motor responses to button pressing. The attended modality was counterbalanced amongst dual trials, i.e., there was an equal number of VS attend-to-V and VS attend-to-S trials. In each condition, there was an equal number of 0,1 and 2 target trials. There were five trials per condition in each run, presented in a pseudo-randomised order. Each run lasted for 13 minutes. There were four runs recorded per subject, giving a total of twenty trials per condition and the total duration of the experimental session was 90 minutes.

A 3T Philips Achieva scanner (Philips Medical Systems, Best, Netherlands) was used to acquire MRI data with a transmit body coil and 32-channel head coil. We used gradient-echo EPI to acquire T2* weighted BOLD fMRI data with multiband factor = 2 and SENSE = 2.3, TR = 1.5s, TE = 38ms, flip angle = 70º, FOV = 96 x 96 and 40 slices with 0.2 mm slice gap and a voxel size of 2.5mm isotropic providing whole head coverage. Cardiac and respiratory signals were recorded using the scanner's inbuilt pulse oximeter (PPU) and bellows.
The scanning protocol for this experiment was to conduct two stimulation runs, then to allow the participant to rest for 5 minutes and reduce the chance of task fatigue a whole-head T_1-weighted anatomical image with 1 mm isotropic resolution (TR=2000ms, TE=2 ms, TI=880 ms, flip angle=8 degrees, FOV 256x256) was acquired to facilitate image co-registration. The participant then underwent two more stimulation runs except for one participant for whom only two stimulation runs could be conducted.

Behavioural Data Analysis

We wanted to analyse the behavioural data to explore if any particular condition was too difficult for the participant i.e., performance at a chance level of below to ensure participants were paying attention throughout the experiment. Behavioural data (% correct responses per condition and per subject) were analysed and averages and standardised error means can be seen in Table 2.2 below. Additionally, to compare the behavioural data of the single modalities to each dual condition a series of one-way ANOVAs were conducted each with a dual condition compared to each single modality condition which matched the stimuli presented in the dual trial i.e., visual-somatosensory, visual, and somatosensory. As the ANOVA was a one-way ANOVA there was one factor, the stimulation pairing, and the levels were the two single stimulation trials respectively, and then the combined dual condition which involved both of the stimulation types i.e., visual, auditory, and then visual auditory.

fMRI Data Analysis

fMRI data were pre-processed and analysed in FSL v6.01 (http://www.fmrib.ox.ac.uk/fsl). The BOLD data were motion-corrected using FLIRT (Jenkinson and Smith 2001, Jenkinson et al 2002), spatially smoothed using a 5mm FWHM Gaussian kernel, high-pass temporally filtered (>0.01Hz), and spatially normalised by coregistration to the subject's T1 anatomical (7 DOF) which was itself coregistered to the 2mm MNI template (12 DOF) using FLIRT.

The PPU and respiratory data of each subject were input to the PhysIO toolbox (Kasper 2017) which was used to calculate time course regressors that modelled variability in physiological noise. A total of 3 cardiac and 4 respiratory terms were used along with 1 interaction term, to create RETROICOR style regressors (Glover 2000). Also, the respiration per volume time (RVT) (Birn 2008) and heart-rate variability (Chang 2009) regressors were modelled. These regressors were included, as covariates of no interest, in the first-level general linear model (GLM) design matrix, along with the six main parameters of head motion output by MCFLIRT.

First-level GLM analyses were performed using FSL FEAT v6.01 for each run from each participant. Each of the six conditions was modelled as a separate regressor using the respective stimulus timings. The timings of each subject's button-press responses to each trial were also included to regress out the motor component of finger movement. Each of the regressors were convolved with a double-gamma haemodynamic response function. Their temporal derivatives were also included in the design matrix. Both positive and negative contrasts were set on each regressor to identify regions of PBR and NBR respectively. The resulting contrasts were compiled across all four runs using fixed effects to give the mean response per condition and per participant at the second level. The third-level analysis was then used to calculate group-level results, using mixed-effects FLAME 1 for PBR and fixed-

effects for NBR due to the lower signal-to-noise ratio of that response ($Z>3.1$ for PBR and $Z>2.3$ for NBR, all at $p<0.05$ cluster corrected). These third-level contrasts provided the group means of each condition to provide maps of the activations per condition and regions showing a cross-modal and within-modal NBR. Further analyses were then conducted to test for differences in response between dual and single stimulation conditions. We first tested for a difference between dual and single condition responses, independent of modality, by contrasting the sum of all single conditions (V+A+S) against the sum of all dual (VA+AS+VS) conditions. We next contrasted each dual condition against every single condition that was delivered in the dual condition i.e., visual-somatosensory contrasted against visual alone, to test whether the addition of somatosensory stimulation changed BOLD responses to visual alone. In addition, we contrasted each dual condition against the combination of the single conditions that were delivered in that dual condition i.e., visual-somatosensory contrasted against the combination of visual and somatosensory single conditions, to test if the NBR to dual stimulation was equivalent to the sum of that induced by the separate stimuli.

Finally, as the dual conditions featured the participant attending to either one modality or the other, for example, the visual or somatosensory modality, these conditions were also analysed specifically to compare if the focus of attention influenced NBRs in NTRRs during dual stimulation. Each of the dual condition regressors was divided into two separate regressors depending on the direction of attention simply comparing the condition vs baseline.

ROI definition and single-trial BOLD timecourse extraction

ROIs were defined per participant as the voxel with peak activations per condition at the 2nd level to generate auditory, somatosensory, and visual ROIs. Time courses were extracted from the pre-processed BOLD data from each ROI and baseline correction was used to

normalise the signals to percentage signal change. All subjects were compiled to give an average per condition with each ROI's response per condition

Results

Behavioural results

The group means of the participants' accuracy from the behavioural data for each condition can be seen in Table 2.2 below.

The visual alone condition showed the highest performance in target detection (80.5%). The percentage of correct responses in the VA condition matched the mean performance across the visual alone and auditory alone conditions (76.6%). This suggests that participants performed equally as well when attention was directed to either visual or auditory during the dual stimulation condition as when they were processing the stimuli during single modality stimulation. The somatosensory alone condition showed the lowest performance (54.7%), performance increased in the AS and VS conditions but was still lower than the V, A, or VA conditions. VS and AS conditions were of comparable difficulty with only a 1.5% difference between these two conditions. Both VS and AS conditions were within 1% of the mean performance of both contributing single modality conditions.

Condition	Group mean accuracy (% trials correct) ± SEM
V	80.5% ± 5.8%
A	72.6% ± 5.5%
S	54.7% ± 5.0%

VA	76.6% ± 5.7%
AS	66.3% ± 4.7%
VS	63.4% ± 4.9%

Table 2.2. *Group means for performance for each condition with standard error in the mean.*

Three one-way ANOVAs were conducted to compare the accuracies of single modalities against the dual conditions which shared that modality. The ANOVAs compared the following conditions:

1. V, VS, and VA conditions
2. A, VA, AS conditions
3. S, AS, and VS

All ANOVAs were conducted with both Least Significant Difference and Bonferroni posthoc corrections. These ANOVAs were all non-significant, the nearest significant finding was the Visual & auditory condition vs the Visual alone condition, $p = 0.7$, Standard Error 7.67, indicating that there was no difference in performance between dual and single conditions.

fMRI results

Whole-brain statistical maps of the group mean PBR to each stimulus condition can be seen in Figures 2.4-2.9. To enable viewing of whole-brain responses we show a separate figure per condition, with responses shown axially on the MNI brain. Equivalent figures for NBR to each condition are displayed in Figures 2.10 - 2.15. Figure 2.17 provides a summary of the key responses together on the same image, for selected brain slices, and allows for a detailed comparison of their spatial location between conditions. Figure 2.18 shows PBR and NBR timecourses.

PBRs

We replicated previous results showing PBR in the primary sensory cortex of the stimulated modality in all single conditions (Figures 2.4 – 2.6) (Mozolic et al, 2008; Kastrup et al, 2008; Hairston et al, 2008; Mayhew et al, 2013). Dual modality stimulation-induced PBR in the primary sensory cortex of both modalities (Figure 2.7 - 2.9). For the lateralised visual and somatosensory stimuli PBR was primarily observed in the contralateral primary sensory cortex, as previously reported (Kastrup et al, 2008; Mayhew, Ostwald, Porcaro and Bagshaw, 2013). Auditory PBRs were observed bilaterally due to the bilateral stimulation used, we further note that the auditory cortex does not show the same response lateralisation as other modalities which is in line with previous work (Mayhew et al, 2010; Mayhew et al, 2013).

Additionally, we observed a variety of activations beyond the sensory cortices. In all conditions, activations were found in the superior temporal gyrus near the insula but in the dual sensory conditions, this extended into the frontal lobes suggesting greater recruitment of frontal attention networks. Bilateral insular and left medial frontal gyrus activation can be seen across PBR contrasts independent of condition. Recruitment of attentional regions was observed via activation of bilateral parietal cortices, however, in the auditory and somatosensory singular conditions, this activation was more predominantly more dorsal than in other conditions. The dual conditions also show increased activation in the parietal cortex compared to single conditions further suggesting that the dual sensory conditions recruited greater attentional resources.

To further explore such effects, Figure 2.2 shows the regions where PBR was significantly stronger during dual than during single stimulation in general (calculated by the contrast [VA+AS+VS] > [V+A+S]). PBRs were larger during dual than single stimulation in all primary sensory regions, as well as parietal, anterior cingulate, and medial frontal cortex

regions of the task-positive attention network. There were no brain regions where PBR was stronger to single than to dual stimulation.

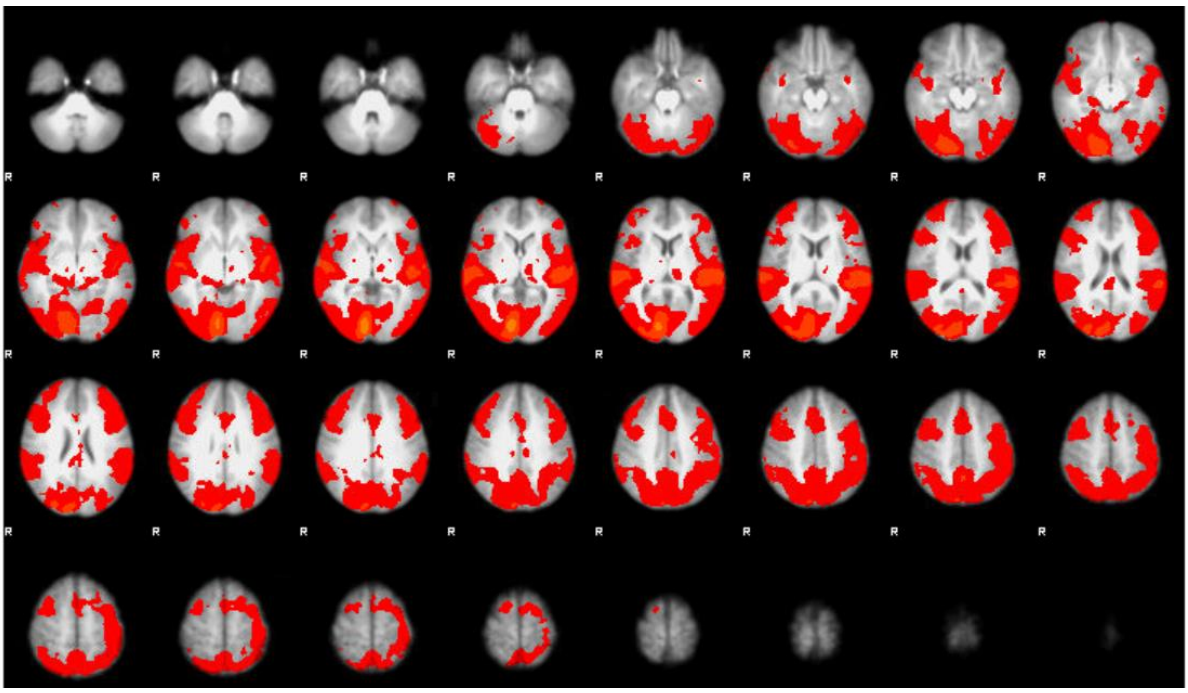

Figure 2.2 *Group contrast of all dual PBR > all single PBR, showing regions where the PBR to dual stimulation was significantly stronger than to single. Z-statistic 3.5-6.5*

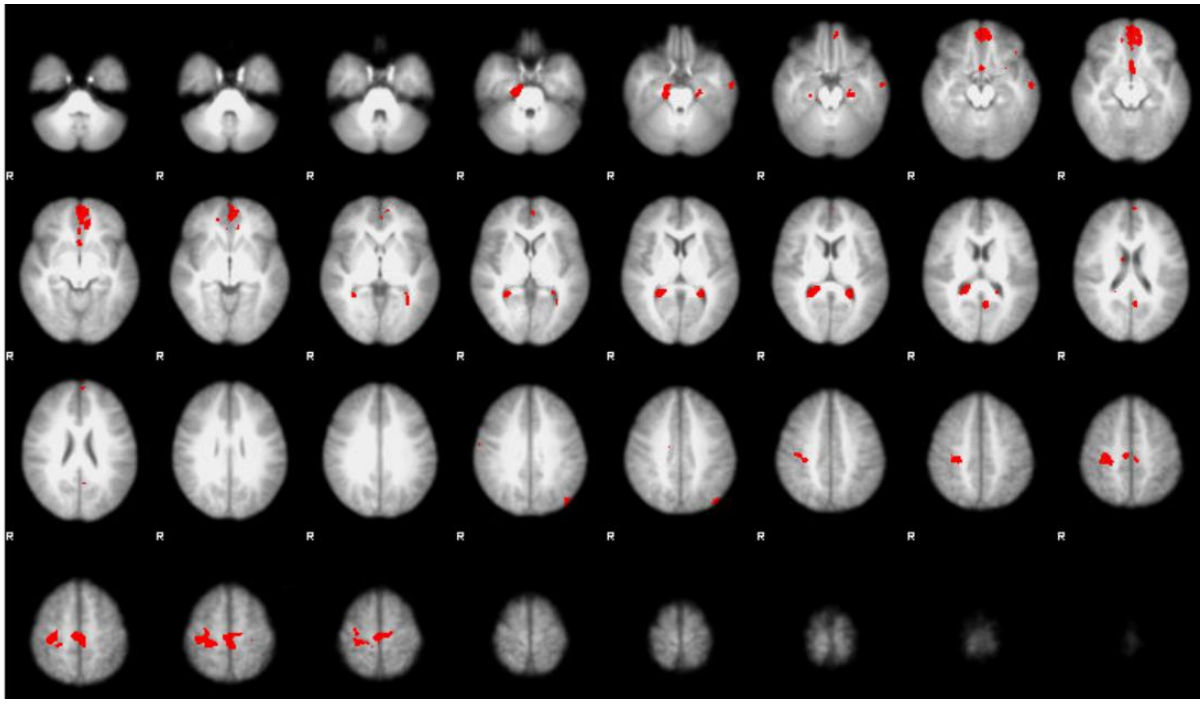

Figure 2.3. *Group contrast of all dual NBR > all single NBR, showing regions where the NBR to dual stimulation was significantly stronger than to single. Here we observed that NBR was stronger to dual than single stimulation in specific regions of ipsilateral S1 and the medial prefrontal cortex of the DMN. Z-statistic 3.5-4.6.*

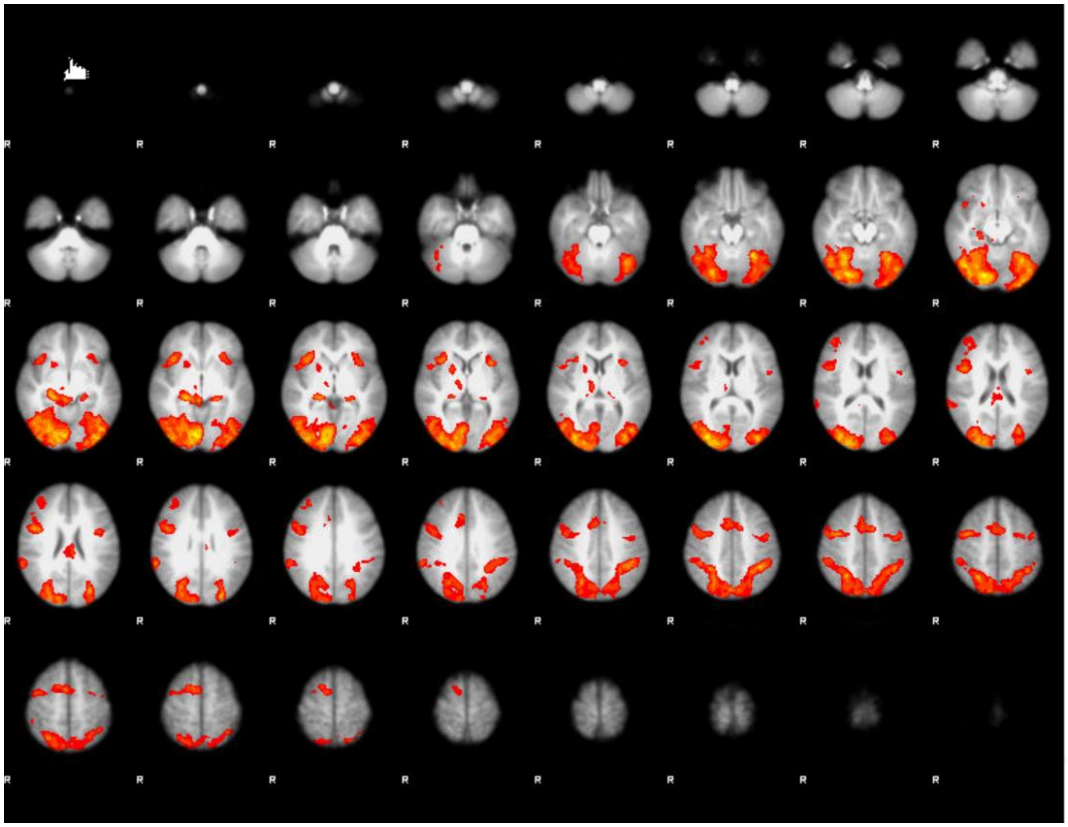

Figure 2.4. *Group mean PBR to visual stimulation – Z-statistic 3.1-7.1*

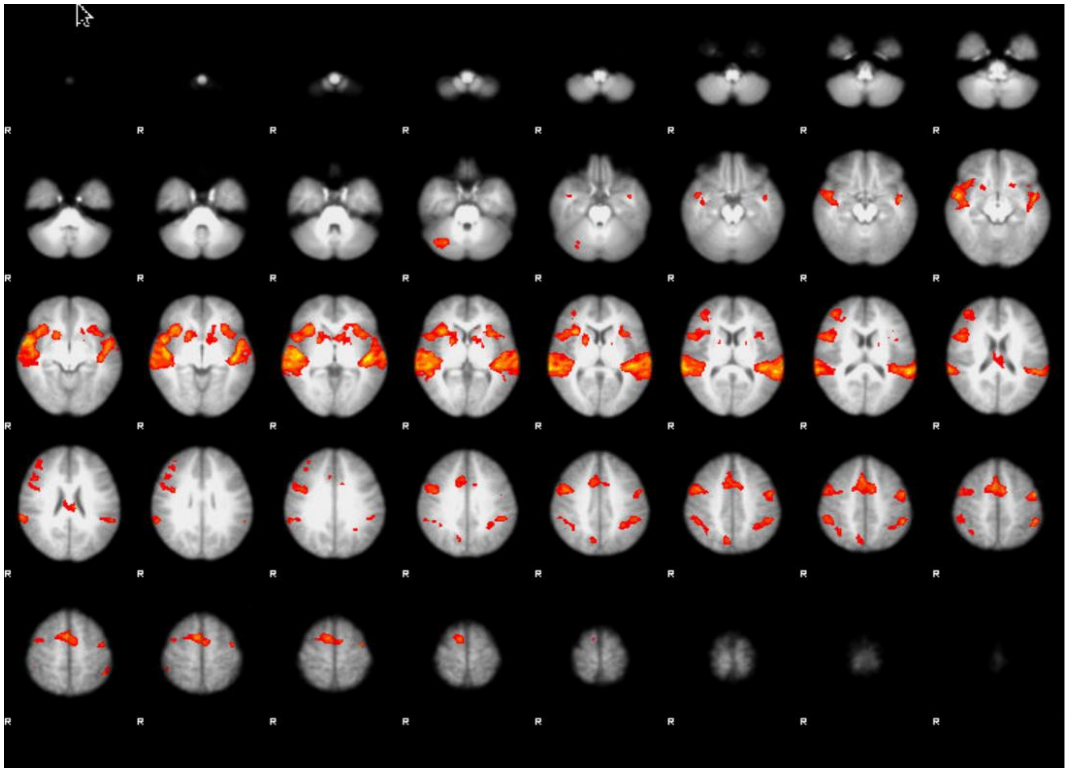

Figure 2.5. *Group mean PBR to auditory stimulation– Z-statistic 3.1-6.6*

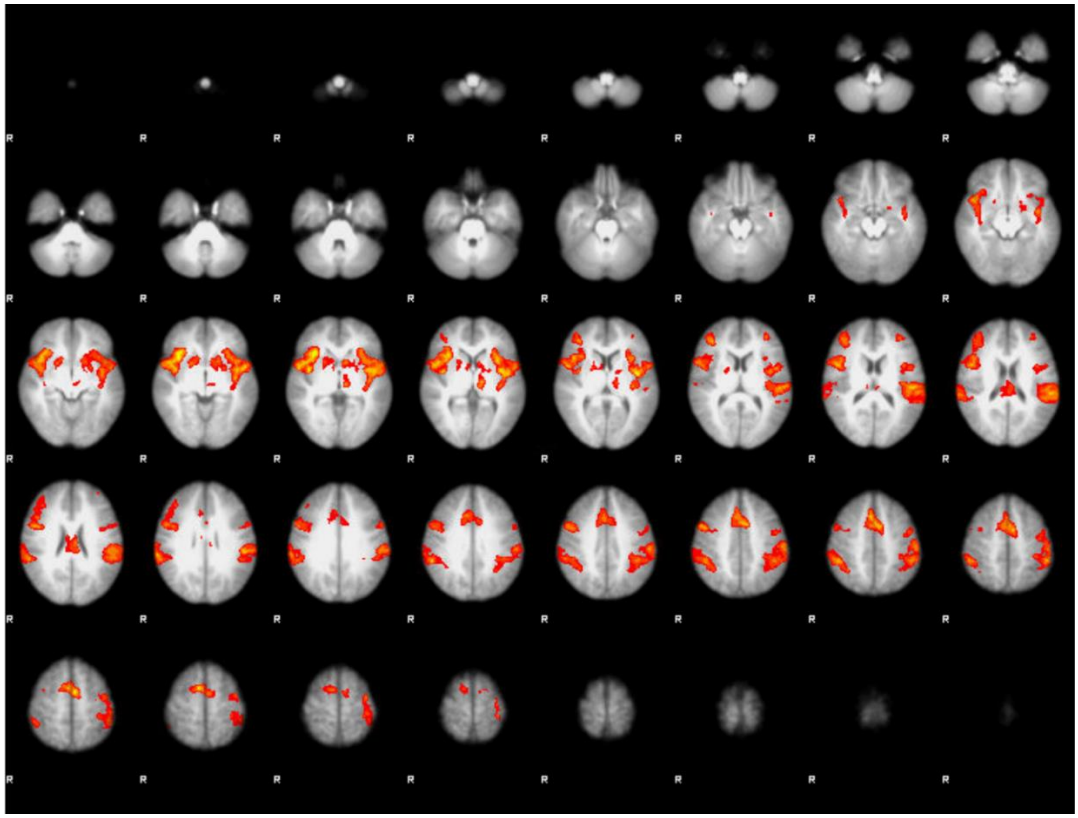

Figure 2.6. *Group mean PBR to somatosensory stimulation– Z-statistic 3.1-6.2*

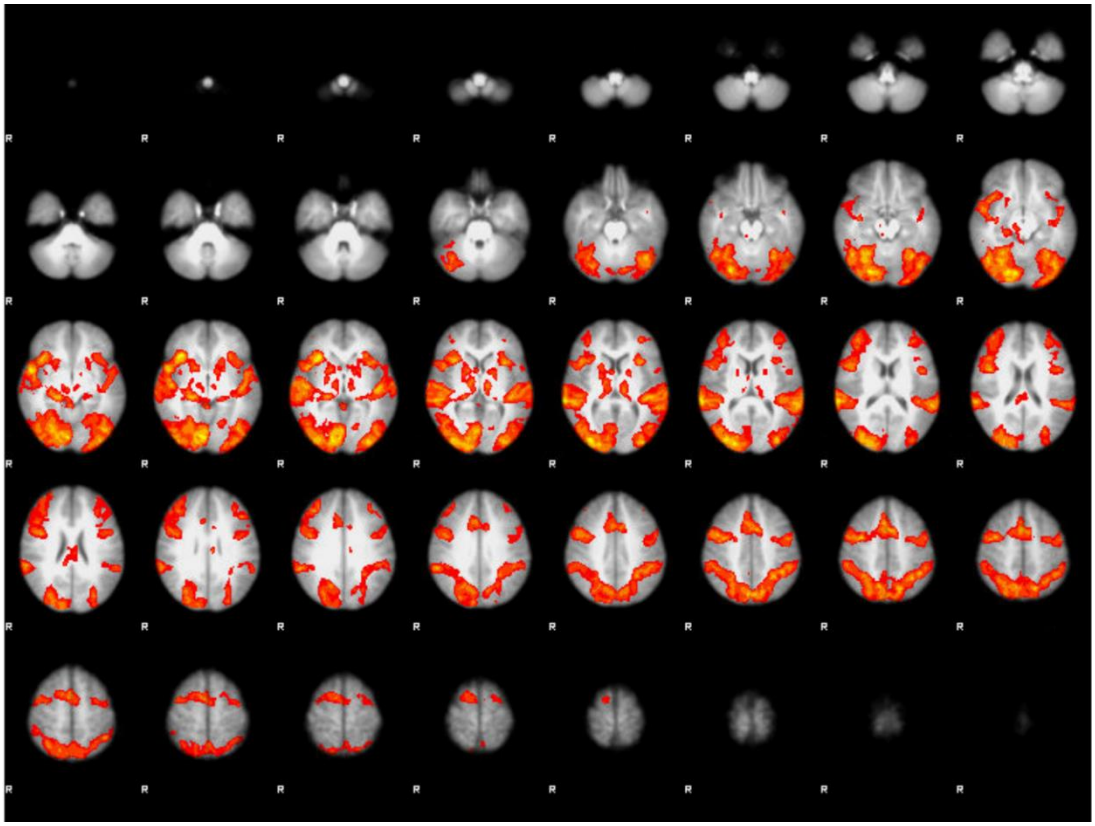

Figure 2.7. *Group mean PBR to visual & auditory (VA) stimulation– Z-statistic 3.1-6.9.*

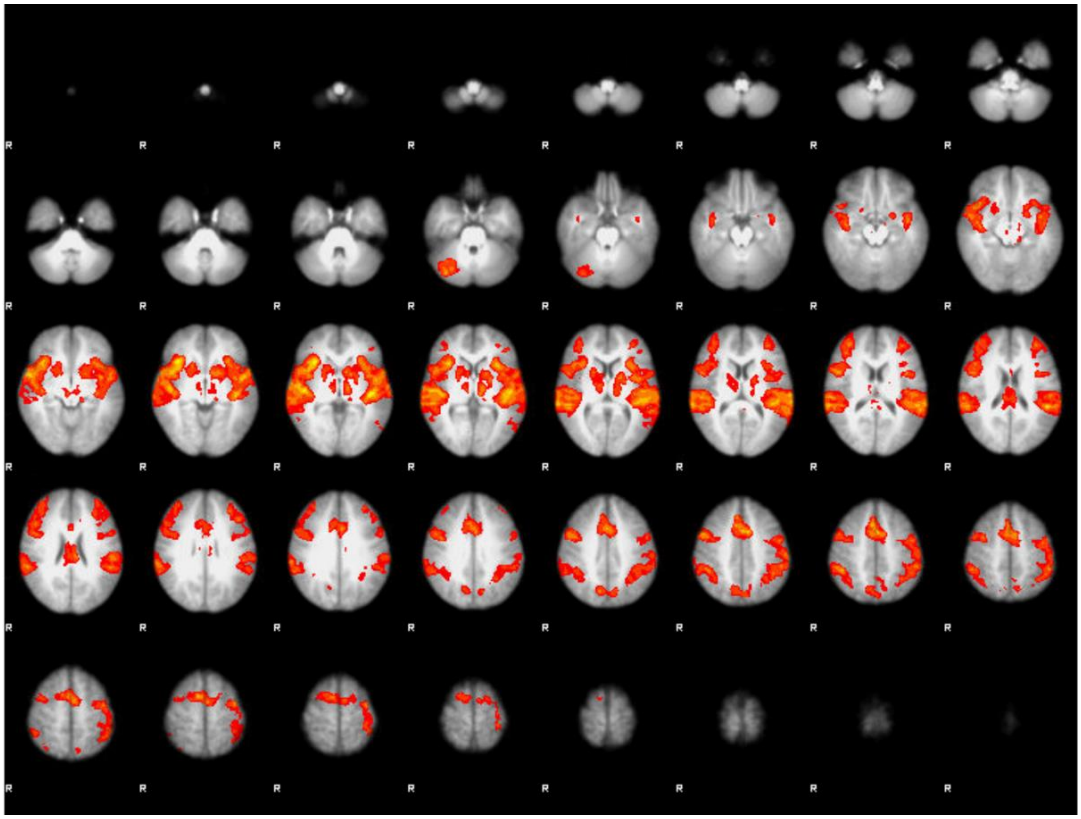

Figure 2.8. *Group mean PBR to auditory & somatosensory (AS) stimulation – Z-statistic 3.1-6.9.*

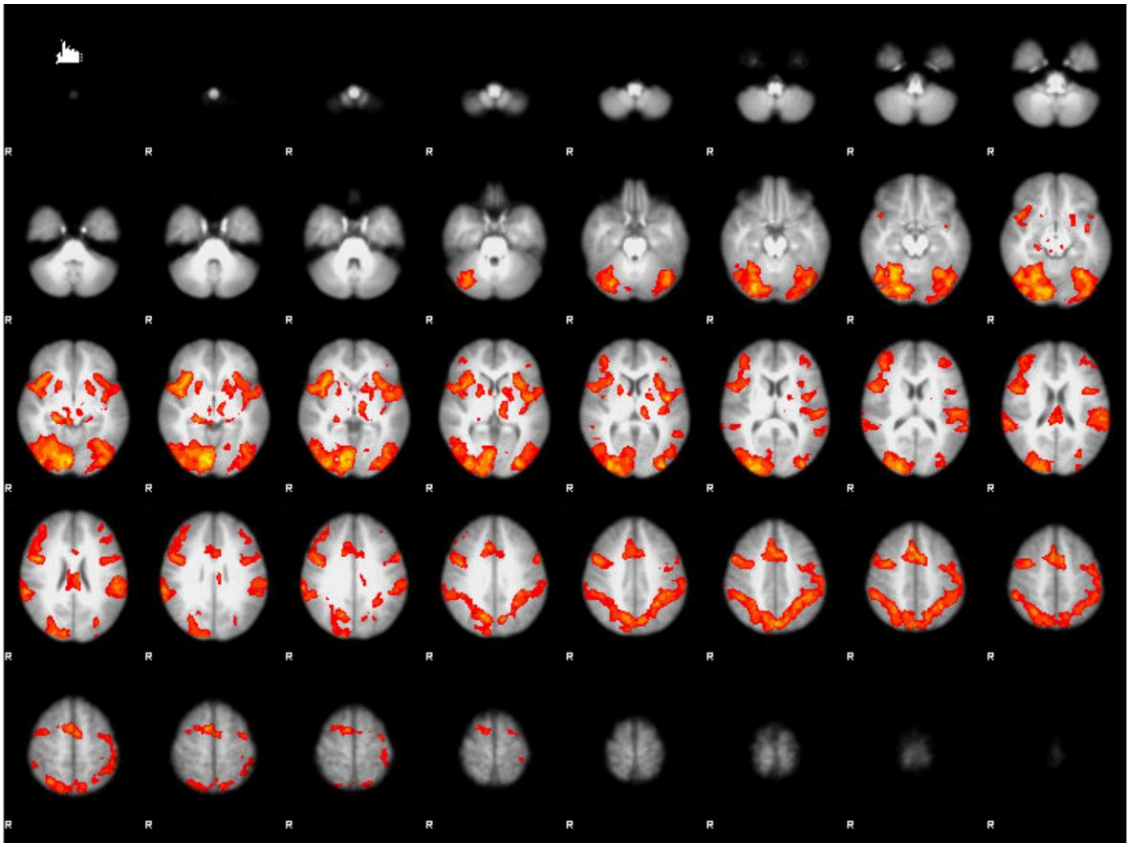

Figure 2.9. *Group mean PBR to visual & somatosensory (VS) stimulation– Z-statistic 3.1-7.1*

NBRs

In general, each of the conditions induced NBRs across the default mode network replicating previous literature (Chang and Glover, 2009) as well as a cross-modal NBR in the non-task-relevant sensory cortices. Within modality, NBRs were only observed in the somatosensory cortex during all somatosensory relevant conditions (S, AS, and VS). Ipsilateral V1 did not show a significant NBR during V, VA, or VS conditions at the group level. Hypothesised reasons for this unusual failure to replicate are in the discussion below.

Single stimulation conditions

Visual stimulation-induced cross-modal NBRs bilaterally in the primary auditory (A1) and somatosensory (S1) cortices, see Figure 2.10. Auditory stimulation-induced cross-modal NBRs bilaterally in the anterior primary visual (V1) cortex and S1, see Figure 2.11. The cross-modal NBR in S1 was highly comparable in both amplitude and spatial location between visual and auditory stimuli. Somatosensory stimulation-induced cross-modal NBR in A1 and V1 and within-modal NBR in ipsilateral S1 (Figure 2.12).

Dual stimulation conditions

The dual conditions showed NBR in the unstimulated sensory modality (Figure 2.13-15). V&A stimulation-induced within-modality NBRs bilaterally (Figure 2.13) in similar regions of S1 to that observed in the single conditions. A&S stimulation-induced cross-modal NBR bilaterally in the anterior V1 and within modality NBR in ipsi S1 (Figure 2.14). V&S stimulation-induced cross-modal NBR bilaterally in A1 and within modal NBR in ipsi S1 (Figure 2.15).

Dual vs single condition contrasts (e.g., VS vs V)

We contrasted dual vs single conditions to investigate whether NBR magnitude was modulated by the addition of a second stimulus, i.e., due to a combination of inhibitory effects and/or further withdrawal of attention from the remaining unstimulated modality.

In answering H5 does dual stimulation cause larger magnitude NBRs than single stimulation? The answer is no. The non-sensory region NBRs are similar between single and dual conditions. However, we found that ipsilateral S1 NBR was stronger when the stimulation

included somatosensory stimulation compared to any other condition (figures 2.12, 2.14, 2.15, 2.17 – 2.20, and 2.21). The visual and auditory systems did not show differing NBRs depending on the type of stimulation or if the stimulation was from single or multiple modalities.

Dual vs single condition contrasts (e.g., VS vs V+S)

Regarding the H4 and more specifically if multimodality vs single modality stimulation will result in greater NBRs in NTRRs, we did not find evidence for greater NBR in the dual vs single condition except in ipsilateral S1 (Figures 2.18 and 2.19). On further analysis, this is because the visual and auditory conditions do not cause ipsilateral S1 deactivations to the same level as somatosensory conditions (single or dual) as seen in the AS vs A+S and VS vs V+S Figures 2.15 and 2.16. However, we do see greater NBR in the dual-modality conditions in the DMN due to an increase in stimulated modalities as seen in the AV vs A+V (figure 2.20).

We only found supra-additive effects in sensory modalities in the ipsilateral S1 (Figure 2.18 and 2.19). There was a supra-additive inhibitory effect that occurred in the VS and AS conditions when contrasted to the A+S and V+S. However, the time courses plotted for these conditions show that the increased NBR was primarily due to the addition of the somatosensory stimulation in those conditions (see Figure 2.17). This shows that the somatosensory stimulation, and the relationship between the contralateral and ipsilateral somatosensory conditions, are unique regarding the inhibition of the non-relevant region.

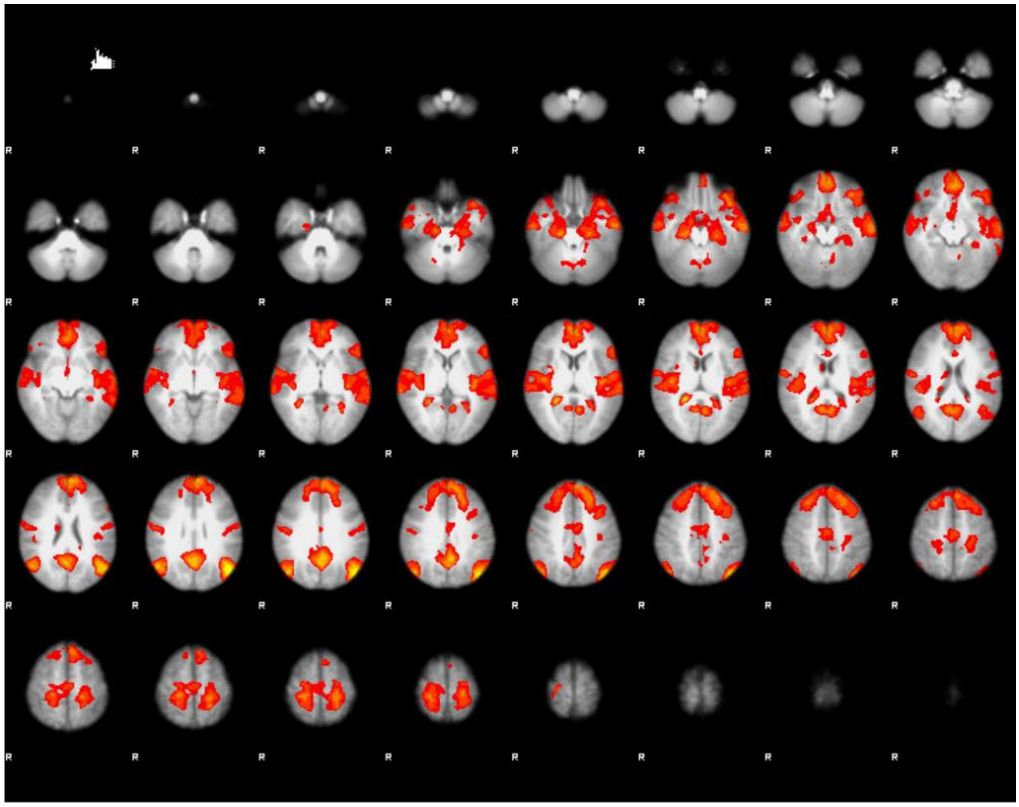

Figure 2.10. *NBR to V stimulation– Z-statistic 2.3-15.7.*

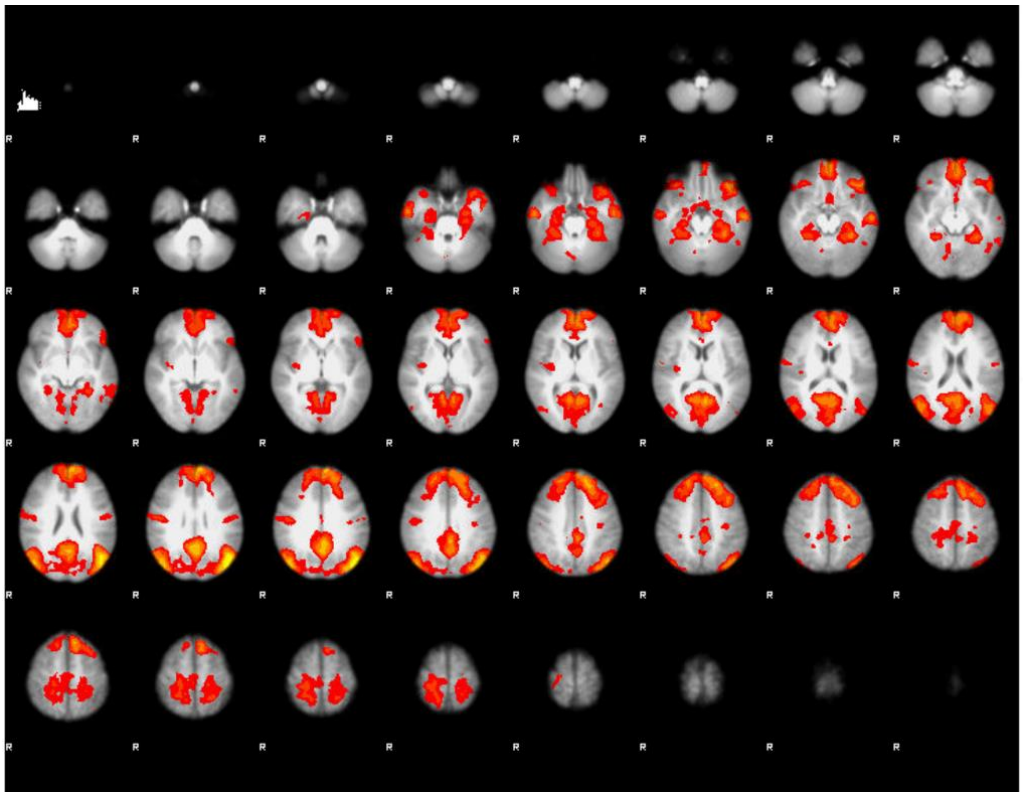

Figure 2.11. *NBR to A stimulation– Z-statistic 2.3-18.4.*

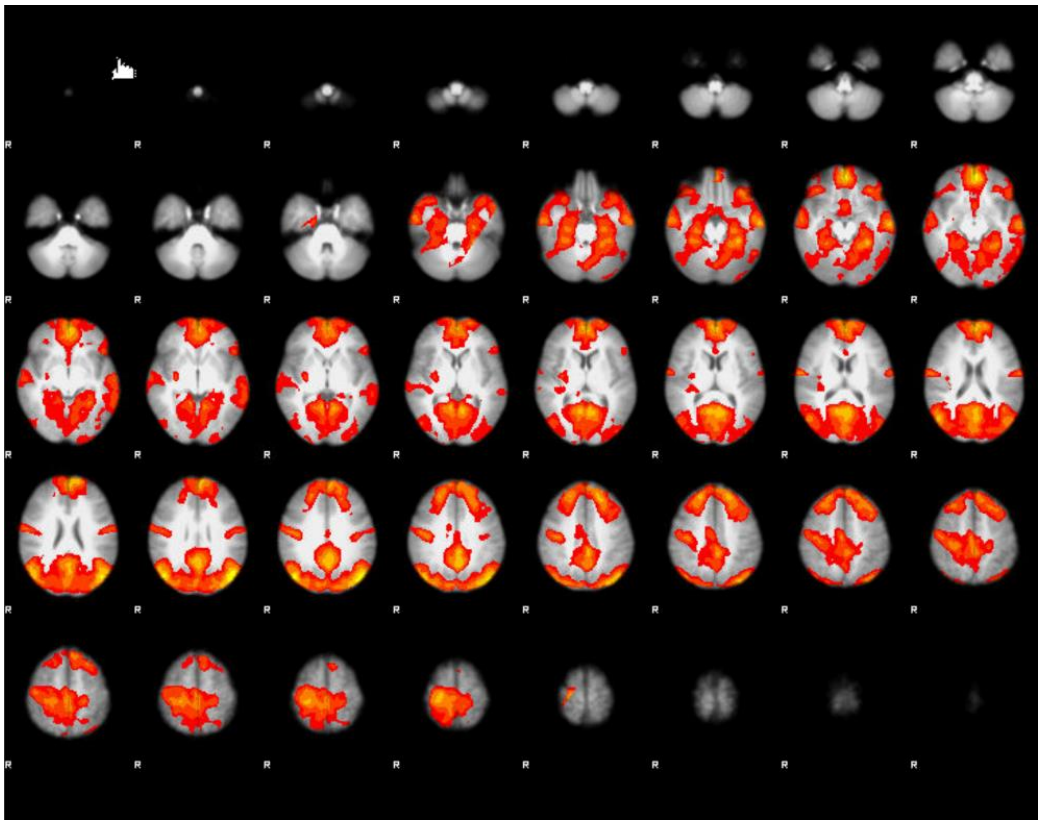

Figure 2.12. *NBR to S stimulation– Z-statistic 2.3-22.0.*

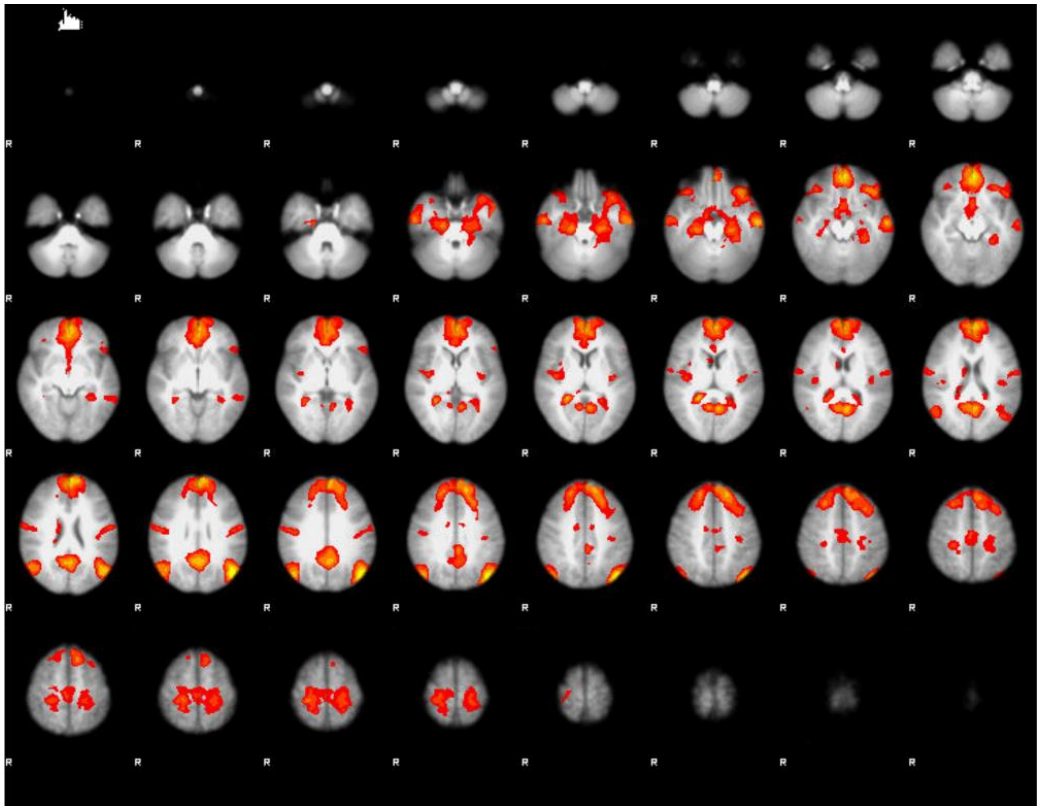

Figure 2.13. *NBR to VA stimulation– Z-statistic 2.3-22.*

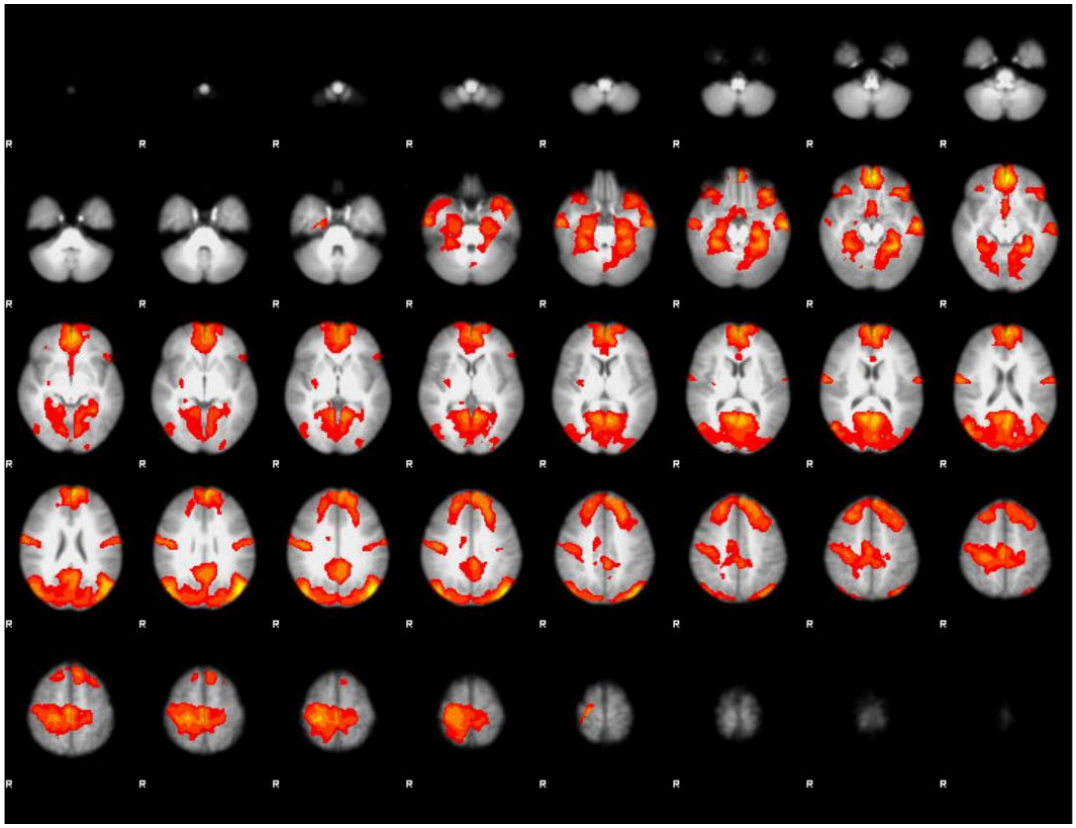

Figure 2.14. *NBR to AS stimulation– Z-statistic 2.3-18.4.*

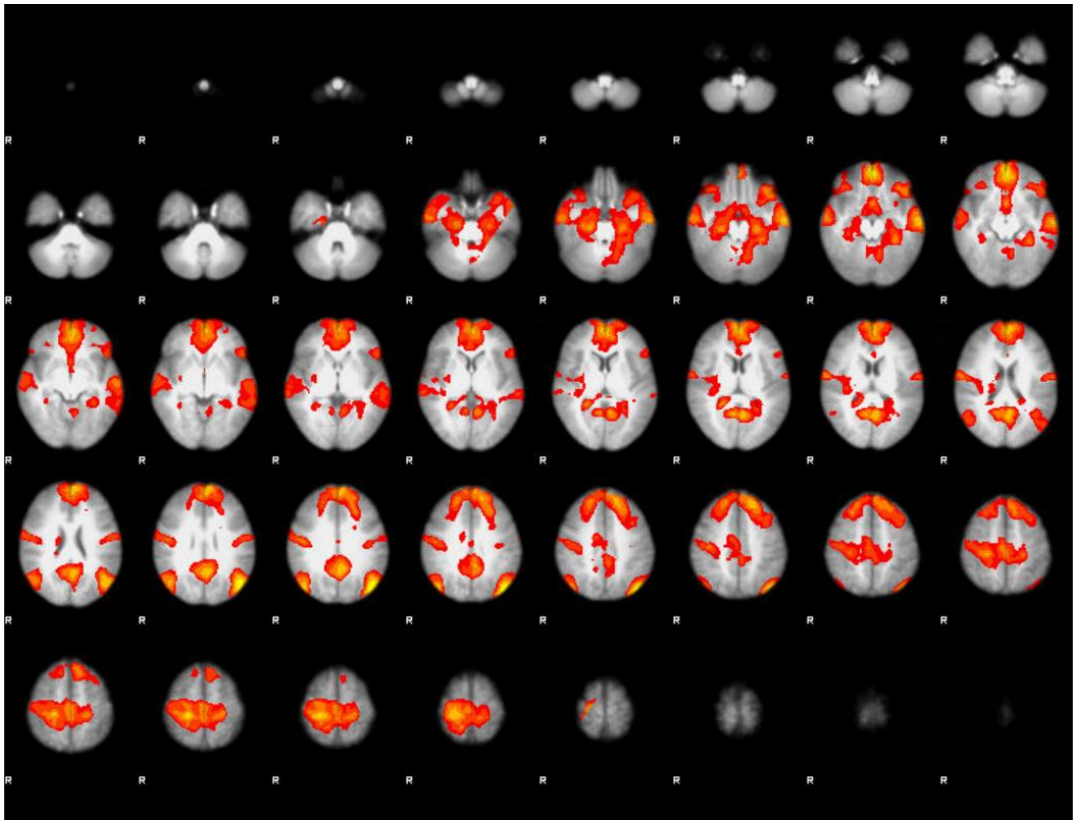

Figure 2.15. *NBR to VS stimulation– Z-statistic 2.3-22.1.*

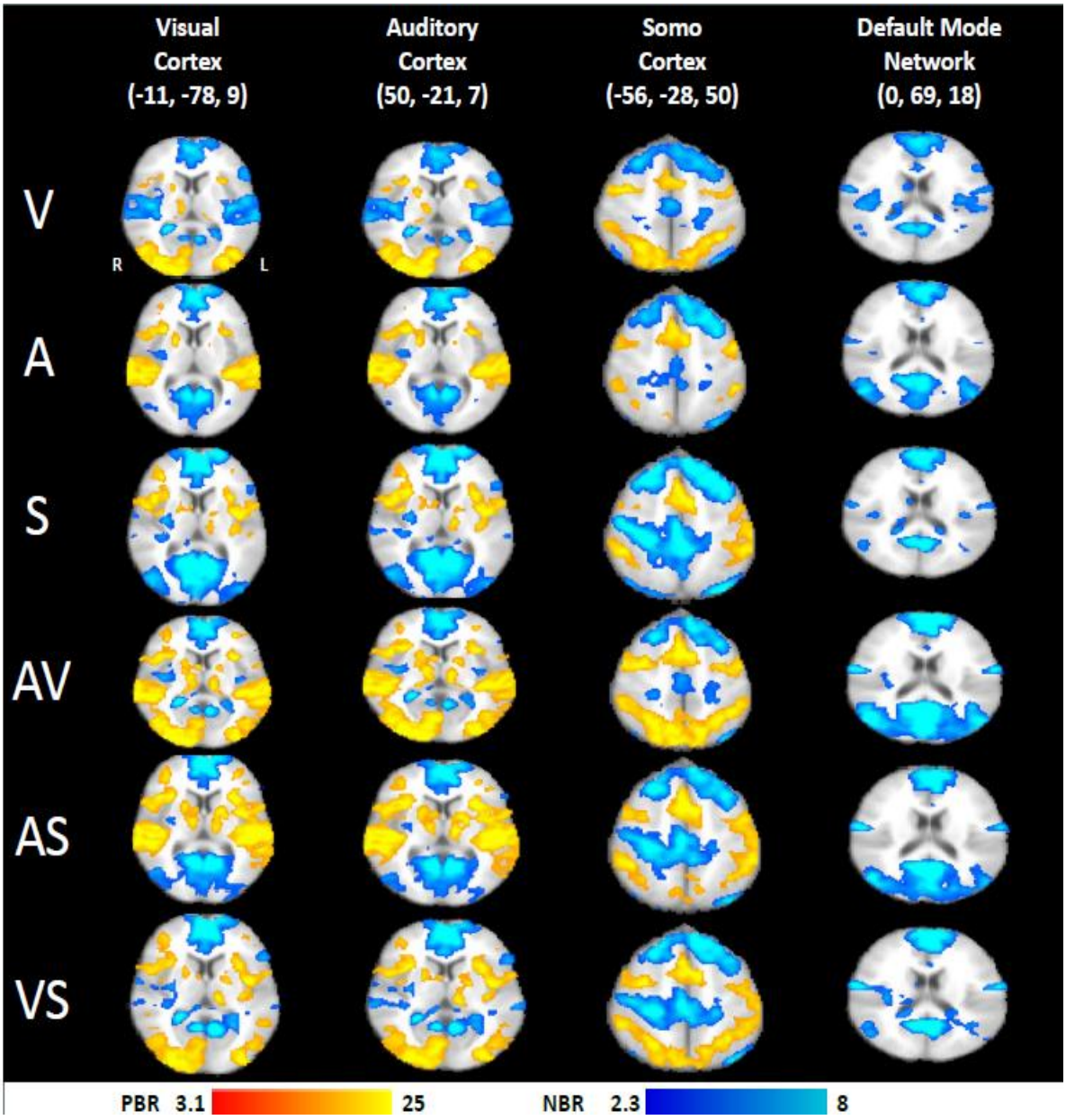

Figure 2.16. *Condition BOLD responses. Group means PBR (orange/yellow) and NBR (blue) are displayed on the same axial slices to allow spatial comparison. Rows indicate responses to each stimulus condition. Columns show selected axial slices through the key sensory cortices and regions of the DMN.*

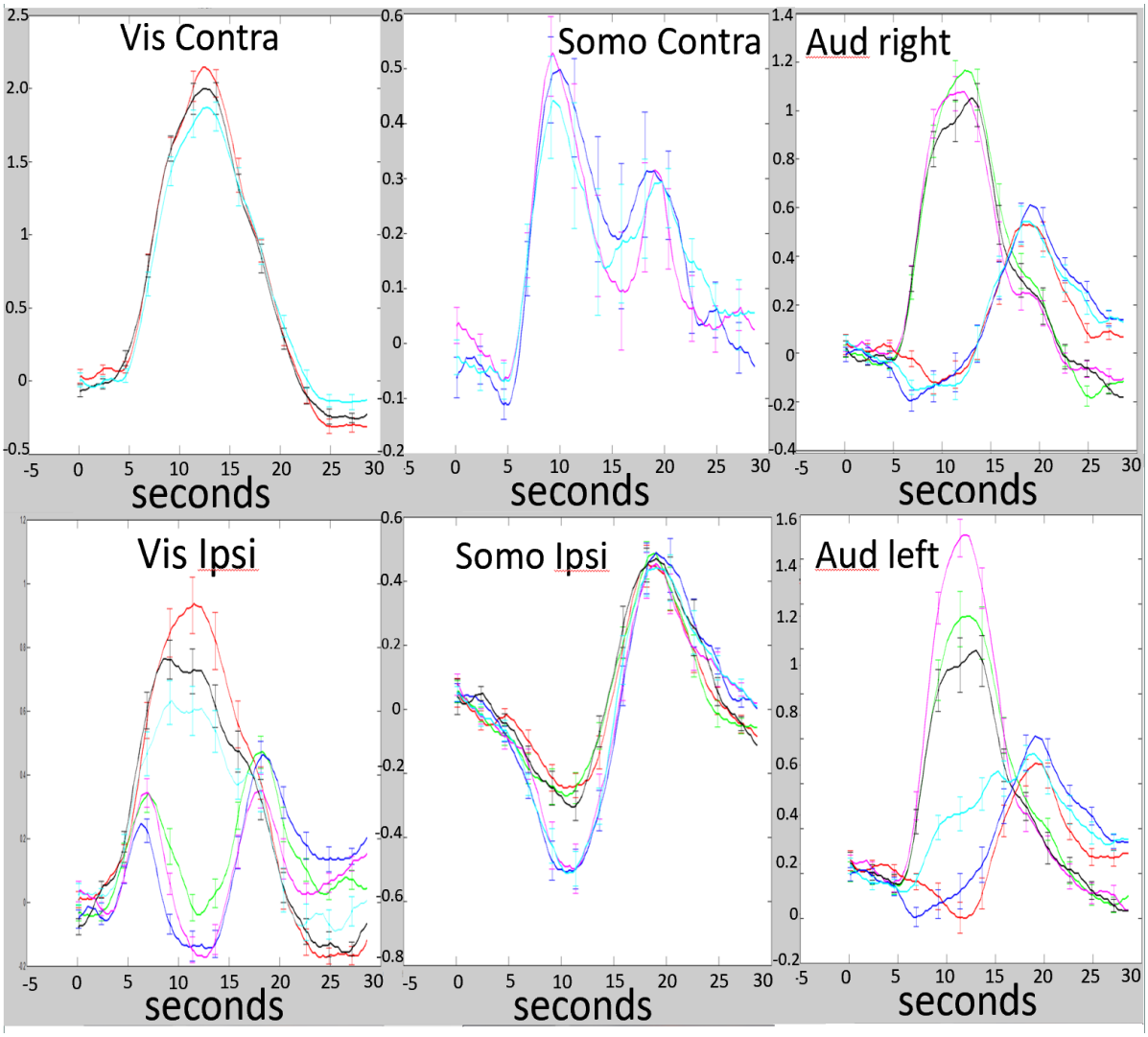

Figure 2.17. *Vertical axis = % change in BOLD signal, horizontal axis = time in seconds. Red – visual, Green – auditory, Blue – somatosensory, Magenta – auditory and somatosensory, Black – visual and auditory, Cyan – visual and somatosensory.*

The timecourses in Figure 2.17 illustrate the shape of the PBR and NBRs in the sensory cortices and further evidence comparisons between conditions. They show that the ipsilateral S1 NBR magnitude was significantly greater for somatosensory-involved stimulation regardless of the specific combination of modalities active. Some interesting differences in the shape of cross-modal NBR in the auditory cortex are seen between V and S stimulation, with the NBR peaking earlier for S than V.

The timecourses in Figure 2.17 show a multi-phasic response in the ipsilateral visual cortex in conditions not featuring visual stimulation. An initial, transient increase in BOLD is seen (due to the presentation of the visual cue) followed by an NBR and then a post-stimulus overshoot (Mullinger, Mayhew, Bagshaw and Francis, 2013). NBRs are also followed by post-stimulus overshoots in the auditory and the ipsilateral somatosensory cortex. The multiphasic PBR in contralateral S1 is due to the later button press response.

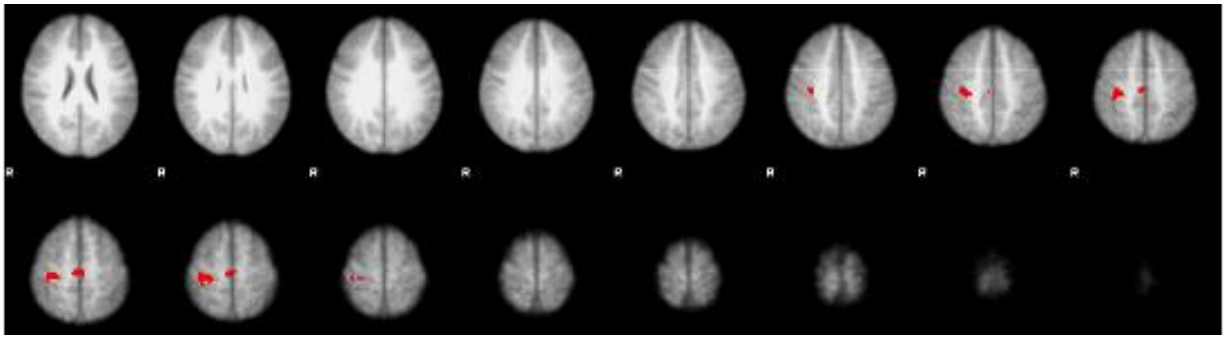

Figure 2.18. *AS vs A+S - Z-statistic 3.1 - 26.9.*

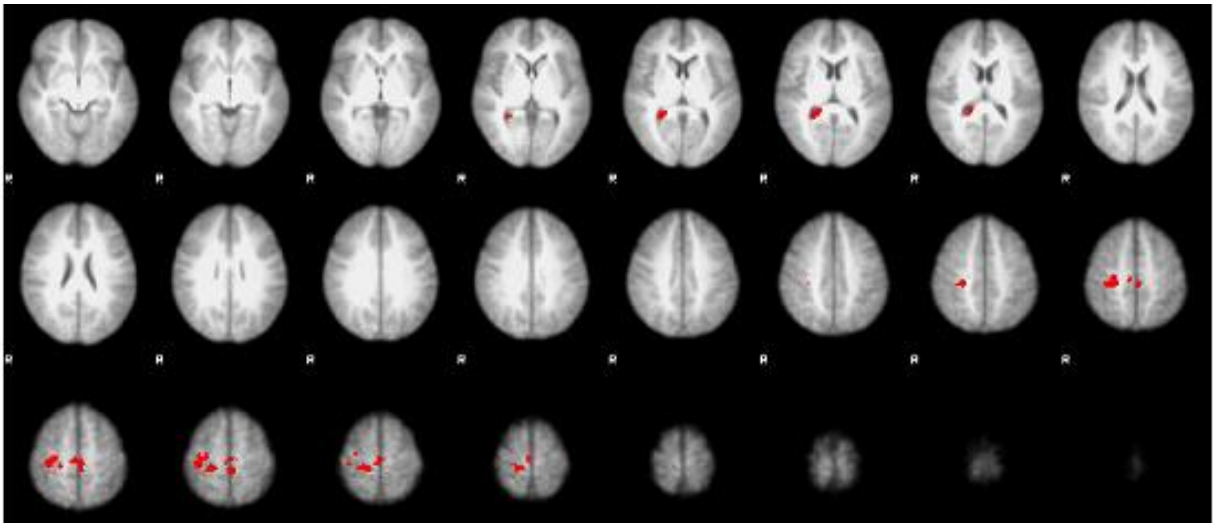

Figure 2.19. *VS vs V +S - Z-statistic 3.1 - 34.4.*

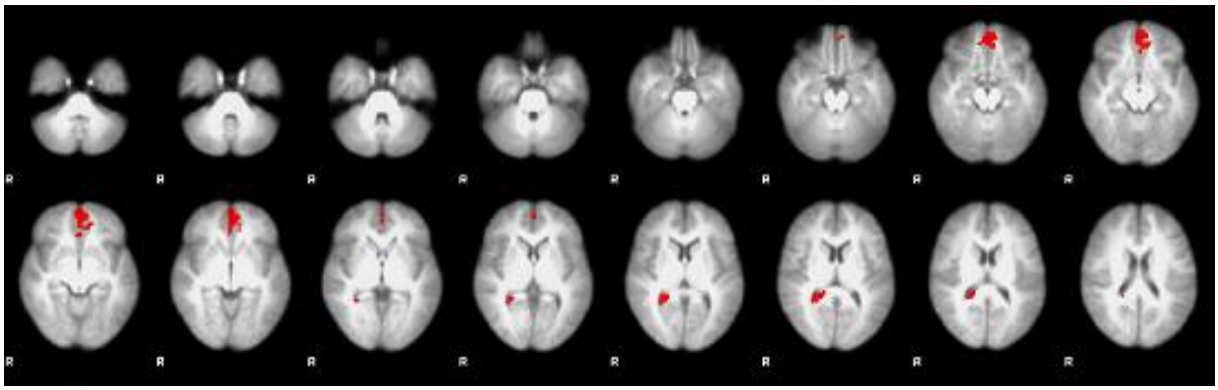

Figure 2.20. *AV vs A+V - Z-statistic – 3.1 - 34.4.*

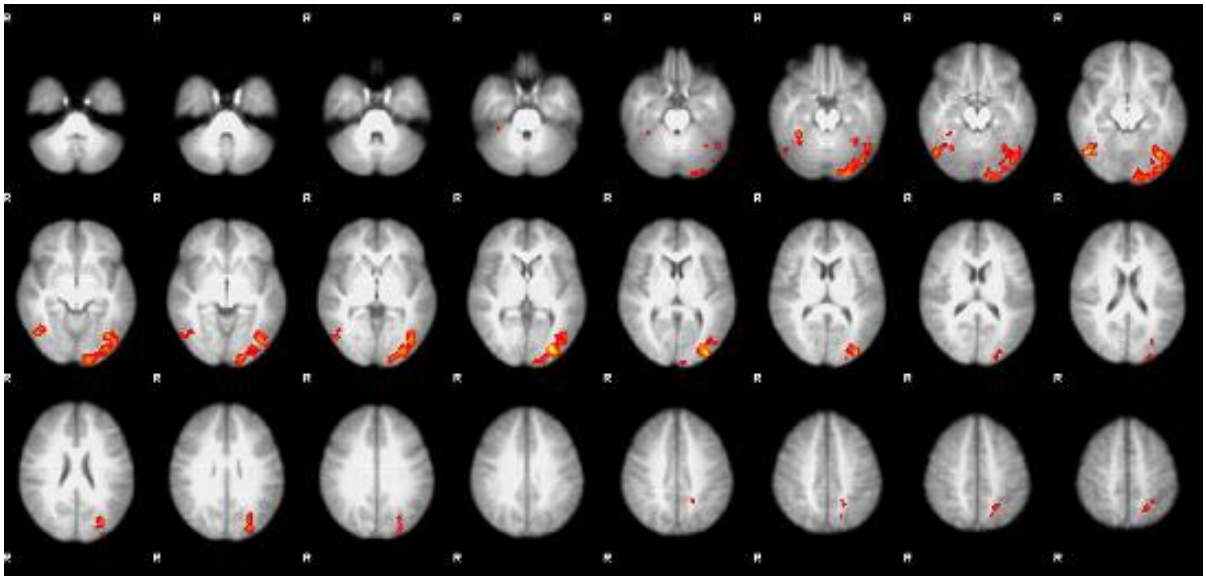

Figure 2.21. *Visual and Somatosensory dual trial comparing trials where the participant was cued to either the visual or somatosensory condition, z stat 3.1 to 5.6*.

Effects of attention cueing

We also created contrasts of multisensory trials to study whether BOLD responses differed depending on the modality to which subject's attention was cued i.e., comparing responses to AS between when attention was cued to A vs cued to S. Our comparisons only showed greater PBRs in the contralateral visual regions during VS trials where attention was cued to V (figure 2.21). NBRs showed no change according to attention either, the responses were only a bottom-up response to stimulation.

Discussion

Key results

This experiment aimed to study the following hypotheses:

- H1: Do sensory NTRR consistently show an NBR both within and across a modality?
- H2: NBR behaviour is consistent across different stimulation modalities.
- H3: There are differences are observed in cross-modality NBRs compared to within modality.
- H4: Increases in the amplitude of the NBR will be related to an increased need to suppress distraction and activity in NTTRs.
- H5: NBR amplitude/location is modulated differentially between single vs. dual stimuli conditions

In more simplistic terms the experiment aimed to understand what are the differences in NBRs in NTRRs by comparing between single modality and dual-modality stimulation.

Firstly, the experiment was mostly successful regarding replicating both the PBRs and NBRs to stimuli that were found in other literature (Bressler, Spotswood, and Whitney, 2007;

Mozolic et al, 2008; Mayhew et al, 2013a; Mayhew et al, 2013b; Wilson et al, 2019) except for the intra-modal visual NBR. Each stimulated region responded with a clear PBR either bilaterally or unilaterally as per the stimulation and NBRs were seen in the NTRRs. From these findings, we accept the alternative hypothesis for H1 (Do sensory NTRR consistently show an NBR both within and across a modality?), that a sensory NTRR consistently shows an NBR both within and across modalities.

H2 is "Is NBR behaviour consistent across different stimulation modalities?" and in this regard, we have to accept the null. The reasons however are very interesting and begin to show the individuality of different sensory modalities in handling the intra and intermodality inhibition discussed throughout this chapter. The auditory systems due to be stimulated bilaterally do not show intra-modality inhibition, however, did have a repeatable pattern where auditory stimulation was correlated to NBRs in the somatosensory and visual systems. Unilateral visual stimulation did not induce NBR in the ipsilateral visual regions at the group level. Inspection of individual subject 2nd level results showed bilateral visual PBR in some and lateralised PBR and NBR in others, we, therefore, speculate the lack of group-level ipsi V1 NBR is because of poor behaviour by some participants and whilst they were instructed to attend to a central fixation point several of them moved their fovea to the centre of the unilaterally presented checkerboard. This will be discussed more in the discussion of limitations and future experiments but has little bearing on the overall findings. The stimulation of the visual system, just like the auditory system, resulted in repeatable NBRs across the other NTTRs, particularly the somatosensory cortex. The reason the null needs to be accepted is due to the corresponding NBRs generated from the stimulation of the somatosensory system. The somatosensory system firstly responded strongly with a replicable NBR in the ipsilateral S1 region which was not seen in the other modalities and the magnitude of the NBR was also greater than other conditions involving only visual or

auditory stimulation and somatosensory stimulation was also capable of generating inter-modal inhibition (see timecourse figure 2.2). From this finding, we see a level of disparity between the different sensory modalities, and instead of simply saying a given modality was stimulated - so logically the sensory cortices of all others must show an NBR - a greater level of nuance and precision is required to understand the stimulated region and the inhibited locations to better understand the kind of functional inhibition response that should be expected.

H3 was "We expect the spatial extent and amplitude of cross and within modal NBRs to be comparable for conditions of comparable sensory input (e.g., ipsilateral visual NBR and auditory NBR to visual stimulation)" and for this hypothesis, we do see some evidence because while the within modality ipsilateral S1 NBRs were significantly larger than any other NBRs, we saw across all the other conditions a parity in cross-system inhibition. A potential confound in the experiment is whether intra and inter-modal NBRs are particularly strong during somatosensory stimulation in general or if specifically, the use of a median nerve stimulator is the cause of the high magnitude and replicable responses seen particularly in the ipsilateral S1 region. It is difficult to create parity between the senses without deliberating aiming for overstimulation in modality. Given the uniqueness of the response by the somatosensory cortex further study in how different stimuli which specifically trigger the many different types of nerves in our peripheral nervous system and particularly the hand (pg. 232 Carlson, Physiology of Behaviour) is an area to be approached in the future. Auditory stimuli generated inhibition in the non-task relevant visual and somatosensory cortices, and visual stimuli generated inhibition in the non-task relevant auditory and somatosensory cortices. In the strictest sense, the null must be accepted because as mentioned regarding hypothesis 2 each of the modalities do show a level of individuality but this

individuality in responses is subtle and a general pattern of inhibition in NTTRs (except regarding ipsilateral somatosensory inhibition) does hold across the data.

H4 discussed the expected "Increases in the amplitude of the NBR will be related to an increased need to suppress distraction and activity in NTTRs." Additionally, H5 was "H5: Non-relevant modalities will show a significantly greater NBR to dual stimulation conditions than single modality conditions" and will be considered alongside H4. In this section, we must accept the null because there does not appear to be any increased NBRs as a function of increased sensory stimulation or the increased need to suppress distraction in stimulated NTTRs. NBRs from our data simply present a system whereby a system is either inhibited but the magnitude of the inhibition is not influenced by the amount of stimulation or interference. The magnitude of the NBRs in the observed modalities is variable given the difference in NBR in the ipsilateral S1 and its variable response to somatosensory or non-somatosensory stimulation, but this was not affected by increased distraction i.e., from multisensory stimulation. In summary, there is no clear evidence that NBRs alter due to an increased requirement for suppression as a function of the shift between single to multi-sensory stimulation.

The data from the above experiment shows that while NBRs are replicable they have two clear distinctions from PBRs that were not elucidated previously in the literature. The first is that the cortex shows different inter and intra modality inhibition responses when different sensory modalities are stimulated, meaning a clearer level of clarity is required when understanding NBRs. We need to know both what is stimulated and where the inhibition is expected to occur in order to understand the full dynamics of how the NBR will be represented both within the stimulated modality or modalities and outside the stimulated modality or modalities. We also find that PBRs dominate NBRs, in that sensory stimulation causes PBRs irrespective of whether that modality is task-relevant. Therefore task-relevant

information is not required to generate a PBR and even when a cortical region needs to be inhibited because it is strictly non-task relevant, the bottom-up stimulus generates a PBR whose amplitude is not significantly different from the single stimulus condition. We see this effect clearly in the VA condition where the visual modality is the target, and the auditory stimulus is not relevant to the task. Purely from the point of view of the task, an NBR could be expected in the auditory system, or at least a reduced PBR, but we instead see a standard PBR comparable or larger in size than in auditory alone condition. From a neural and cognitive perspective filtering of the stimulus to not distract the attentional spotlight and allow above chance performance is not being performed through an NBR/functional inhibition here but through other mechanisms.

The other interesting finding is that NBRs do not scale with an increase of sensory modalities and instead seem to exhibit a more simplistic response system, whereby a region is either resting or inhibited. Previous work has shown that the amplitude of both visual and somatosensory within modality NBR increases with stimulus intensity and/or duration (Shmuel 2002; Kastrup 2008). This provides evidence that NBR can scale with the stimulus demands even in passive tasks. However, here, with a target detection task, the NBR amplitude in an NTRR was not increased by the addition of a different sensory stimulus. We have shown that all sensory stimuli can reciprocally induce within and cross-modal NBRs. But when two stimuli are delivered, no concurrent increase in NBR is observed despite the increased need to suppress distraction/interference from the NTRR, the increased cognitive load of the dual stimulus task, and the increased withdrawal of attention away from the non-task relevant sensory modality.

While the magnitude of NBRs in non-task-relevant modalities is not uniform across the modalities, as shown with the greater level of ipsilateral S1 inhibition as a function of somatosensory stimulation, even then the NBRs do not alter due to greater stimulation. This

provides increasing grounds for studying over-stimulation and scaling stimulation levels. As mentioned in the previous paragraph even NTR stimulation generates PBRs and a stimulation paradigm growing from non-perceptible to the point of pain would help to create an exploration of how NBRs gate non-task relevant sensory information. We do not suppose that during a visual/auditory stimulation there is no somatosensory information that is being processed i.e., the feel of the fMRI bed, the pressure on the fabric, and the sense of not having been able to move for a period, but NBRs do occur. This presents a question about what level of background stimulation allows for an NBR and at what level of stimulation does the region instead show a PBR? Where is the threshold and is it due to lower-order sensory stimulation or higher-order attention systems? Logically even if the feel of the bed is not enough to generate a PBR in the somatosensory region through the trials and instead we need median nerve stimulation for that if we directly told the participant to attend to the feel of the fMRI bed and the fabric it would generate a PBR by itself as the participant focuses on all the experiences. To date how this shift in attentional focus relates to NBRs both intra and intermodality has not been conducted and is a rich field for future study.

Limitations

The main limitation of the study is that participants were able to view the visual stimulation bilaterally simply by disobeying the pre-experiment instructions and moving their fovea away from the fixation cross to the centre of the checkerboard in the left hemifield. This is in contrast to previous studies which have used this methodology before and found intra-modality inhibition in the visual cortex (Bressler, Spotswood, Whitney, 2007). To correct this providing a separation between the two visual fields through a separating panel thereby isolating the two visual hemifields would be needed and likely provide the expected result of a clear ipsilateral visual region NBR during visual stimulation.

Future experiments

The experiment could have integrated the information between the modalities and provided a better understanding of how NBRs are generated in NTTRs during a more ecologically valid scenario. This is not explicitly a limitation of the study because the study aimed to understand the foundational neuroscience in NBR generation between single and multisensory presentations, but it is now a gap in the literature. In chapter 5 an experiment has been designed to test a battery of different sensory and cognitive regions including multisensory integration through the use of a TV show.

We never provided integrated multisensory stimulation where both modalities provided information on the task. This is what the movie part of chapter 5 is meant to do.

Another future experiment could be testing different definitions and paradigms related to the need for suppression in a multisensory stimulation paradigm. Multisensory stimulation cannot just involve the addition of another sense since in the strictest sense that could simply be a marginally above threshold stimulation and as discussed, the somatosensory, auditory, and visual systems always had stimulation from the environment of the fMRI but that was not in itself enough to generate a PBR or stop an NBR. It is clear to create a PBR a direct level of stimulation requiring the attention of the participant is needed and because of that tests involving the use of different sensory modalities, the difficulty of the task, and the intensity of the stimulation would need to be tested with each as a variable factor to better understand how the need to suppress information works. As an additional note, all the experiments in this thesis do not test NBRs during painful/noxious stimulation but this is logically an area of study to approach also.

Another interesting area of study is relating to the sense modalities for taste, smell, and the perception of flavour. Under the current theories discussed in the introduction to both this

thesis and this chapter the sense modalities for olfaction and gustation are not task-relevant throughout the paradigm and as far as we can report not even mentioned during the briefing and training for the experiment. If they are NTR then we should expect to see NBRs in these regions. A meta-analysis on the neuroscience behind the perception of flavour has shown that the bilateral anterior insula and frontal operculum along with bilateral mid-dorsal insula are the primary regions correlated (Veldhuizen et al, 2011) with the Rolandic operculum, bilateral posterior insula, left lateral orbitofrontal cortex and right mediodorsal thalamus (Veldhuizen et al, 2011) along with the amygdala and ventral putamen (Seubert, Freiherr, Djordjevic and Lundstrom, 2013). However, in our experiment, we find PBRs in the insula (see figures 2.3 to 2.9) which is to be expected during both sensory stimulation and the insula's dual involvement in processing taste/smell information (Veldhuizen and Small, 2011). To this effect, a new paradigm would be required to disentangle the multiple correlated functions of the insula with regards to this question and better understand if a replicable NBR can be seen in olfaction and gustation responsible regions or if these regions also have idiosyncratic behaviours.

Finally, an area for future analysis instead of experimentation is the study of the causality resulting from stimulation and in the generation of NBRs. Throughout this chapter, I have refrained from saying a given modality 'caused' an NBR in another modality because we simply do not have the data to claim that a given sensory modality has the neural architecture to generate NBRs. There is evidence that higher-order frontal and parietal regions are involved in the generation of inhibitory alpha/NBRs (in monkeys, Buschman and Miller 2007; in humans, Bressler et al, 2008 & Li, Gratton, Yao and Knight, 2010.) but this has not been studied in the context of multisensory stimulation and how one modality's stimulation may result in inhibition in another modality but then have that communication shift during the stimulation of two modalities. Does the originally stimulated sense continue to be the

driving force through higher-order regions to generate the impetus to inhibit? Does that signal simply integrate during multisensory or is the inhibition we see generated by two sources during multisensory stimulation? On a final note, given the binary systems reported here do both respective signals half in power to maintain the same level of inhibition from single to multisensory stimulation paradigms?

Chapter 3 - Differences in alpha ERS and ERD in non-task relevant sensory regions during single and multi-sensory stimulation across the visual, auditory, and somatosensory domains.

Introduction

This chapter is an extension and, in part, replication of the previous chapter's study of multisensory stimulation and resulting inhibition across the cortex but using EEG as the imaging modality instead of fMRI. The previous chapter showed robust activation to stimulation, as measured by a positive BOLD response (PBR), of brain regions according to their functional roles i.e., visual stimulation resulted in visual cortex activation/PBR. We also saw negative BOLD responses (NBRs) in non-task-relevant regions (NTRRs) i.e., visual stimulation resulted in auditory and somatosensory NBRs. We did not however see evidence that increasing the number of stimulated modalities, or the interference from increased task load, resulted in greater NBRs in NTRRs.

However, chapter 2 used fMRI which is only an indirect measure of neural activity. To better comprehend how inhibition is used by the brain and represented by different imaging modality signals we need to understand the neural signatures of NBR, so in this chapter, we use the same paradigm (with minor adaptations to suit EEG) to investigate whether EEG alpha oscillations in NTRRs show responses (changes in power) during stimulation that resemble those of the NBRs from the previous chapter and whether they differently respond to single vs multisensory stimuli.

The alpha oscillation as an inhibitory neural signal

Fluctuations in the power of the alpha oscillation have long been linked with inhibitory neural function (Klimesch et al, 2007; Jensen and Mazaheri, 2010) and variations in the balance of excitation and inhibition, known as cortical excitability (Romei et al, 2008a). Alpha power is a direct measure of neural activity that originates from the dendritic spines of pyramidal neurons in the cortex (da Silva, 2013). NBR amplitudes have been found to be correlated to trial-by-trial variability in alpha power (Mayhew et al 2013; Mullinger et al, 2014, Mullinger et al, 2017) (with a more in-depth review in the introduction of this thesis) which provides an avenue for research to better understand the inhibitory neuronal signals through EEG. We intend to study the EEG component of how multisensory stimulation induces cortex-wide inhibition and see whether alpha power can provide insights into the different responses to single vs multisensory stimulation which fMRI did not.

Periods of high alpha power were originally thought to reflect an idling state of the brain e.g., when participants rested with their eyes closed and the visual cortex was not processing any sensory inputs (Adrian and Matthews, 1934). The alpha inhibition hypothesis however proposed alpha not only as an idling state but also as a functional inhibitory system (Klimesch, Sauseng, Hanslmayr, 2007). This theory proposed that an NTRR would present a synchronised, high power, alpha oscillation reflecting its inhibited state i.e., the motor cortex would show alpha synchronisation (ERS) during a visual task with no motor component. The concept behind this theory is that NTRRs will generate inference during a task so increased alpha power acts to suppress gamma frequency activity and information transfer (Jensen and Mazaheri, 2010) allowing for the task-relevant region to process information without inference. This theory has been very successful to date in explaining how single modality stimulations result in suppression of distraction, facilitation of important information, and inhibition of NTRRs across the brain. Since then, alpha has been studied across several

different sensory regions with an array of paradigms and its inhibitory effect is replicable and well researched (Kelly, Lalor, Reilly, Foxe, 2006; Romei, Brodbeck et al 2008; Sauseng et al 2005a, b +c; Thut, Nietzel, Brandt, Pascual-Leone 2006; Worden, Foxe, Wang, and Simpson 2006; Jensen and Mazaheri, 2010). However, a current gap in the literature is how multisensory processing affects NTRRs and the expression of functional alpha inhibition during stimulation.

The alpha oscillation across different cortical regions

When studying multisensory inhibition, the first area to investigate is if different cortices do present the alpha inhibitory effect (ERS in an NTRR) and to discuss their suitability for inclusion into the experiment. The alpha inhibition effect has been shown to occur in the hippocampus (Klimesch et al, 1999; Huang et al, 2013; Bonneford 2015; Fu et al, 2015), visual/occipital cortex (Pfurtscheller, 1992; Jensen and Tuladhar, 2002, Tuladhar et al, 2007) and somatosensory cortex (Hummel et al, 2002; Haegens et al, 2011) and auditory cortex (Hartmann, Schlee and Weisz, 2012) suggesting its influence extends to widespread cortical systems and behavioural circumstances. In each case, the NTRR is shown to present an alpha ERS to inhibit functioning. However, each of the papers have only focussed on a single modality stimulation paradigm. These studies inform a theoretical understanding of how increased cognitive load may affect NTRRs, but further study of how multisensory stimulation affects alpha ERS and functional inhibition in an NTRR is required.

To this end, the work of Klimesch in 1999 (Klimesch, 1999) provides evidence on memory-based load and its interaction with alpha ERS with further evidence for cross-region alpha inhibition provided by Huang (Huang et al, 2013). Both studies showed that during a Sternberg memory task the right and posterior occipital regions showed alpha ERS during the encoding period except during trials where the subject had to process visual information. The

authors argued that the activity of the visual cortex showed a modulatory relationship with the hippocampus where during visual processing theta ERS increased in the visual cortex, but during the retention period when the hippocampus was active, the visual cortex showed theta ERD and alpha ERS. This highlights a similar relationship as seen in Klimesch in 1999 (Klimesch, 1999) and together with other evidence (Jensen and Tuladhar, 2002) shows load-dependent effects on alpha ERS. These studies present strong evidence that a similar relationship with increased load arising from a paradigm-changing from single to dual-modality stimulation may result in the same pattern of increased alpha power in NTRRs.

Finally, the somatomotor cortex also shows the alpha inhibitory effect of alpha ERD in stimulated task-relevant regions alongside alpha ERS in NTRR providing further evidence for cross-region functional alpha inhibition. Hummel et al (2002) found that during a go-no-go task, somatomotor regions showed greater inhibition in the no-go trials vs. the go trials suggesting that the regions required inhibition to ensure compliance with the task. This is supported by evidence from Pfurtscheller (1992) where the activation of the somatosensory cortex caused alpha ERS in the visual system and vice versa highlighting both the effect of functional inhibition and the reciprocal interplay between different sensory modalities. Most recently Haegens et al studied modulations in alpha power in behaving monkey brains focusing on the somatosensory cortex (Haegens et al, 2012). Their work found that alpha power decrease was stronger during correct trials vs incorrect trials and argued that increased power during the decision delay portion while assessing the frequency of a train of stimulation compared to a first stimulus sample. Haegen's work, however, is only in monkeys and while interesting lacks any discussion of cross-modality communication which is the focus of this chapter (Haegens et al, 2012).

In review alpha, ERS is exhibited across multiple different sensory modalities with a clear interaction with increased cognitive load increasing the ERS in NTRRs. It follows that

multisensory stimulation and its associated increase in cognitive load would result in greater ERS in an NTRR but precisely how and if the alpha ERS in the NTRRs matches the sustained NBRs seen in NTRRs in chapter 2 is a key area for investigation in this chapter.

Visual lateralisation and effects of top-down, proactive allocation of spatial attention upon alpha

The papers (Klimesch et al, 1999; Huang et al, 2013; Bonneford 2015; Fu et al, 2015; Pfurtscheller, 1992; Jensen and Tuladhar, 2002; Tuladhar et al, 2007; Hummel et al, 2002; Huang et al, 2013) mentioned above makes it clear that the alpha inhibitory effect is ubiquitous across the sensory systems as inter-modality inhibition has been shown as well as evidence for cognitive systems driving sensory inhibition through modulations of local alpha power. However, a key area of the alpha inhibition literature has not been mentioned, that of the lateralisation of alpha power during the allocation of visuospatial attention, such as seen in Posner tasks where a participant attends to a cued location on a screen (usually left vs right) in preparation to detect a subsequent target stimulus (Posner, 1980; Nobre et al, 2007; Doricchi et al, 2009). During the allocation of visuospatial attention, alpha power decreases over the visual hemisphere contralateral to the location of attention and increases in the ipsilateral hemisphere, to facilitate necessary processing and suppress distraction respectively (Thut et al, 2006 Rihs et al, 2007; Romei et al, 2008a; Romei et al, 2008 b; de Graaf et al, 2013; Marshall et al, 2015; Mazzetti et al, 2019).

These proactive paradigms have greatly shaped the literature of alpha inhibition. However, the alpha inhibitory response is measured just after a cue and just before the actual stimulus presentation. There is very little data on how the alpha inhibitory response is sustained throughout stimulus presentation while an area is still non-task relevant. In chapter 2 we see a sustained NBR but here we want to investigate if there is a comparable alpha ERS response. For the rest of this chapter, this means we will be referring to the alpha response during

stimulation as the ‘sustained response’ if present compared to the usual shorter prestimulus response seen in Posner tasks (Posner, 1980; Nobre et al, 2007; Doricchi et al, 2009).

Multisensory stimulation and alpha

To date, the current literature has not studied the interaction between multisensory stimulation and inhibition across the cortex. We see this as a gap in the literature and want to understand how alpha ERS in NTRRs is modulated as a function of increased sensory load, through the addition of sensory stimuli, in not just one modality but two at once. This gap in understanding how functional inhibition responds to increased cognitive load through multisensory stimulation is as true for EEG and alpha inhibition measured by increased alpha power and synchronisation as it was for fMRI and NBRs in chapter 2. We aim to study whether the NTRR alpha power alters between different combinations of sensory stimuli and how it varies with task difficulty and the ‘need to inhibit’. By ‘need to inhibit’ we mean that interference from an NTRR becomes doubly problematic to efficient processing as more senses are engaged and cognitive load increases. As such we expect to see increased alpha ERS representing greater functional inhibition as the number of regions stimulated is increased, to allow for better task performance on the task-relevant stimuli. However, while we are studying multisensory stimuli in this case, we do not intend to study multisensory integration. The integration of multisensory stimulation provides an additional complexity (Park and Kayser, 2019) that is not the aim of this study.

As mentioned at the beginning of this thesis the goal is to eventually understand inhibition during integrated sensory presentations, but the world still has many different stimuli from different sources which are not integrated i.e., viewing a landscape and the sounds of cars in the distance but out of view. The information in that example would be expected to result in inhibition in non-task relevant regions but it is unclear how additional stimuli affect those

non-task relevant regions. For example, if we presented a visual presentation and an audio-visual presentation, we would expect to see an alpha ERS in the somatosensory region on both occasions. We would expect to see a greater alpha ERS response during the dual audio-visual presentation but the amplitude changes in the response from a single to dual presentation representing greater inhibition as cognitive load increases are not understood and the aim of this study.

Rationale and hypothesis

The rationale for this experiment is to replicate the previous experiment in chapter 2 however using EEG as an imaging modality instead of fMRI. The first reason for this is to use a direct measure of neural activity to understand any potential neural correlates, primarily alpha ERS, of the sustained NBRs we saw in chapter 2. We also want to compare if alpha ERS will present with the same response amplitude between single and dual-modality stimulations as seen in chapter 2 or if there is a distinction between how NBRs and alpha are expressed. Another key rationale for this experiment is to understand if the alpha synchronisation, usually seen briefly just after a cue in a visual lateralisation task, will present a sustained synchronisation in the same way the NBRs were sustained throughout the stimulation period in chapter 2.

We hypothesise that we will see:

H1. Replicable patterns of alpha ERS as a neural signature of deactivation in NTTRs to both single and dual sensory stimulus conditions, comparable to the NBRs seen in chapter 2

H2. An increase in alpha ERS in NTRRs during dual stimulation compared to single sensory stimulation. We expect to see this increase in alpha power in NTTRs regardless of which modalities are being stimulated in the dual condition and which modality was stimulated in the single condition comparison.

Methods

Participants

18 (10 M, Average age 24.6 years old) participants were recruited from the University student and staff population. All participants were in good health, did not need corrective lenses or a hearing aid, and reported no safety contraindications for either EEG or MRI. The study was conducted with the approval of the University of Birmingham Ethics Board and informed consent was obtained from all subjects before their participation. Participants were debriefed upon their completion of the study and their participation was compensated with either university credits or financial payment.

Materials

EEG was used to record participants' event-related oscillatory responses to visual, auditory, and somatosensory stimulation. This experiment featured the same six conditions as the experiment in chapter 2. Sensory modalities were either stimulated separately (e.g., Visual), or in pairs (e.g., Visual and Auditory), see below for further details. Participants detected targets presented in a single, attended, sensory modality that was delivered either alone or whilst another sensory modality was stimulated (see Table 3.1 for a description of conditions). The resting baseline in this experiment was altered to be only 4-seconds long as we did not need to wait for the haemodynamic response to recover. A 7Hz stimulation rate was chosen specifically for both experiments as any stimulation causes a signal in the recording at the frequency of the stimulation Herrmann (2001). With the frequency range of alpha being 8-13 Hz (Klimesch, Sauseng, Hanslmayr, 2007) this meant any stimulation at a rate of 8-13Hz would contaminate the oscillatory alpha response with evoked potentials. By stimulating at 7Hz we avoided this and allowed for a more reliable measurement of alpha power. Secondly, harmonics of the

stimulation frequency would occur at 14 Hz which again means it falls outside the 8-13 Hz alpha range, Herrmann (2001).

In this experiment, however, we are not expecting to be able to reliably measure the EEG alpha response from the auditory cortex due to physiological difficulties (cortical folding) reliable measurement of alpha power was unlikely across all subjects (Costa et al, 2011). Hence auditory stimulation was included to induce alpha effects in the visual and somatosensory cortices, but auditory cortex responses were not central to the hypotheses or data analysis.

Experimental condition	Stimulation modality	Attended modality	Modality to be inhibited	Measured for ERD	Measured for ERS
1	Auditory (A)	Auditory	Visual and Somatosensory	N/A (not expecting reliable auditory ERD)	Visual and Somatosensory
2	Somatosensory (S)	Somatosensory	Visual and Auditory	Somatosensory	Visual and ipsilateral somatosensory cortex
3	Visual (V)	Visual	Auditory and	Visual	Somatosensory and

			Somatosensory		ipsilateral visual cortex
4	Auditory and Somatosensory (AS)	Auditory and somatosensory	Visual	Somatosensory	Visual and ipsilateral somatosensory cortex
5	Visual and Auditory (VA)	Visual and auditory	Somatosensory	Visual	Somatosensory and ipsilateral visual cortex
6.	Visual and Somatosensory (VS)	Visual and somatosensory	Auditory (though not expecting reliable auditory ERS)	Visual and somatosensory	Ipsilateral visual cortex

Table 3.1. *A table showing the conditions of the experiment and the areas that are to be attended to and inhibited as well as the expected response in the alpha band.*

Design and Procedure

The EEG signal was recorded at 500Hz using a 63-channel MR-compatible EasyCap following the extended international 10-20 system layout. An electrocardiogram (ECG) channel was also attached just below the subject's clavicle. Electrode AFz was used as the ground and FCz was used as the reference electrode. All electrode impedances were maintained below 20 kΩ (Mayhew, Ostwald, Porcaro, and Bagshaw, 2013). Data was acquired using BrainAmp MR-

plus amplifiers (Brain Products, Munich) and Vision Recorder (Version 1.10). A Polhemus isotrack 3D system (Polhemus, Vermont, USA) was used to digitise electrode positions for co-registration to the subject's T1 MRI scan.

The participant had the EEG cap placed on their head and then isopropyl alcohol was used to clean the scalp and abralyte electrode gel was used to provide a conductive connection between the scalp and electrodes. They were seated facing a computer monitor, at 50cm distance, with over-ear headphones and MNS electrodes taped onto the inside of their right wrist. A 5-10-minute demonstration of the stimuli was given which allowed the subject to practise target detection. This ended once the participants confirmed they could complete the task satisfactorily, to approx. 70% accuracy which was deemed to be a suitable threshold to pass the training segment.

The experimental procedure was the same as in chapter 2 except for the following parameters:

• A 4s stimulus (active period) instead of 6s, containing either 0,1 or 2 target stimuli. The targets were brief, deviant stimuli presented amongst the 7Hz stimuli.

• A 1.5 fixation interval, instead of 3s, to separate the stimulus-response from the motor component of the target response

• Finally, 4s of resting fixation as a passive, baseline period. (While there is evidence for longer oscillatory responses i.e. post movement beta rebounds (Jurkiewicz et al, 2006) our analysis will focus only on alpha which does not have these longer lasting features.

The changes were made to reduce the time of the trials as the low pass filter of the BOLD signal (Stephan et al, 2004) is not a constraint with EEG and this means we could include more trials

and reduce the strain on the participant's ability to attend over the trials. On each trial, the subject's task was to attend to the cued modality and detect targets presented, whilst ignoring any other modality stimulated. The attended modality was counterbalanced amongst dual trials, i.e., there was an equal number of VS-attend V and VS-attend S trials. In each condition, there was an equal number of 0, 1, and 2 target trials. Each run held 32 trials presented in a pseudo-randomised order. Each run lasted for 8 minutes. There were four runs recorded per subject, giving a total of 4 of each type of condition in a given run and 16 total trials for each condition, and the total time for the experiment to be completed was over 90 minutes including preparing the participant for the trial structure, responses and the MRI itself.

Two further measures of participant's alpha power were obtained: spontaneous resting alpha power; and alpha ERS during eye closure. In a separate recording, subjects performed sixteen trials of 10s periods of eyes closed (visually cued with the words "eyes closed") alternating with 10s periods of eyes open (audio cued with a recording of the spoken word "open") a fixation cross was displayed throughout eyes open periods. Resting alpha was recorded both before and after the main experimental runs during a 4-minute period of resting fixation.

Data Analysis

Pre-processing

Firstly, Brain Vision Analyser was used to crop the data to start and end markers of each run of the experiment. After that, the initial broadband filtering was set to 1-90Hz. Data were imported to the MATLAB toolbox EEGLAB (Delorme & Makeig, 2004) and an ICA analysis was performed to remove components related to eye blinks and movements (Jung et al, 2000). Eye blinks were identified from their strongly frontal topographies and transient activites according to Jung et al (2000). Following this, a visual inspection was performed to identify

noisy data. Noisy channels and trials (any channel corrupted with a signal over 100 Hz indicative of high impedance) were removed. We also removed trials with signs of obvious movement, jaw clenching, muscle artifacts, or trials where the voltage exceeded 100mV. Spatial interpolation was used to fill in the missing channels. The data were then converted to an average reference using all non-noisy channels. Three participants were removed at this stage, two due to poor data quality and a high number of trials requiring rejection. The third removed participant was due to performance scores at or below chance showing a lack of attention to the task. Additionally, the individual alpha frequencies (IAF) during rest were calculated using the pwelch MATLAB function to estimate the power spectral density in the alpha range which was taken from an average of the activity in the channels covering the occipital cortex (O1, O2, Oz, PO3, POz, PO4). IAF was measured from the peak in the power spectrum density (PSD) analysis between 8-13Hz.

The continuous data were loaded into the Fieldtrip toolbox (Oostenveld, Fries, Maris, Schoffelen, 2011) in MATLAB and filtered into the alpha frequency band for each participant set at ± 2Hz of each participant's IAF. We then epoched the data into 4s duration active and passive periods ready for beamformer source analysis.

Beamforming

Using a T1 MRI anatomical image, acquired using a 3T Philips Achieva MRI with 1mm isotropic resolution, for each subject we created a 4-layer (skull, skin, cerebrospinal fluid, brain) boundary element head model using the dipole method in Fieldtrip (Oostenveld, Fries, Maris, Schoffelen, 2011, https://www.fieldtriptoolbox.org/). Conductivities were specified using a custom volume conduction headmodelling script with brain tissue conductivities (Siemens per metre, S/m) report at 0.33 S/m, skull conductivity at 0.0042 S/m, cerebral spinal fluid conductivity at 1 S/m and skin conductivity at 0.33 S/m. An LCMV beamformer (Van

Veen, Van Drongelen, Yuchtman, Suzuki, 1997) with a regularisation factor of 3 was used to localise changes in alpha activity during each of the six stimulus conditions. Pseudo-t-statistic maps of differences in source power between active and passive periods were calculated which allowed identification of the peak (largest magnitude) alpha ERD and ERS responses.

MNI space anatomical masks of the visual and somatosensory cortex were registered to each subject's T1 (using FSL FLIRT) and used to enable the identification of peak voxels of ERD and ERS inside the relevant cortices. Auditory masks were not used as auditory cortex responses were not reliably observed. For each condition, we extracted the virtual electrode (VE) timecourse of alpha activity from the location of peak ERD and peak ERS in both the visual and somatosensory cortices. A virtual electrode is a point representing a set of coordinates in the beamformer source solution. To enable VE extraction the beamformer weights are calculated over the whole dataset and then the weights for the VE location are multiplied by the EEG channel data to construct an estimate of the neural signal at that point in the brain. The absolute value of the Hilbert transform of the VE was calculated to provide a measure of the signal power for every time point in the experiment (Hahn, 1996). We selected the virtual electrode from the location of the largest magnitude ERD during the single stimulation for that respective cortex i.e., the peak ERD during single visual stimulation in the visual cortex.

T-tests

Timecourses for both VEs (visual and somatosensory) were extracted for each condition. For each participant, 4-second windows were epoched representing the stimulation period and baseline periods respectively for each trial. The initial 300ms of the stimulation period were cropped to remove the ERP to not cause significant deviation in the alpha oscillation power.

The corresponding first 300ms of the baseline was then also removed to ensure both stimulation and baseline periods matched in length. For both VEs, for each subject and each condition, the mean power of the epoched stimulation periods and baseline periods were calculated along with standard deviation and standard error measurement. IBM SPSS Statistics for Windows, Version 24.0 was used for all the following statistical tests. To answer H1 paired t-tests were used to compare each stimulation condition and mask iteration to their respective baselines to test for significant ERD or ERS. To answer H2 of if dual stimulated modalities cause a different effect on a non-task relevant modality to single stimulation paired t-tests were conducted comparing alpha power the following instances:

- S V_{ERS} vs AS V_{ERS}
- A V_{ERS} vs AS V_{ERS}
- V S_{ERS} vs VA S_{ERS}
- A S_{ERS} vs VA S_{ERS}

Here we adopt a notation X Yresponse where the stimulus condition is listed first as X, followed by Y as the cortical location of the VE (either V or S), and lastly, whether ERD or ERS was expected is written in the subscript.

An FDR correction was used on all t-tests to provide a corrected set of p values using the Benjamini and Hochberg method (Benjamini and Hochberg, 1995).

Results

The behavioural data from the experiment shows that the auditory task was the easiest and the somatosensory was the hardest from the single stimulation conditions (Figure 3.1 below shows the performance scores with the error bars.). The multisensory conditions were not significantly harder. The somatosensory conditions, particularly the somatosensory alone and

auditory/somatosensory were the hardest. All conditions were performed over a chance level of 33% and figure 3.1 below shows each of the target conditions (0, 1, and 2).

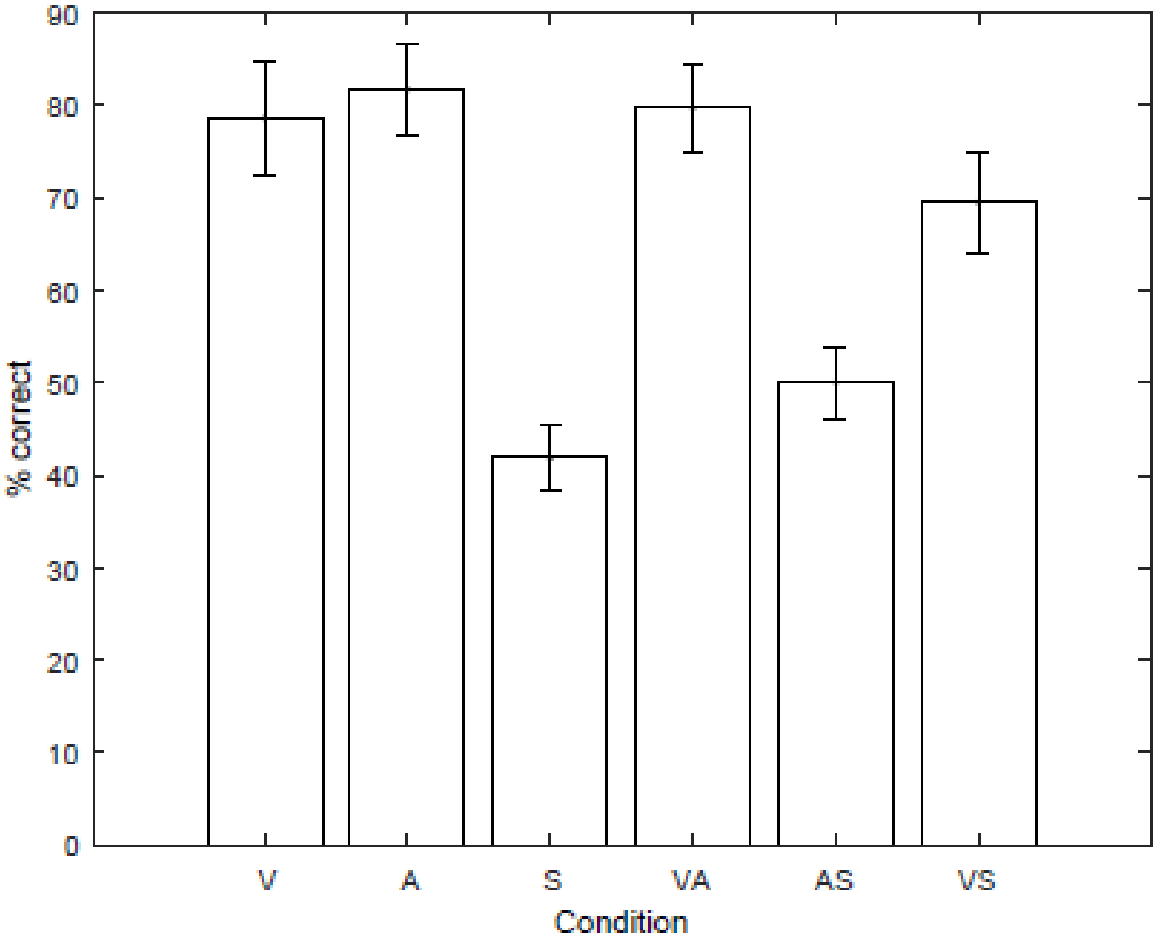

Figure 3.1. *A figure representing the accuracies per condition. Error bars denote standard error in the mean.*

.

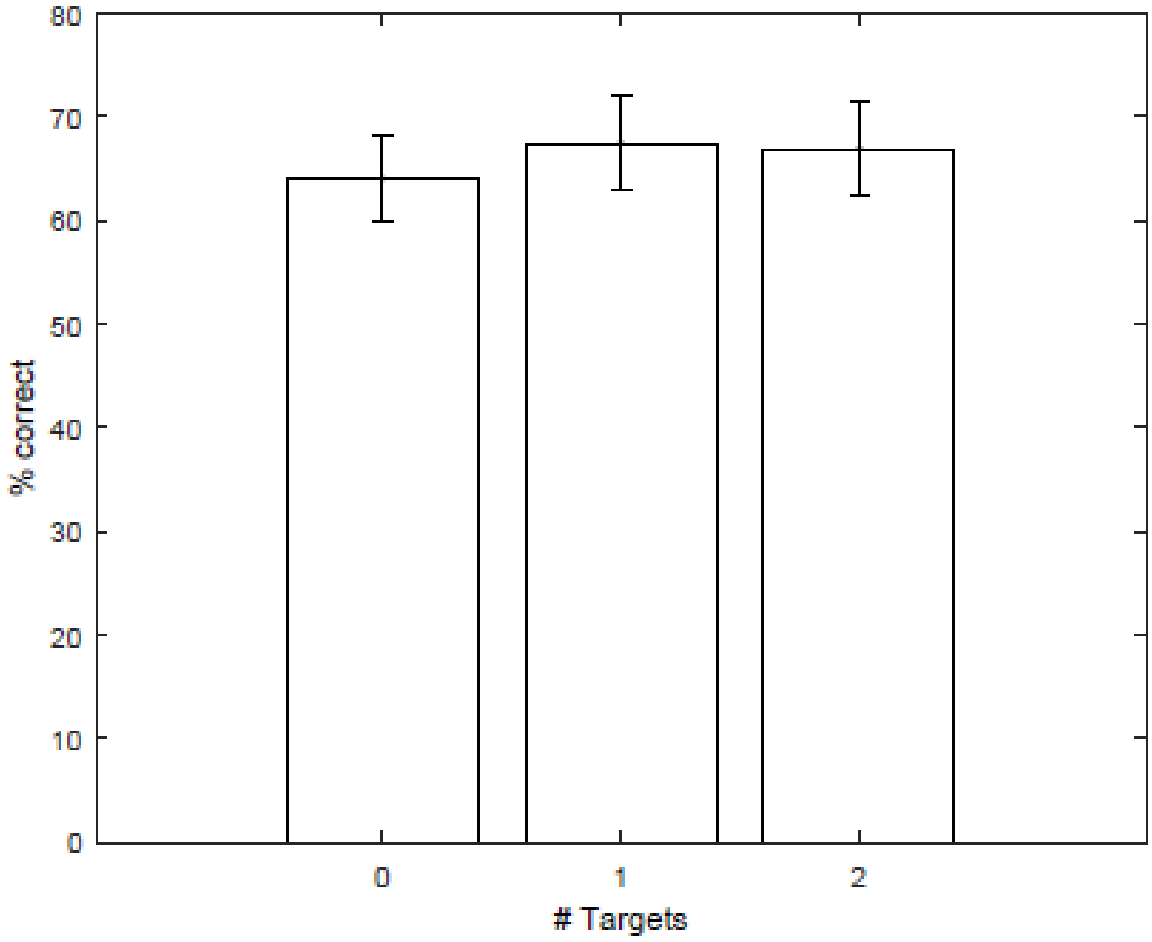

Figure 3.2. *A figure showing the accuracy per trial type when grouped by the number of targets as a bar chart. Error bars denote standard error in the mean.*

Results of the t-tests are displayed in Table 3.2 and show that consistent and significant alpha ERD was observed in both the visual and somatosensory cortex, during each condition (V, VA, VS, S, AS) in which the respective regions were stimulated, in both the single and dual conditions. We only saw significant ERS in the visual cortex during somatosensory stimulation ($p<0.05$). No other conditions produced a significant ERS in either the visual or somatosensory cortex. There was no instance of a difference in alpha response between any pair of single vs dual conditions.

Condition/Comparison	P-value	FDR corrected P-value threshold
V_V_{ERD} vs baseline	0.0011	0.0125
VA_V_{ERD} vs baseline	0.0001	0.006
S_V_{ERS} vs baseline	0.021	0.0222
S_S_{ERD} vs baseline	0.004	0.019
AS_S_{ERD} vs baseline	0.002	0.016
VS_V_{ERD} vs baseline	0.000001	0.003
VS_S_{ERD} vs baseline	0.0003	0.009
V_S_{ERS} vs baseline	0.113	0.031
A_S_{ERS} vs baseline	0.207	0.038
A_V_{ERS} vs baseline	0.085	0.025
VA_S_{ERS} vs baseline	0.355	0.041
AS_V_{ERS} vs baseline	0.361	0.044
A_V_{ERS} vs AS_V_{ERS}	0.718	0.05

S_V_{ERS} vs AS_V_{ERS}	0.105	0.028
VS_S_{ERS} vs VA_S_{ERS}	0.176	0.034
AS_S_{ERS} vs VA_SERS	0.545	0.047

Table 3.2. *Statistical significance (active vs baseline) of alpha power change in each condition using ERD-based VE's in Visual and Somatosensory cortex.*

The group mean VE timecourse responses to V, S, and VS stimuli from the visual and somatosensory cortex are plotted in Figure 3.3. The first 4 seconds of each sub-panel show the mean baseline time course across all trials. After 4 seconds all responses show a steep decrease in alpha power representing an ERD which persists until 8s when the stimulus ended. It is interesting to note that all timecourses show effectively similar response with a decrease to 0.4 millivolts squared in either responsible region i.e., V1/S1 regardless of if there were one or two modalities used.

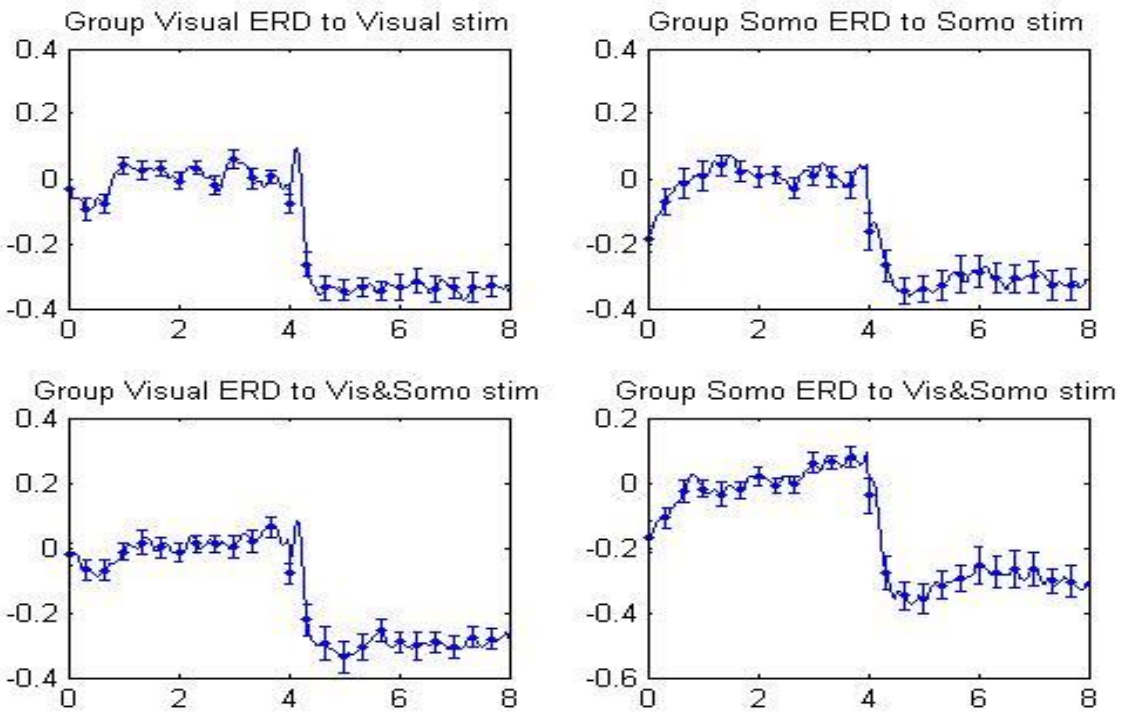

Figure 3.3. *The group mean timecourses for each ERD in non-relevant modalities. Error bars denote standard error in the mean.* The X axis on the above graphs is Time in seconds and the Y axis is the percentage change in power.

The following subfigures are 1. Group V_S_{ERS}, 2. Group S_V_{ERS}, 3. Group A_S_{ERS}, 4. Group A_V_{ERS}, 5. Group VA_S_{ERS}, 6. Group AS_V_{ERS}. The y axis is the percentage change in power for each response with a deviation above 0 showing alpha ERS and below 0 showing alpha ERD. The x-axis represents time in seconds with the first 4 seconds being the baseline period then concatenated with the stimulation period for the following 4 seconds. The cue period is not shown in these timecourses nor is the response period. Error bars represent the standard error in the mean.

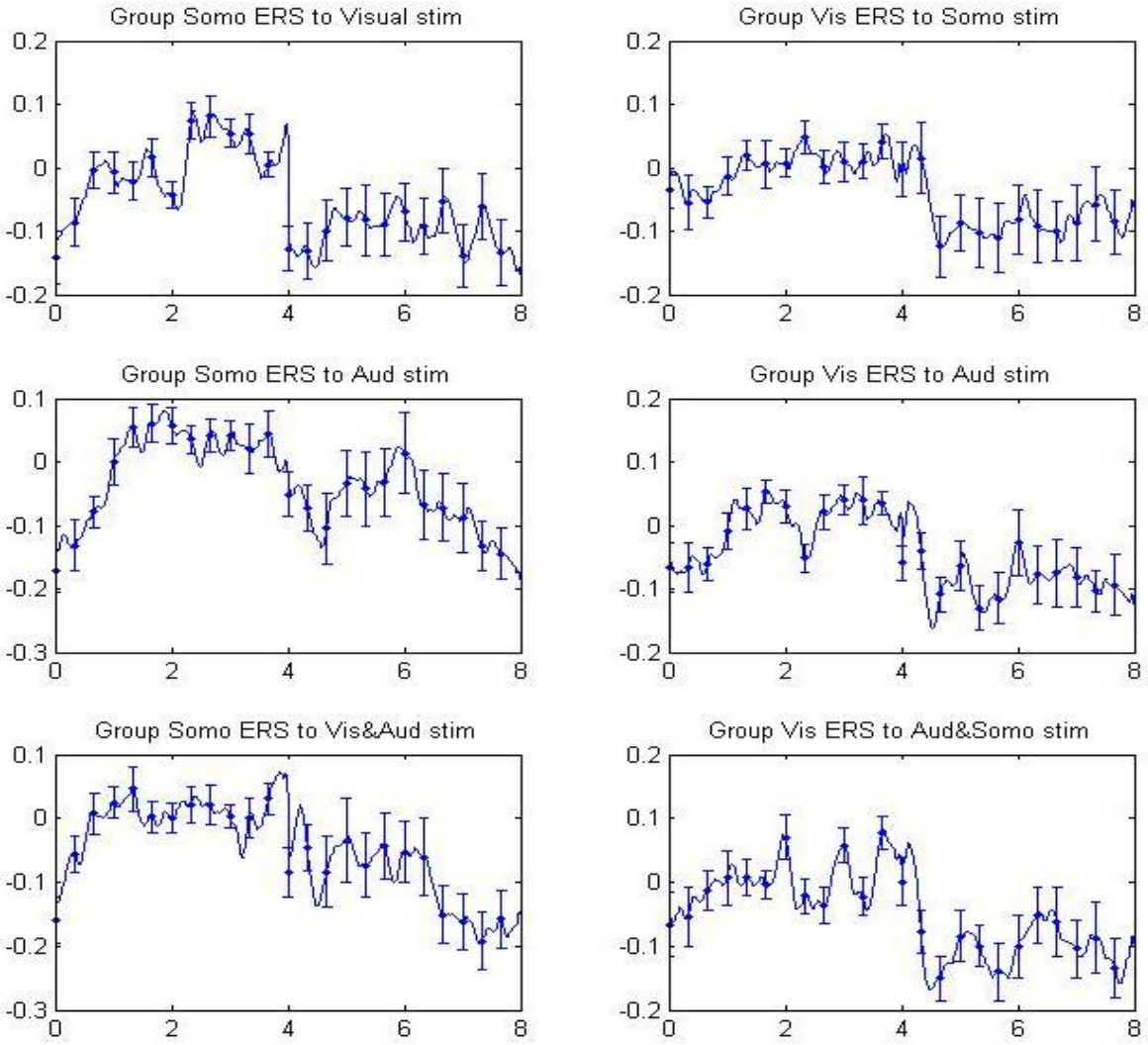

Figure 3.4. *The group means timecourses for each ERS in trial-specific stimulated modalities. The following subfigures are 1. Group V_V_{ERD}, 2. Group S_S_{ERD}, 3. Group VS_V_{ERD}, 4. Group VS_S_{ERD}. The y axis is the percentage change in power (millivolts squared) for each response with a deviation above 0 showing alpha ERS and below 0 showing alpha ERD. The x-axis represents time in seconds with the first 4 seconds being the baseline period then concatenated with the stimulation period for the following 4 seconds. The cue period is not shown in these timecourses nor is the response period. Error bars represent the standard error in the mean.*

Figures 3.5-3.13 provide further detail of the substantial between-subject variability of the alpha responses by plotting the mean timecourse for each subject for each of the conditions. None of the conditions display an alpha ERS, except visual ERS to somatosensory stimulation

alone, and in fact, some of the participant's timecourses present an alpha ERD instead of the expected ERS. Figures 3.5 to 3.7 show the ERD responses, figures 3.8 to 3.13 show the ERS responses.

The beamformer maps (Figures 3.14-3.18) and the t-tests (Table 3.2) further illustrate that in each condition a significant alpha ERD occurred in the primary sensory cortex that processed the stimulated modality, e.g., visual ERD in the visual cortex during visual stimuli (see Figure 3.5 and Table 3.2.)

The beamformer maps in Figures 3.14, 3.15, and 3.17 show examples where alpha ERDs were measured in distinct regions, confined to the stimulated visual or somatosensory cortex. However, Figures 3.16 and 3.18 show examples where this ERD extended beyond the stimulated sensory cortex to encompass most of the cortex which resulted in regions being unable to express an ERS. This was especially observed for visual ERD spreading over the somatosensory cortex. Figures 3.14 and 3.15 however show that some participants, with ERD confined to the stimulated cortex, did express an ERS response which is supported by the individual timecourses displayed in Figures 3.5-3.13. Variability in ERD and ERS expression across the group resulted in mean alpha power which does not overall represent a group level ERS in non-task-relevant regions (except in the case of S_V_{ERS}).

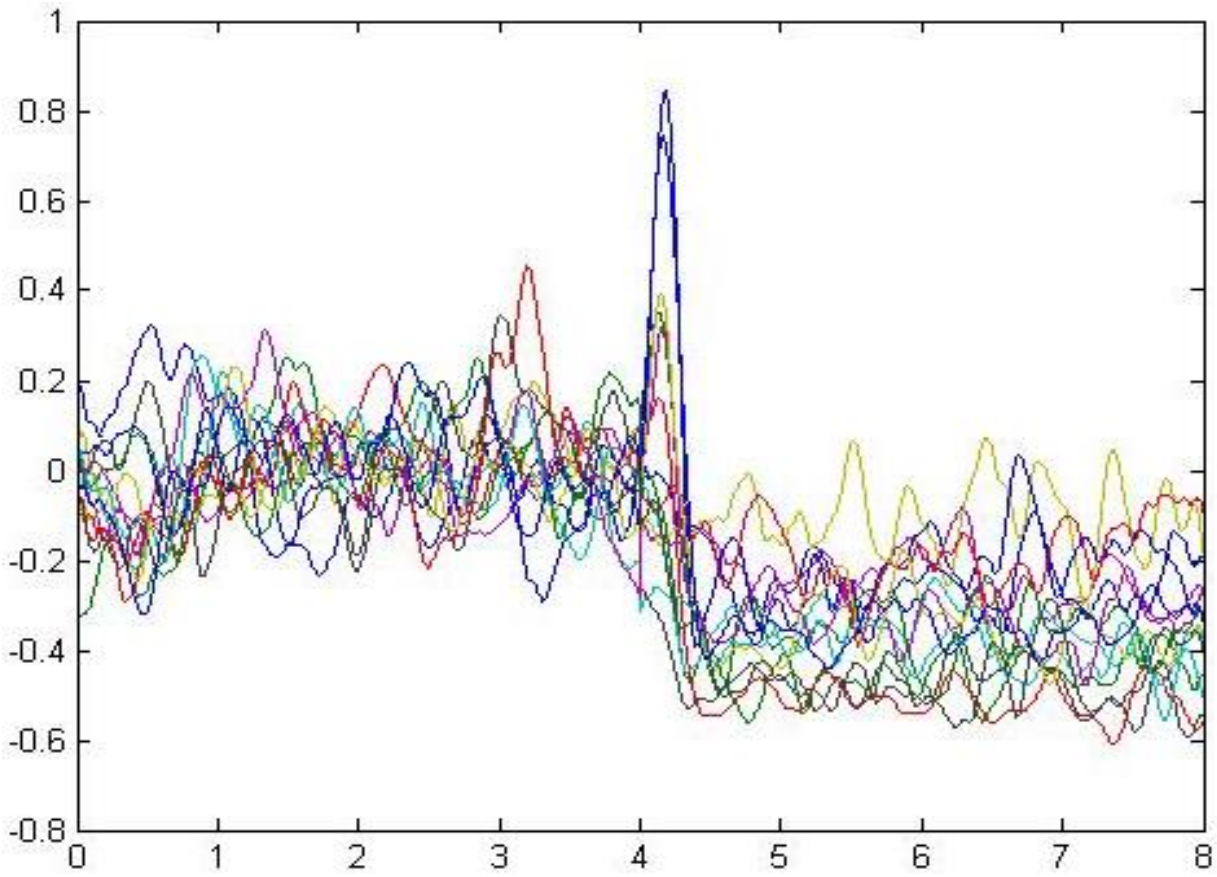

Figure 3.5. *V_V_{ERD} timecourse (visual cortex response Visual alone stimulation) for each subject. Consistent visual ERD is observed across the group. The X-axis is time in seconds, the first four sections presenting a resting baseline and the last four sections presenting the stimulation period. The Y-axis is power in millivolts squared.*

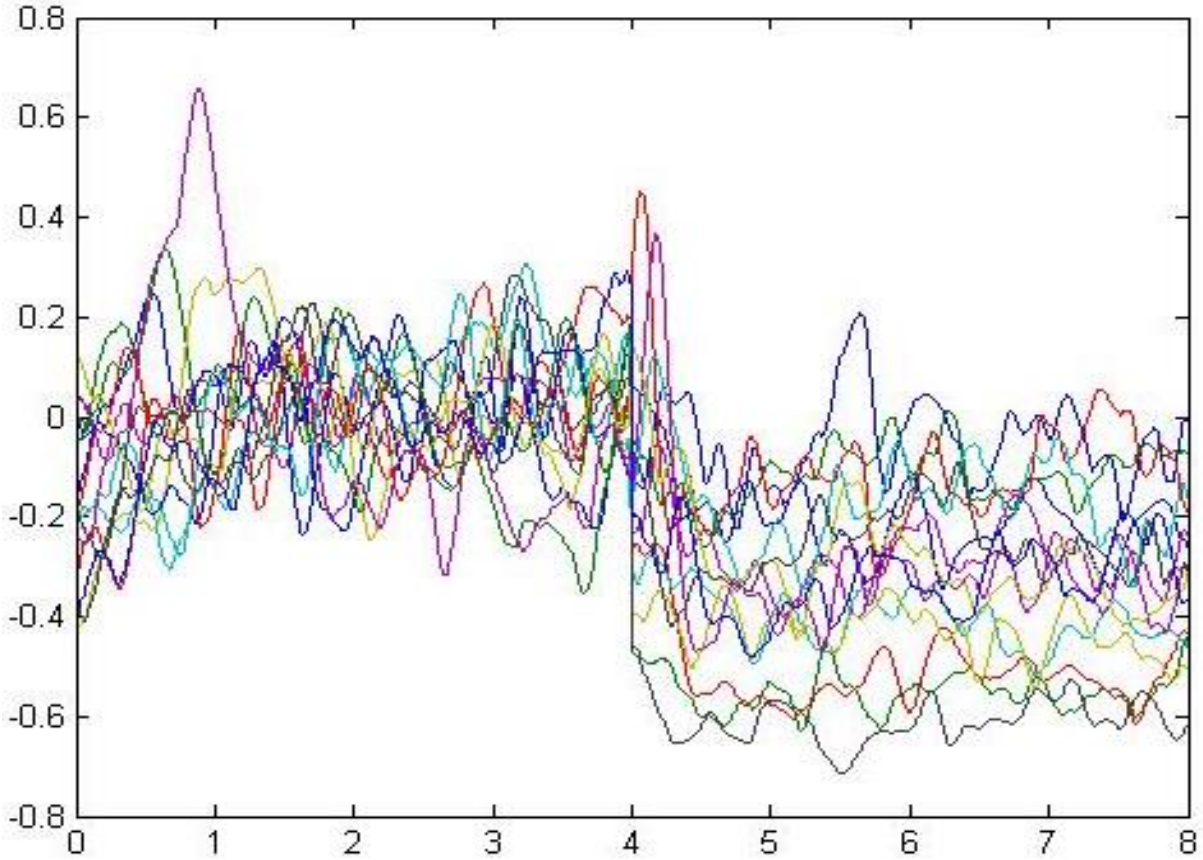

Figure 3.6. *S_S$_{ERD}$ timecourse (somatosensory cortex responses to somatosensory alone stimulation) for each subject. Here we see a clear somatosensory ERD to somatosensory stimulation in all subjects. The X-axis is time in seconds, the first four sections presenting a resting baseline and the last four sections presenting the stimulation period. The Y-axis is power in millivolts.*

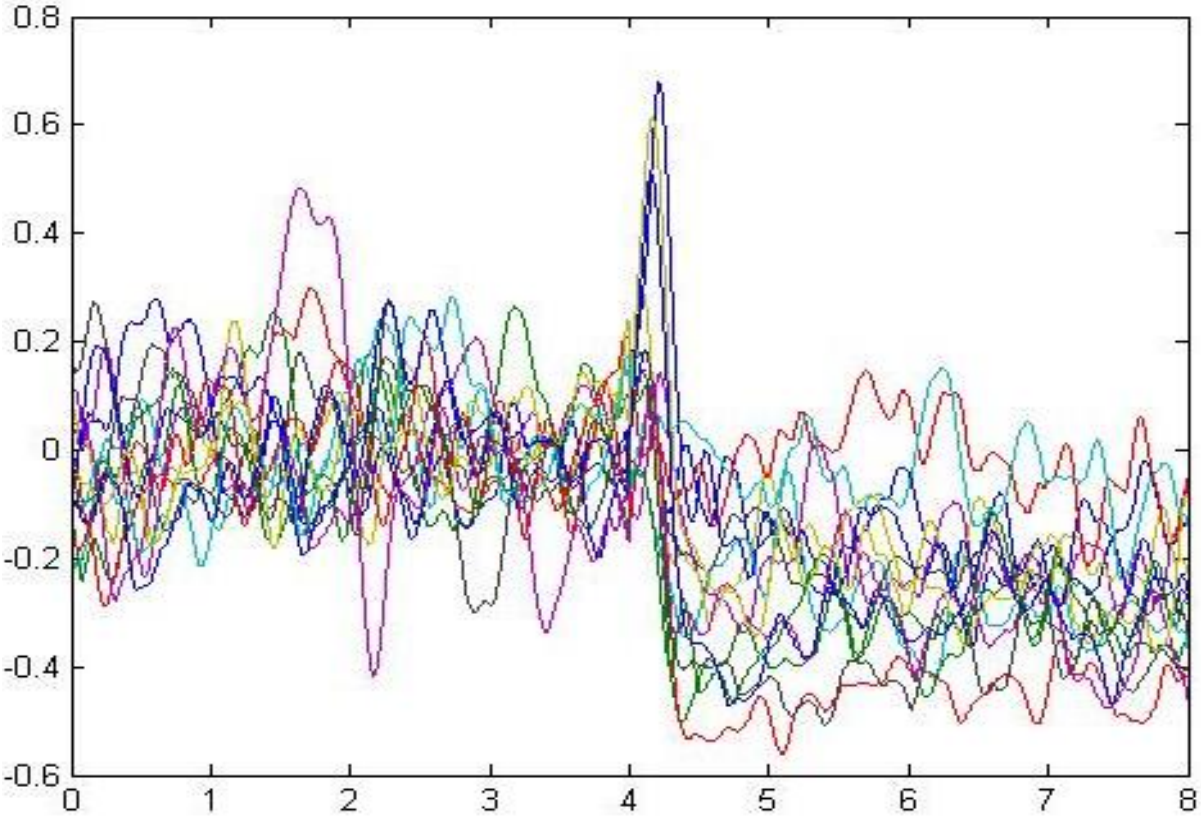

Figure 3.7. *VA_V_{ERD} timecourse (visual cortex responses to visual and auditory stimulation) for each subject. Here we see a clear visual ERD in all subjects. The X-axis is time in seconds, the first four sections presenting a resting baseline and the last four sections presenting the stimulation period. The Y-axis is power in millivolts.*

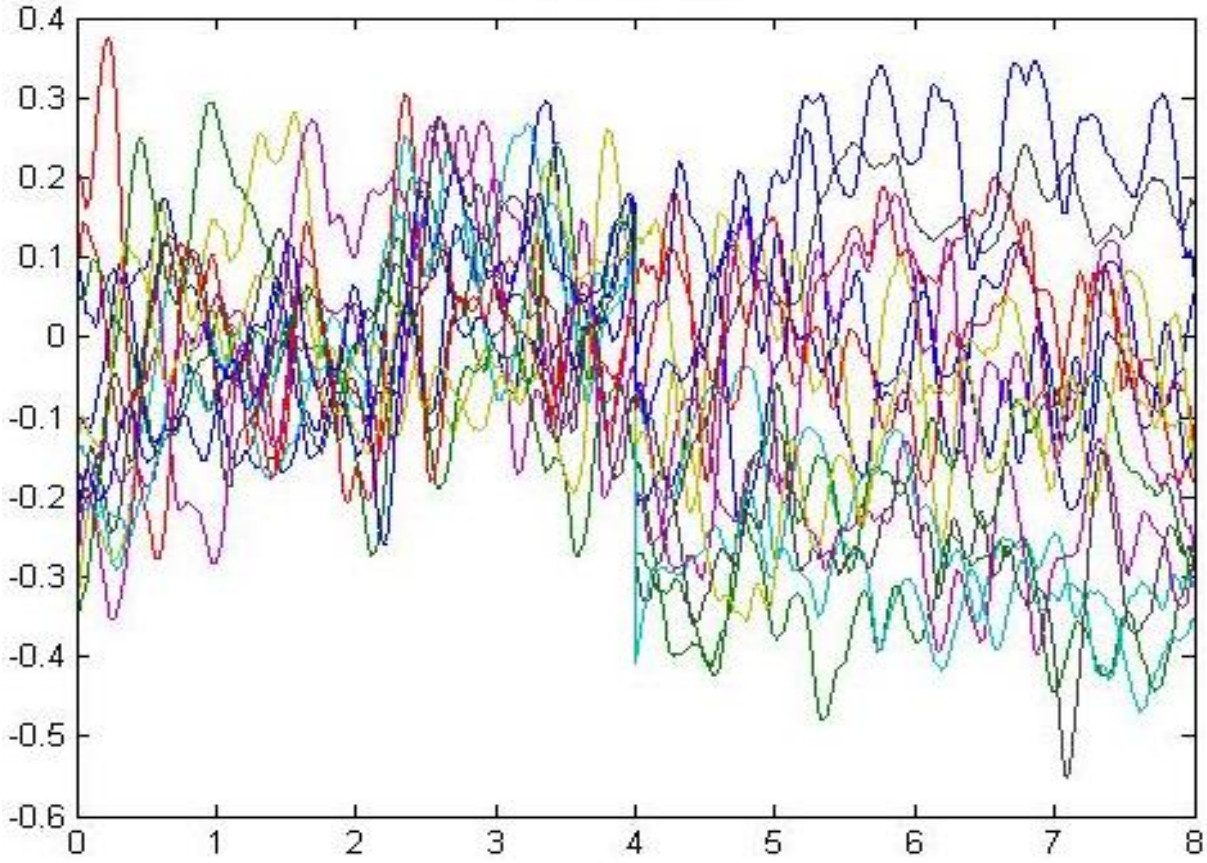

Figure 3.8. *V_S$_{ERS}$ timecourse (somatosensory cortex responses to Visual alone stimulation) for each subject. Inconsistent Somatosensory ERS is seen across participants with some participants showing an ERD despite no somatosensory or motor component to this condition. This shows evidence of high variability in the alpha response, with both ERS and ERD seen across the group. The X-axis is time in seconds, the first four sections presenting a resting baseline and the last four sections presenting the stimulation period. The Y-axis is power in millivolts.*

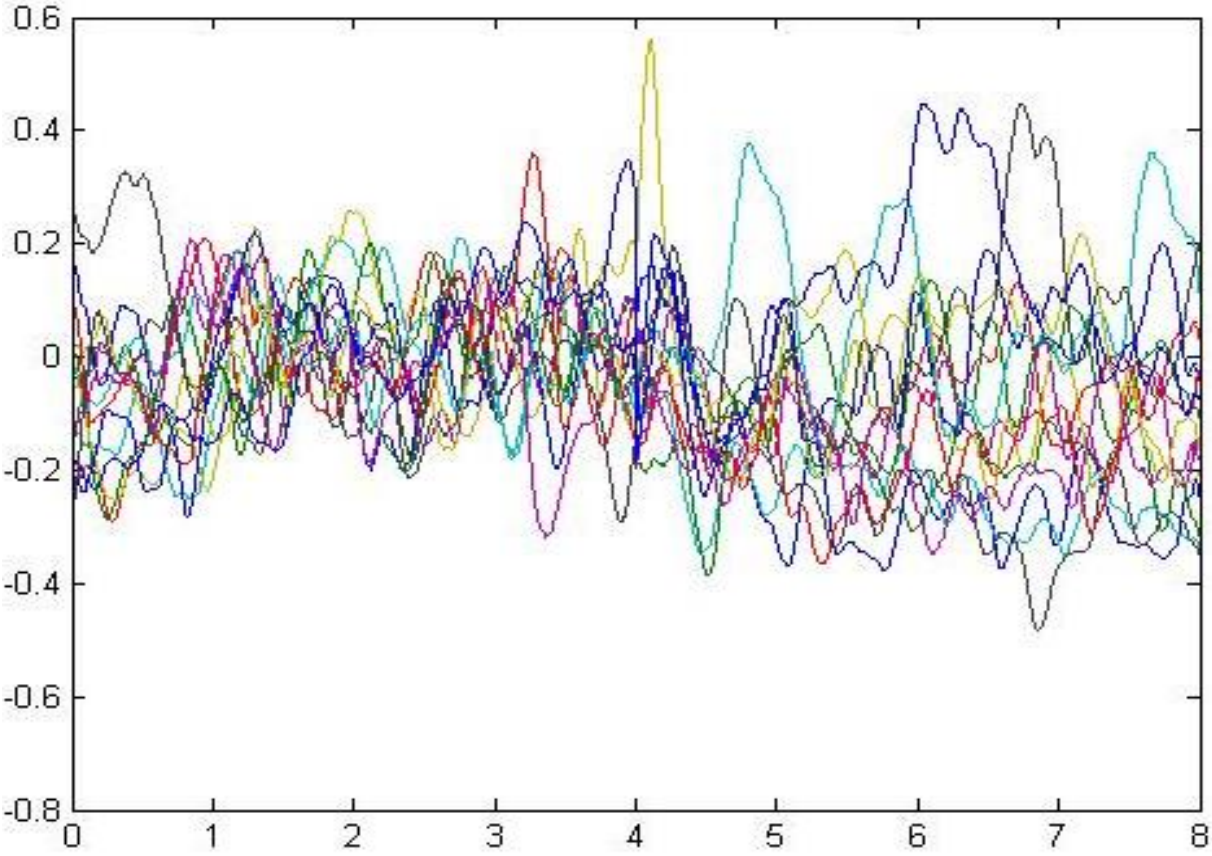

Figure 3.9. *A_V_{ERS} timecourse visual cortex responses to auditory alone stimulation) for each subject. Inconsistent visual ERS is seen across participants again with the participants' alpha power either presenting visual ERS, remaining near the baseline, or showing a small ERD. We do not see evidence of clear group ERD as in the somatosensory cortex during visual stimulation but individual participants do show ERD. This shows further evidence of high variability in ERS response. The X-axis is time in seconds, the first four sections presenting a resting baseline and the last four sections presenting the stimulation period. The Y-axis is power in millivolts.*

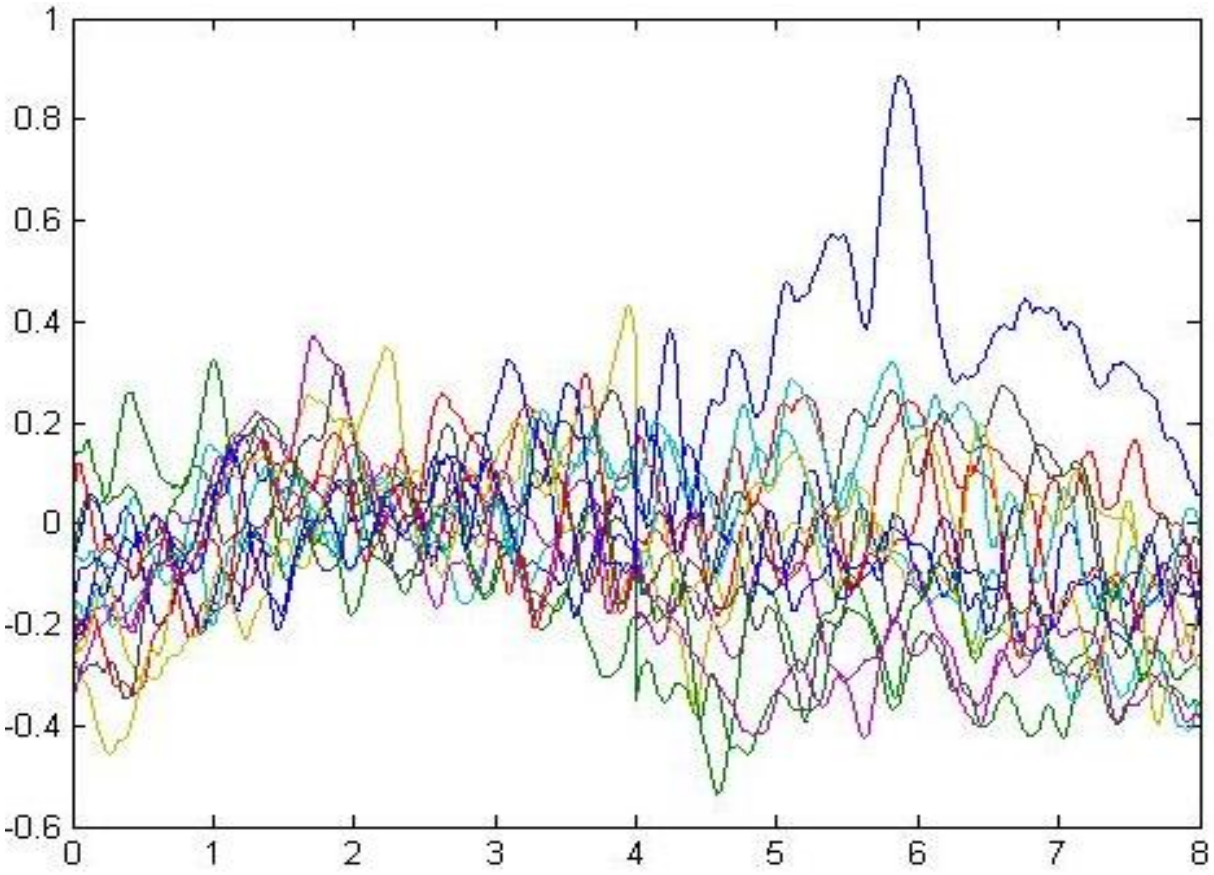

Figure 3.10. *A_S$_{ERS}$ timecourse (somatosensory cortex responses to auditory alone stimulation) for each subject. While insignificant the response is highly variable again with a mixture of ERS and ERD responses. The X-axis is time in seconds, the first four sections presenting a resting baseline and the last four sections presenting the stimulation period. The Y-axis is power in millivolts.*

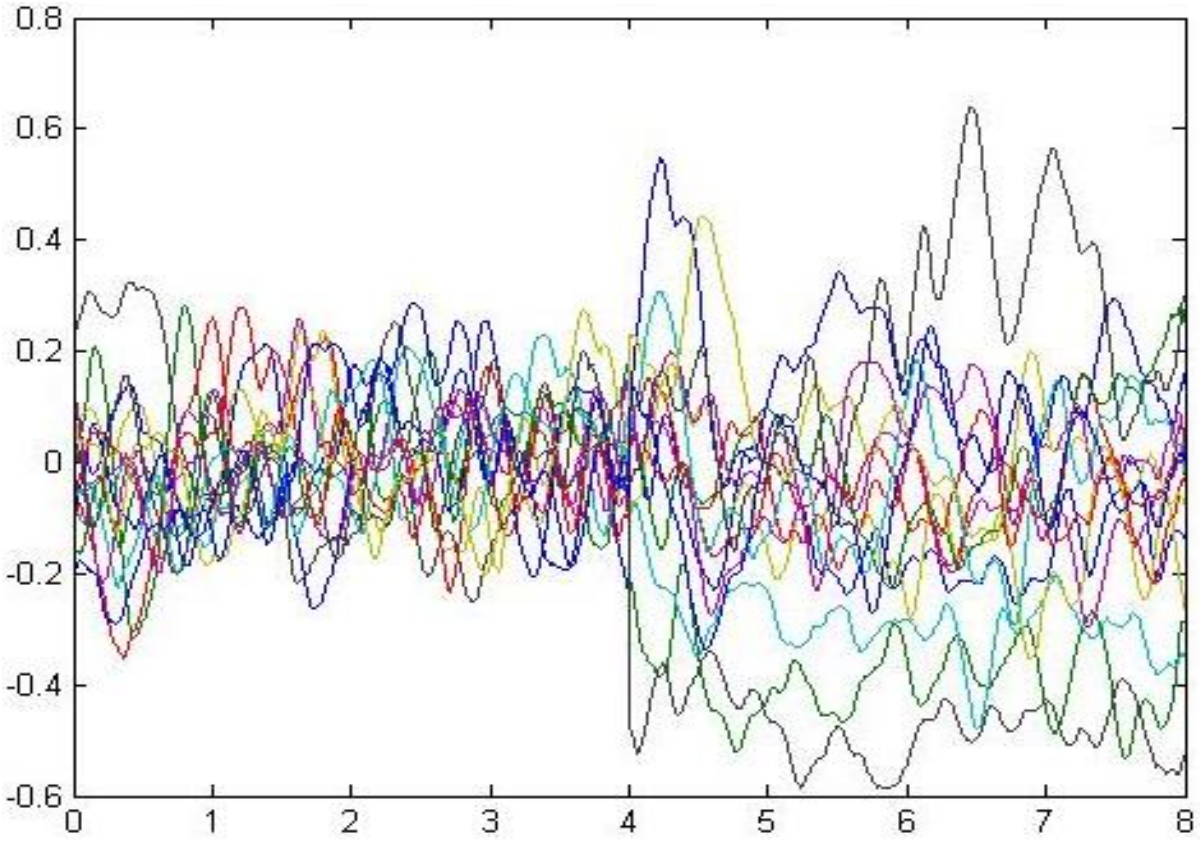

Figure 3.11. *S_V_{ERS} timecourse (visual cortex responses to somatosensory alone stimulation) for each subject. Here we also see highly variable responses with some participants presenting alpha ERS and others ERD even when the visual system was non-task-relevant to this trial. The X-axis is time in seconds, the first four sections presenting a resting baseline and the last four sections presenting the stimulation period. The Y-axis is power in millivolts.*

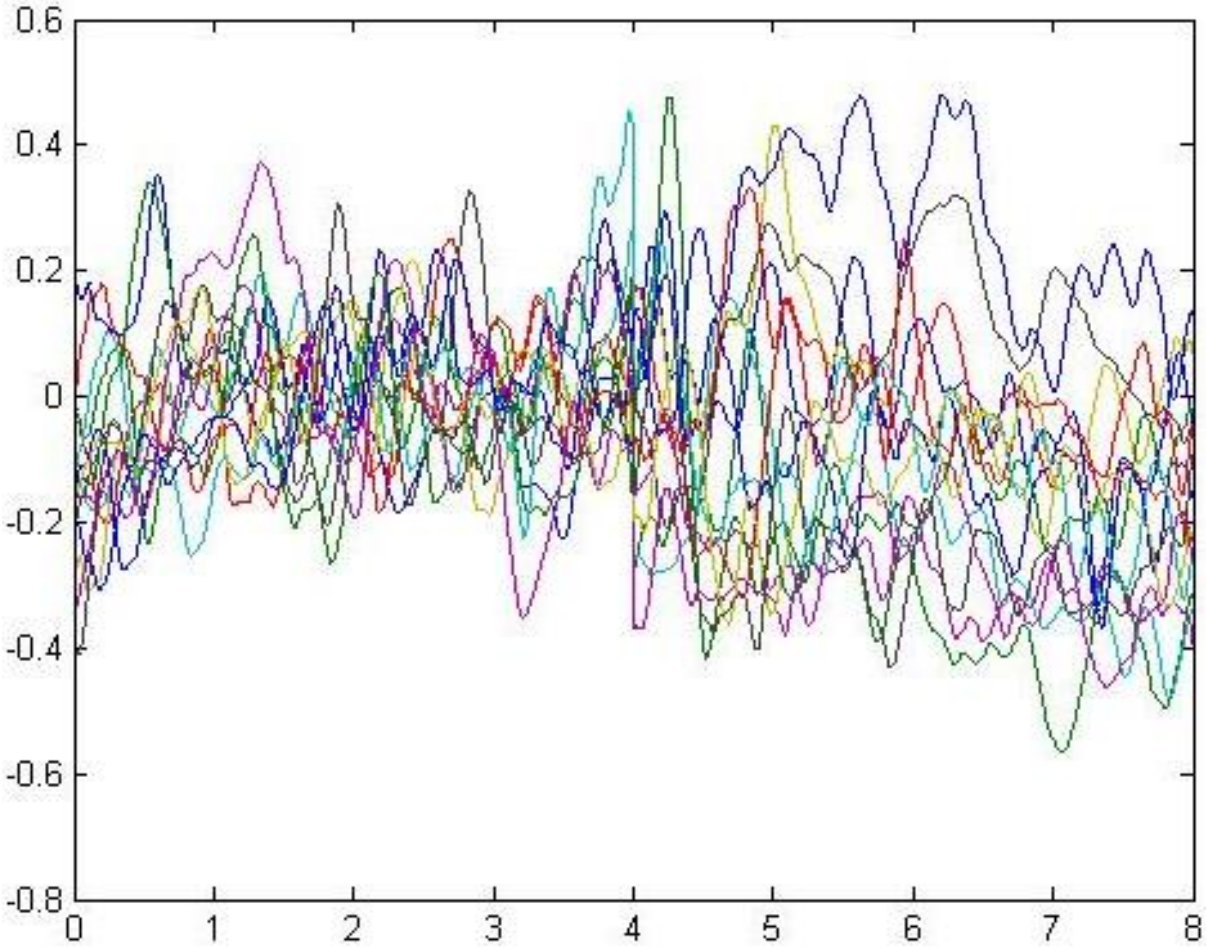

Figure 3.12. *VA_S$_{ERS}$ timecourse (visual cortex responses to visual and auditory stimulation) for each subject. Participants show a mixture of ERS or ERD. The X-axis is time in seconds, the first four sections presenting a resting baseline and the last four sections presenting the stimulation period. The Y-axis is power in millivolts.*

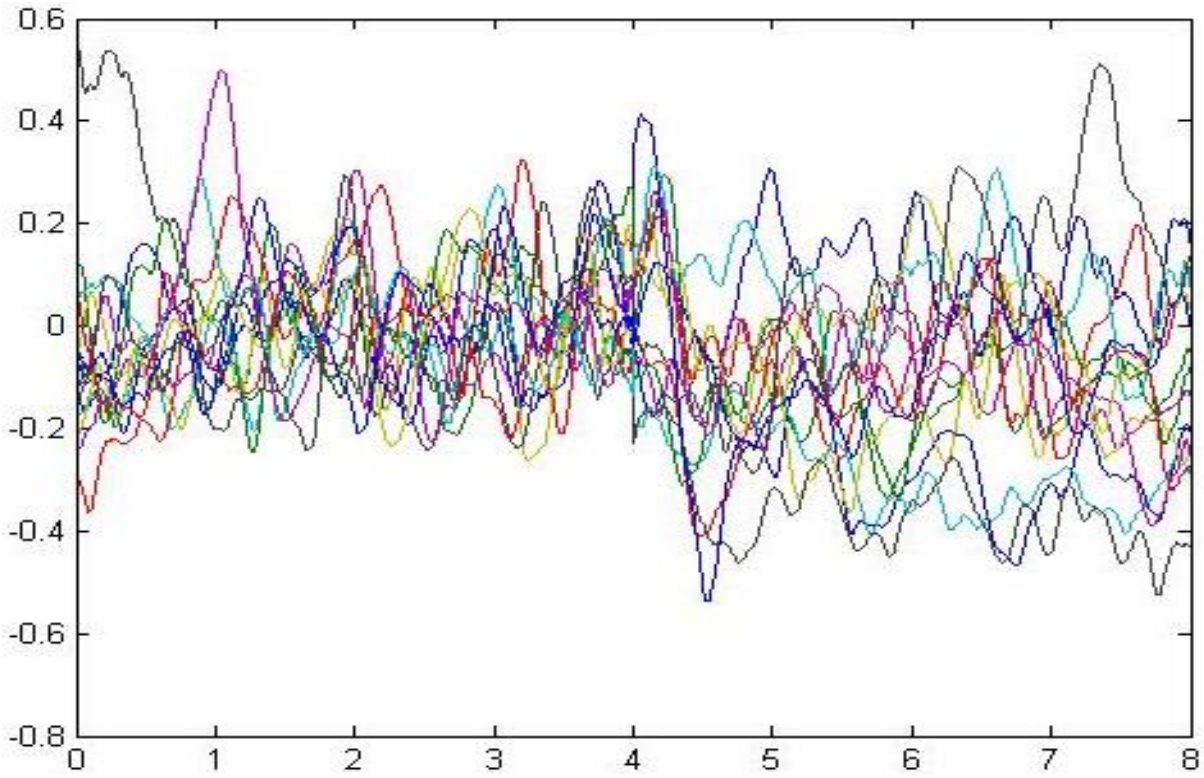

Figure 3.13. *AS_V_{ERS} timecourse (visual cortex responses to visual and somatosensory stimulation) for each subject. There is no clear ERS and variability in participant response means we see ERD in some participants despite the visual region being non-task relevant during this condition. The X-axis is time in seconds, the first four sections presenting a resting baseline and the last four sections presenting the stimulation period. The Y-axis is power in millivolts.*

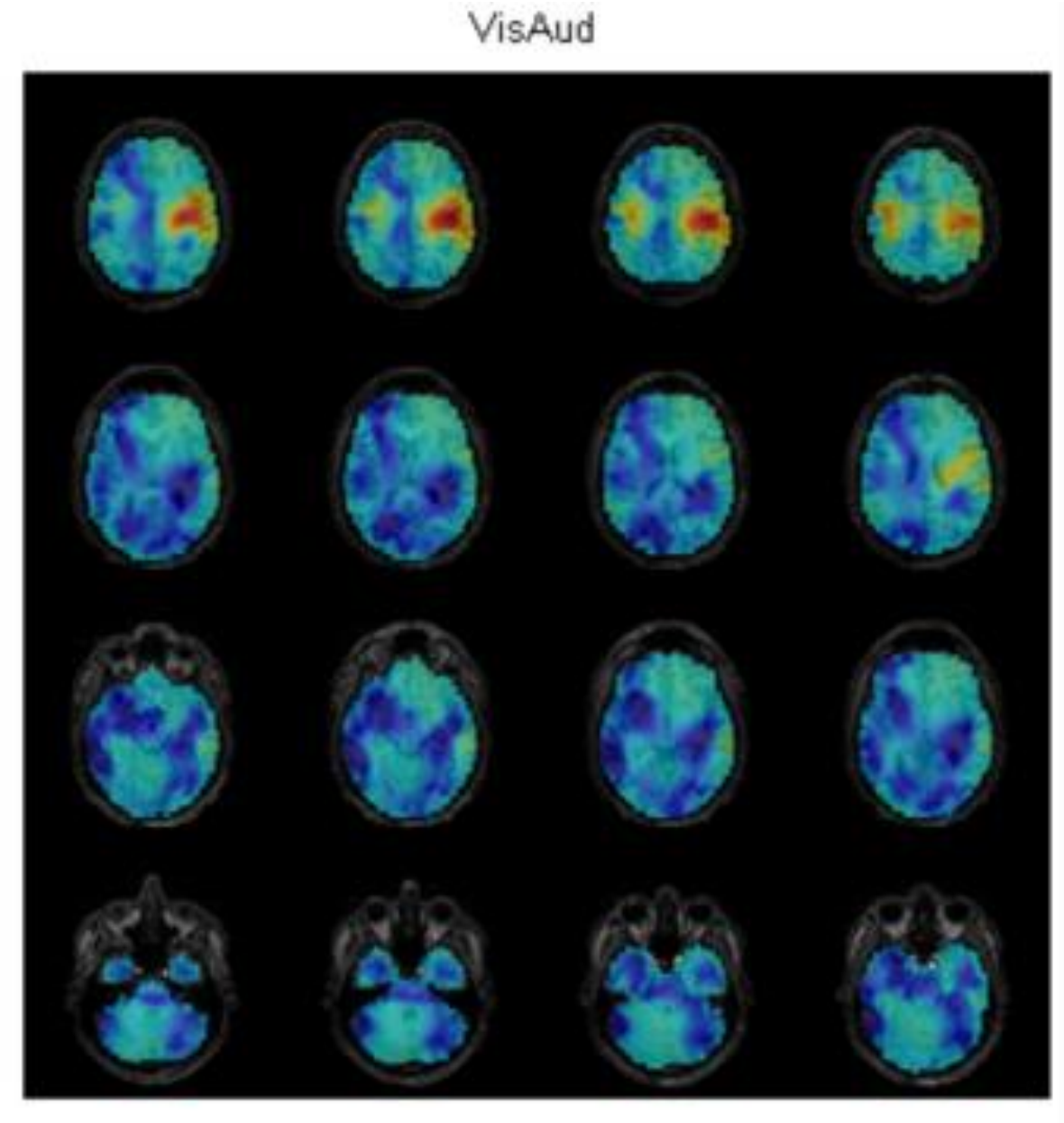

Figure 3.14. *Pseudo-T stat beamformer map from Subject 1 of the alpha power response to the VA condition, showing clear alpha ERD in visual cortex and alpha ERS in somatosensory cortex. Blue represents ERD, Green baseline, and Red/Orange ERS.*

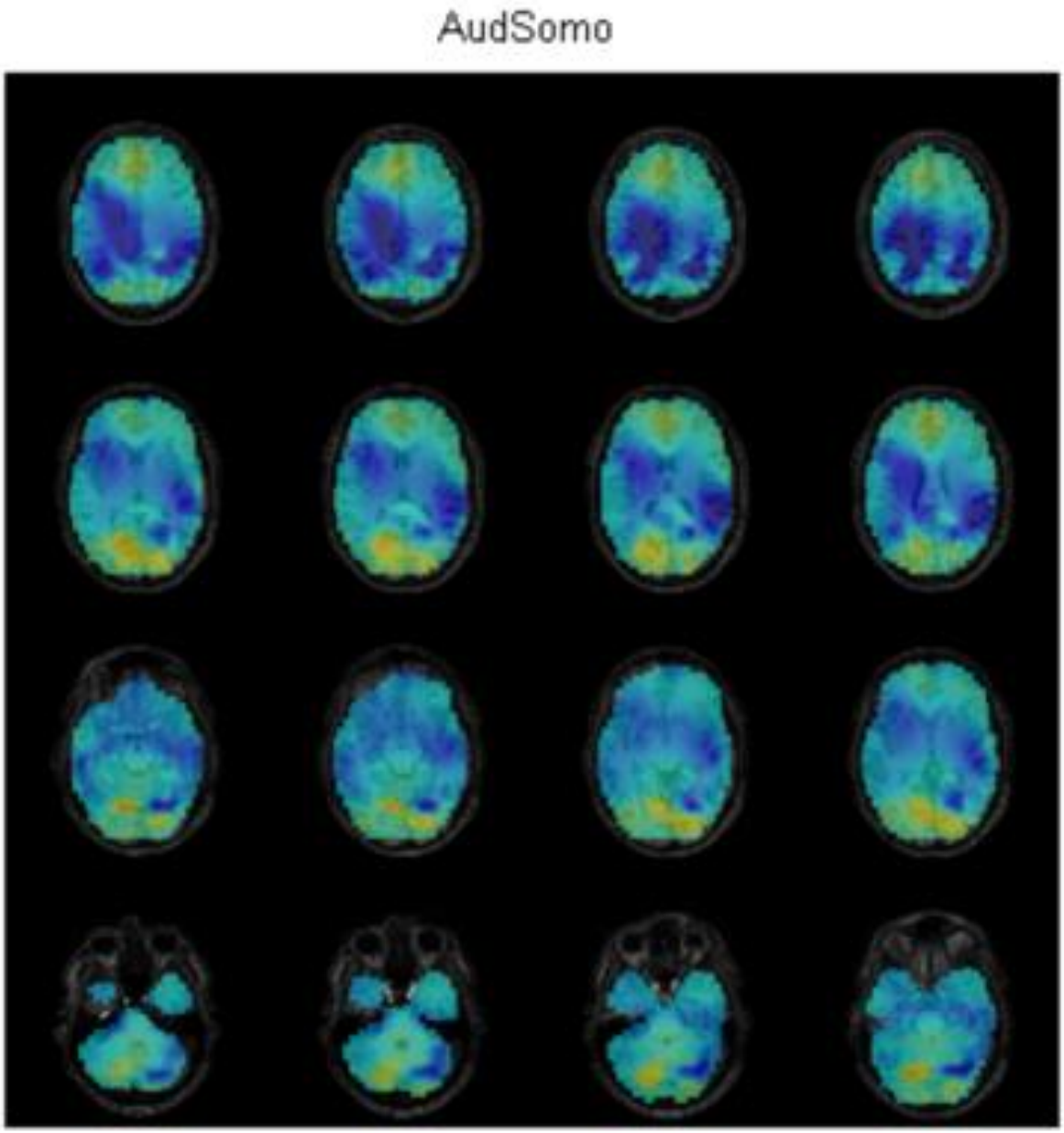

Figure 3.15. *Pseudo-T stat beamformer map from Subject 2 of the alpha power response to the AS condition, showing clear alpha ERD in somatosensory cortex and alpha ERS in visual cortex. Blue represents ERD, Green baseline, and Red/Orange ERS.*

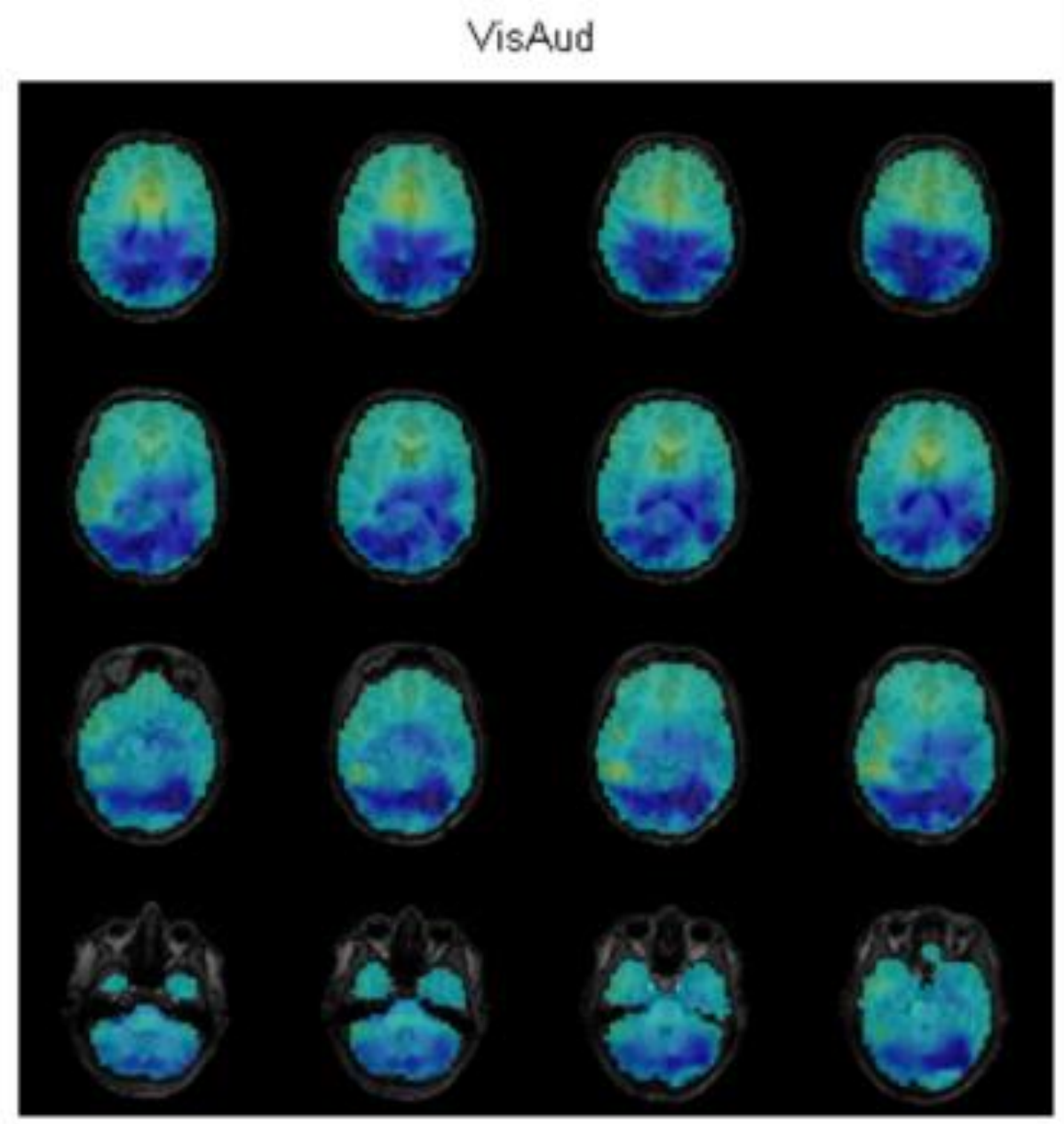

Figure 3.16. *Pseudo-T stat beamformer map from Subject 3 of the alpha power response to the V condition, showing clear alpha ERD throughout the visual and parietal cortex extending up to the somatosensory cortex. Blue represents ERD, Green baseline, and Red/Orange ERS.*

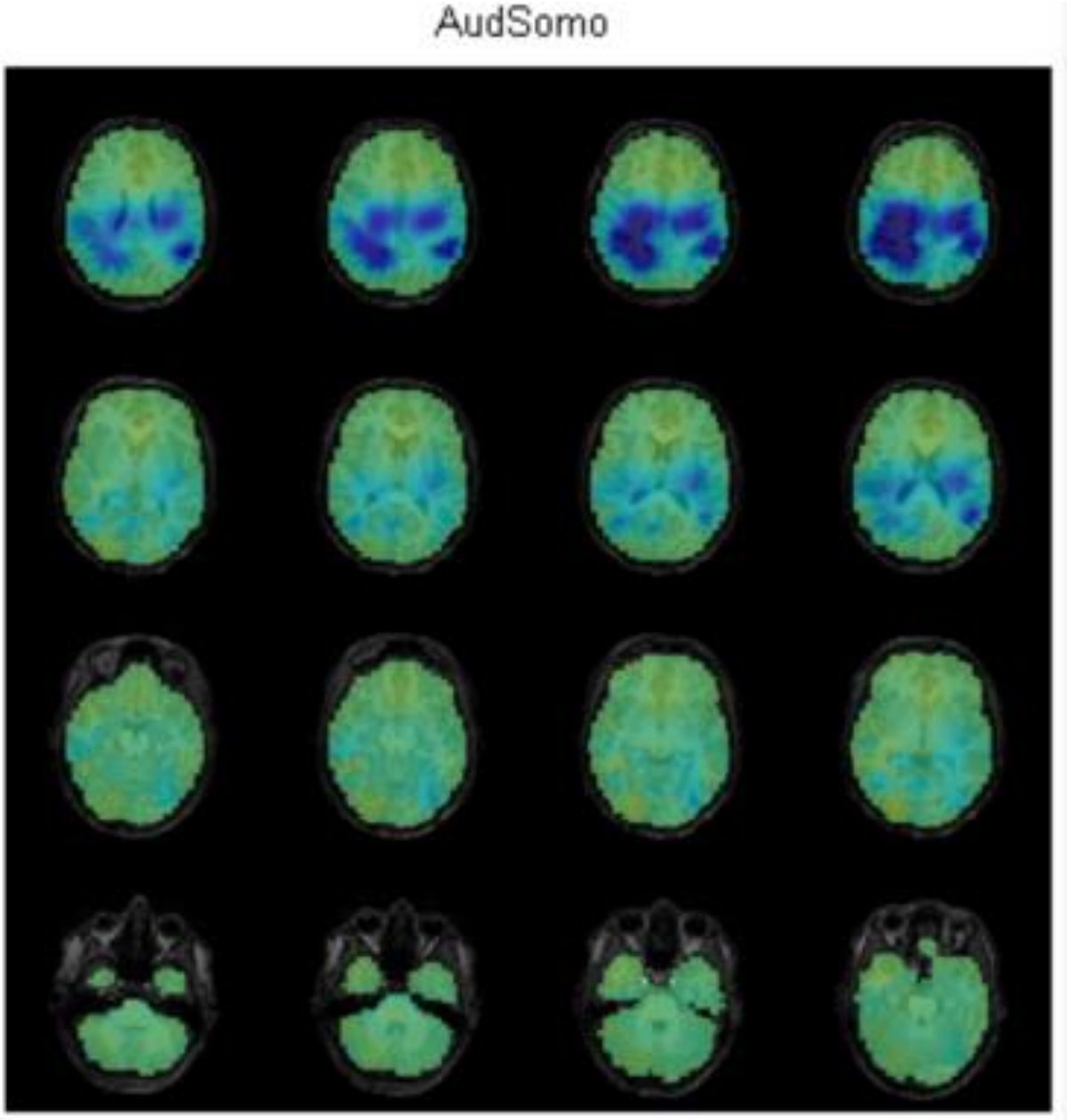

Figure 3.17. *Pseudo-T stat beamformer map from Subject 3 of the alpha power response to the AS condition showing clear somatosensory ERD but no clear ERS throughout the rest of the brain, the green colour represents a response close to the baseline, approximately zero T-stat. Blue represents ERD, Green baseline, and Red/Orange ERS.*

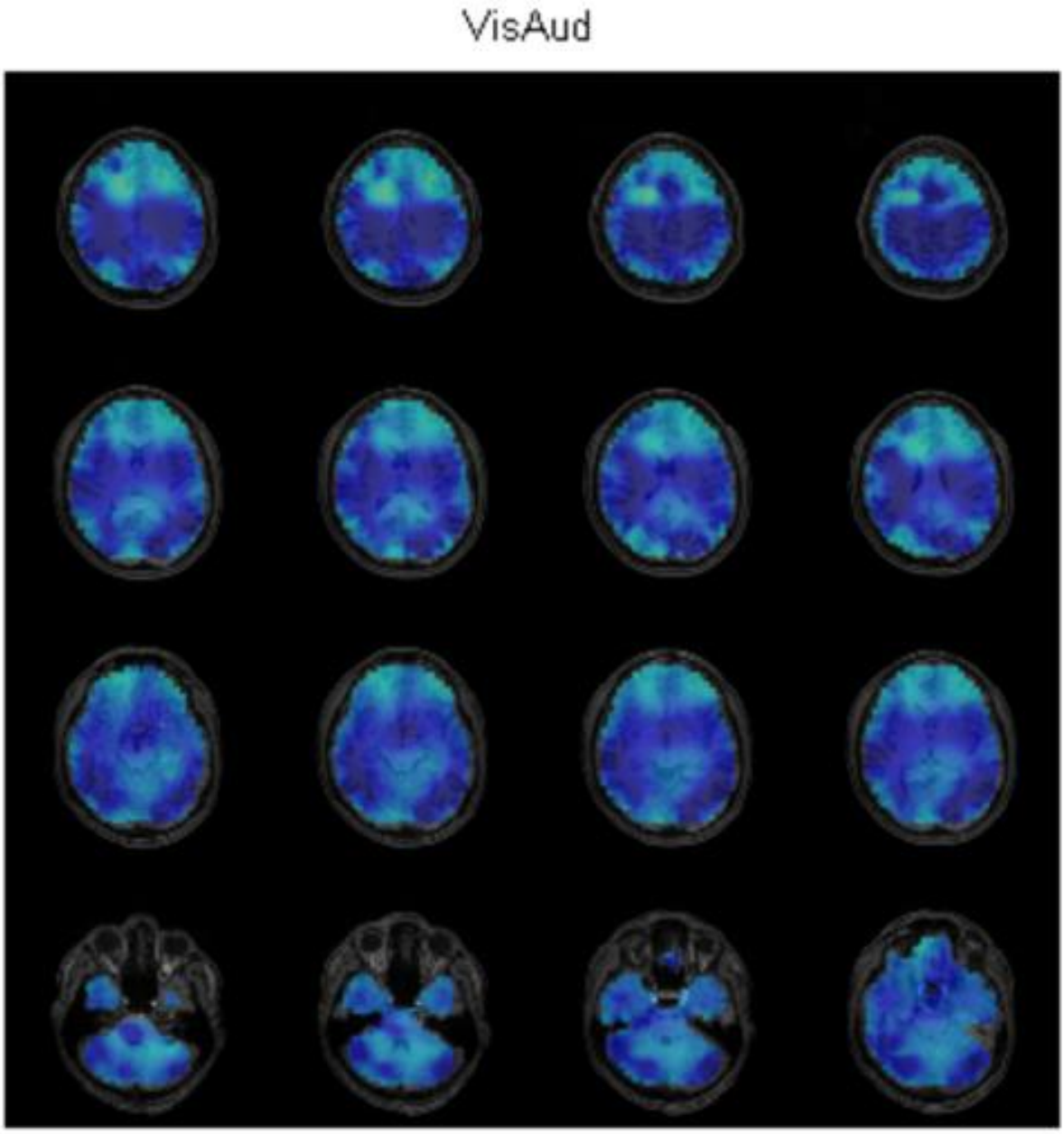

Figure 3.18. *Pseudo-T stat beamformer map from Subject 4 of the alpha power response to the V condition showing an ERD response throughout the entire cortex. Blue represents ERD, Green baseline, and Red/Orange ERS.*

Discussion

Our intention with this experiment was twofold. Firstly, we intended to replicate findings of significant stimulus-induced alpha ERD in the stimulated sensory cortex and to investigate the occurrence of significant alpha ERS in NTRRs during stimulation, and evaluate the alpha ERS

as a neural marker of NBR. Secondly, we wanted to study if the power of alpha ERS in NTRRs was significantly higher during multisensory trials compared to single sensory trials. We wanted to know if the alpha ERS as an equivalent inhibitory response to the NBRs seen in chapter 2 was modulated by task load. We found significant alpha ERD in the visual and somatosensory cortex during visual and somatosensory stimulation respectively, but we did not find consistent evidence for NTRR alpha ERS. The only significant alpha ERS observed was in the visual cortex during the somatosensory alone stimulation trials, but this was not found during concurrent somatosensory and auditory stimulation. The lack of consistent, significant ERS findings appears to be due to substantial between-subject variability in the alpha response. This means that we must accept the null hypothesis for both H1 and H2. The lack of a sustained alpha ERS in this chapter in contrast to the presence of a sustained NBR in chapter 2 is interesting and suggests considerable differences in the manifestation of different inhibitory signals measured by electrophysiological and haemodynamic techniques.

To attempt to explain why this paradigm showed different EEG results compared to those observed in the previous fMRI chapter, particularly regarding the single vs baseline analyses, we will discuss several potential hypotheses on the differences between NBR inhibition and alpha ERS inhibition as well as potential confounding factors.

Alpha ERS as a marker of inhibition

In this experiment we did not see a consistent alpha ERS during the stimulation period in a comparable manner to the NBRs observed in chapter 2. However, we did see strong alpha ERD, providing evidence that the stimulus did induce a response in changing the synchronisation of alpha in the stimulated cortex. The question then is why alpha ERS was so hard to sustainably generate but alpha ERD was not? The first consideration is whether ERD is an innately easier response than ERS to generate? Especially in the case of subjects with

substantial alpha power at rest, the neural system may struggle to substantially increase neural synchrony above this baseline level whereas removal of the pre-existing synchrony can readily generate a large ERD.

One main difference is naturally that in the introduction to this chapter the focus on Posner tasks for studying alpha was identified. Posner tasks, and the vast literature that uses them (Thut et al, 2006 Rihs et al, 2007; Romei et al, 2008a; Romei et al, 2008 b; de Graaf et al, 2013; Marshall et al, 2015; Mazzetti et al, 2019), focus on measuring the changes in alpha in NTRRs for a few hundred milliseconds post the cue presentation and prior to the stimulation period. In our experiment, however, we were measuring alpha during the stimulation period itself. Our data suggests that longer-term (4 seconds) sustained alpha ERS are not common across the cortex and that alpha-inhibition may be more suited to brief (~200ms) synchronisations. Posner himself found that the effect of the cueing on the allocation of attention only lasted a few hundred milliseconds (Posner, 1980). Here the findings simply highlight the difference between the visual lateralisation tasks and the sustained attention tasks; in this experiment sustained alpha ERS was harder for participants to achieve and likely reflects different mechanisms in attentional control.

Another possibility is that alpha ERS is linked instead to the 'need to inhibit'. By this, we mean that inhibition is functional and where/when it is not required it won't be presented (Klimesch, et al, 2007). This is supported by the single modality somatosensory stimulation condition being the most difficult behaviourally (with only a 40% accuracy rate) and being the only condition to successfully generate a significant alpha ERS across the visual cortex for a period of 4 seconds. The other conditions had accuracy rates that were closer to double or above chance level suggesting that a greater level of difficulty across all conditions to a 40% average accuracy rate may have generated consistent alpha ERS in NTRRs for the 4 seconds sustained

period across all conditions, therefore it appears the alpha ERS does not share this characteristic.

Differences between NBRs and ERS

I propose a series of arguments to explain the different results regarding inhibitory signals in NTRRs observed between chapter 2 and chapter 3 despite them sharing the same paradigm. Firstly, that whilst the NBR is modulated by task difficulty (Hairston et al 2008), it is also commonly seen in response to passive stimulation with no requirement to perform a task, or even to attend (Shmuel et al, 2002; Pasley, Inglis, Freeman, 2007; Kastrup et al, 2008). NBRs, therefore, last for the entirety of the stimulus presentations as we saw in chapter 2 and it is usual for the HRF to last over fifteen to thirty seconds (Logothetis, 2001), however, alpha ERS is strongly implicated in the control of attention and information flow over shorter periods of time i.e. under a second (Jensen and Mazaheri, 2010; Hanouneh et al, 2018). Additionally, NBRs are a slow-changing haemodynamic and metabolic function taking thirty seconds or more to reset (Logothetis, 2001), whereas the alpha ERS responses we see are highly variable and sporadic, in most conditions, and as such may present a true but brief neural inhibition and a correlated NBR would take seconds, not milliseconds, to evolve.

The second potential argument is that while inhibition does occur during this paradigm as seen both by the wider literature (Klimesch, Sauseng, and Hanslmayr, 2007 for review) and in the previous experimental chapter that does not mean that NBRs and ERSs are directly comparable. NBRs and alpha ERS do have fundamental differences in their metabolic functions, NBR reflects a local reduction in blood flow and metabolism (Logothetis, 2001), while alpha ERS reflects an increase in neuronal synchrony. This increase in neural synchrony should be involved with a greater level of neuronal firing and demand for metabolites, particularly oxygenated blood but instead we see a NBR which represents a ratio of oxygenated

and deoxygenated blood with a greater percentage of deoxygenated blood than baseline. Despite the strong links between inhibition and alpha in the literature, it is known that alpha alone cannot explain the whole mechanism. Indeed, NBR has been shown to be accompanied by a decrease in gamma frequency local field potential activity (Shmuel 2006; Boorman 2010, 2015) therefore it is possible that the key signature of inhibition originates from ERD of high-frequency activity.

Alpha ERS is also normally measured in short millisecond time frames across the literature (Klimesch, Sauseng and Hanslmayr, 2007 for review) but while present some evidence of a shared neural mechanism between the NBR and alpha responses seen in sustained checkerboard, auditory tones, and MNS paradigms (Mayhew et al, 2013; Mayhew et al, 2014; Mullinger et al 2014; Mullinger et al, 2017) there is not yet a comprehensive theory explaining the relationship between the two responses. In chapter 2 we saw replicable PBRs in stimulated regions and NBRs in non-stimulated regions but in this chapter, we only saw ERD in stimulated regions and a significant ERS in only one condition, with isolated examples in a few subjects in other conditions. The NBR in non-stimulated regions was also very replicable and showed limited between-subject variability. Figures 3.3 to 3.12 show the vast variability of the alpha power responses in NTRRs with some participants even presenting neural behaviour closer to desynchronisation of alpha in NTRRs rather than ERS as the alpha inhibition hypothesis predicts (Klimesch, Sauseng, Hanslmayr, 2007). A potential answer to the question of why the alpha ERS response was more variable and not as replicable, as the NBR is because of the spatial smearing of the EEG response due to the natural issues with volume conduction through the skull. Replicable alpha ERS responses have been measured in both EEG and MEG (da Silva, 2013) so spatial smearing does not negate the ability to measure ERS but in this case, we observe that in many cases the ERD response was so widespreadthat it may explain the poor ability to localise significant ERS. While LCMV beamforming was used to localise the

source of the neural signals and provide a virtual electrode inside the headmodel there is still smearing across the participant response. The beamformer maps shown in Figures 3.15 to 3.18 show that ERD response particularly to visual trials was very widespread and encompasses the entirety of the occipital and parietal cortices and extends into the frontal motor/somatosensory regions also which impaired our ability to separate signals from the two sensory systems and to measure somatosensory ERS alongside visual ERD. Only in the Somatosensory/Visual condition where the targets were in the somatosensory stream did we see a visual ERS due to a relatively localised somatosensory ERD.

Limitations

There are also potential limitations to the experiment which could explain the different findings. The first limitation is the difference in location between chapters 2 and 3. The participants in chapter 2 underwent the experiment in an MRI scanner and while it is a noisy and not very comfortable environment it is isolated, and subjects can easily focus on the task requirements. The experiment of chapter 3, however, was recorded with the participant sat upright in an experimental room at Birmingham University Imaging Centre which was not soundproofed meaning potentially distracting noises could be heard from the corridor, MRI, participant preparation area Participants were given earphones to help reduce distraction from outside noiseAdditionally, the experimental procedure required that experimenters came in after each run of the experiment to reset the task and check on the EEG's cap readings. This means instead of a pure one hour or more of focus on the task as found in the fMRI experiment where everything was automated from the participant's perspective the EEG experiment involved greater distractions, delays, and interruptions. We did not consider these distractions as having a direct effect on the task performance both behavioural and more importantly neuronally. We only saw significant difference in the beahvioural scores during somatosensory or auditory/somatosensory conditions which matches the same increased difficulty in

somatosensory trials that we saw in Chapter 2 in table 2.2. However, the lack of replication leads us to conclude the different environments may have been a confounding factor.

Another confounding factor was that the EEG experiment was longer than the fMRI experiment. The fMRI experiment lasted 90 minutes of testing, including the explanation of the experiment and the application of the MNS before the participant entered the scanner. The EEG experiment was close to 150 minutes long with the participant having to sit for an additional thirty minutes for the application of the EEG cap, MNS, and preparation of the experiment along with the stimulation trials, resting trials, and eyes opening and closing trials. This extended time for the entire experiment with set up and all the runs was compounded by the aforementioned distractions and delays due to setting up new runs of the conditions. This means the participants were not directly comparable in their experience and increased boredom, mental fatigue could again have altered how the participant responded to the task. In their 2018 review Raffaelli et al 2018 discussed that increased alpha is correlated with both increased reported boredom by the participant and the feeling of mental fatigue but not directly the desire to sleep (Raffelli et al, 2018). As such the described conditions and length of the experiment may have resulted in increased alpha power and a skewed recording in the later trials.

The final limitation of both this experiment and equally chapter 2 is that the experiments were conducted separately, and the analysis is between participants instead of within-subjects. This was done due to time limitations during the first year of the Ph.D. and because of requirements to provide training on EEG and fMRI separately before combining such a study. We assumed due to the high replicability of the inhibition literature (Klimesch, Sauseng and Hanslmayr 2007 for review) and the evidence of a shared commonality between alpha ERS and NBRs (Mayhew et al, 2013; Mayhew et al, 2014; Mullinger et al, 2014; Mullinger et al, 2017) meant that comparison between participant groups would not invalidate the study and a combined

EEG-fMRI study was not strictly needed. This assumption did not bear fruit in the actual results.

Future experiments

To test this experimental paradigm in the future I suggest three experiments. The first experiment is to test people on a simple paradigm with only visual, auditory, and visuo-auditory stimulation to compare ERS in the somatosensory cortex. The relevant alteration is to reduce the complexity of the experiment and allow for a simple comparison of conditions. This will provide a greater understanding of the variability of ERS responses to different trials. If the large variability in responses that we see in Figures 3.3 to 3.12 was also seen in this proposed experiment, then separation of the group into 'higher synchronisers' and 'low synchronisers' should be done to measure if this change in neural behaviour shows any difference in behavioural scores. With this experiment completed the next experiment can be conducted.

That is to conduct the experiment again using EEG-fMRI to allow for more direct comparability of the inhibitory neural behaviour as measured through both EEG and fMRI using a within-subject comparison rather than a between-subject comparison as was done here. This has been discussed as a limitation of the experiment in the above section and a combined study with an equal number of participants as chapter 2 and chapter 3 combined would allow for easier within-participant comparisons and be able to partial out participants with low inhibitory responses i.e., participants who present ERD in NTRRs. While above it is expressed that the length of the experiment is a concern and making the paradigm an EEG-fMRI would only lengthen the experiment a suitable modification would be to run shorter sessions over two days. This would reduce participant fatigue and provide participants with the best chance to perform at an optimal capacity.

The final experiment can be added as a modification to either two of the above. That is because we see the only repeatable alpha ERS in the single somatosensory condition and that condition was the only condition with performance marginally above chance we can conclude that task difficulty played an important role. I propose adding a staircase paradigm that would increase and decrease the task difficulty to match participant performance but not just to be marginally above chance but allow for a systematic measure of the participant performance and correlated task-relevant region ERD and NTRR ERS at each interval of training (10% intervals from 0% accuracy to 100%).

Conclusion

In conclusion, this experiment failed to measure NTRRs ERS during most sensory conditions. We attribute this to the high variability in ERS responses, smearing of the ERD response reducing the ability to measure ERS responses, and differences in the set-up and procedure of chapters 2 and 3 which were not part of the experimental stimulation paradigm. The chapter has suggested follow-up studies and corrections to reduce these errors. On a final note, while the experiment did have to accept the null hypothesis the high variability of the ERS response in comparison to the NBRs in chapter 2 is a very interesting finding. The literature to date has ignored individual variability in the alpha response across healthy populations and further corrections and updates to the alpha inhibition hypothesis (Klimesch, Sauseng and Hanslmayr, 2007) would greatly benefit from a review of how individual differences alter the use of functional inhibitory alpha.

Chapter 4 – Does the use of inaccurate cues and the requirement to react to distractors in real-time alter the expression of alpha oscillations in the visual cortex compared to accurate predictive cues?

Introduction

Alpha oscillations and proactive cueing

The allocation of attention has also been highly studied with relation to alpha inhibition (Foster et al, 2006; Rihs et al, 2007; Samaha et al 2016; Worden et al, 2000; Foxe and Snyder et al 2011; Klimesch 2012; Klimesch et al 2007; Romei et al 2008; Romei et al, 2010). As discussed in the introduction the use of inhibition is posited to be a mechanism for more efficient neural processing and the requirement for efficiency is greatest when focusing on a task (Klimesch et al, 2007; Thut, Nietzel, Brand and Pascual-Leone 2006; Bengson; Mangun and Mazaheri, 2012). Posner like tasks, discussed in Chapter 3, (Posner, 1980) have been used to ensure that the participant's attention is focused on the modality/location required (Corbetta, Kincade, Ollinger, McAvoy and Shulman, 2000; Eimer 1994; Hopfinger, Buonocore and Mangun, 2000; Mangun and Hillgard 1991; Wildegger, van Ede, Woolrich, Gillebert and Nobre, 2017; Gould et al, 2011; Worden et al, 2000; Rihs, Michel and Thut, 2007). More specifically, Thut, Nietzel, Brandt, Pascual-Leone (2006) found that when a participant was cued to lateralise their spatial attention on either the left or right side of their visual field (in anticipation of a subsequent target) there was a stronger alpha power in the ipsilateral visual hemisphere than the contralateral. This alpha lateralisation was associated

with poorer detection of targets that were delivered to the non-attended side. Additionally, Foxe, Simpson, and Ahlfors (1998) showed that when participants were cued to attend to a single modality during an audio-visual paradigm there was an increase in alpha power in the other, non-relevant, modality's cortex. This study however did not find any effect on performance and changes in alpha power. Van Djik et al 2008 provide supporting evidence for the effect of alpha upon sensory perception by showing an inverse relationship between the power of the alpha oscillation at the moment of stimulation and the ability to detect near-threshold stimuli. Additionally, alpha was implicated in the participant's ability to perform the task by detecting or not detecting near-threshold stimuli. Following this finding, Matthewson et al in 2009 presented evidence for the detection of a visual target being related to both the power and the phase of the posterior alpha oscillation. Matthewson found that during just one alpha cycle, 100ms, the probability of detecting a visual target altered between conscious perception when the alpha power was low and no conscious perception when the alpha power was higher (Matthewson et al, 2009). The effect of this effect over only one alpha cycle meant this inhibitory effect on conscious perception could occur during an ERP in response to a visual target and was called 'pulsed inhibition' by Matthewson (Matthew et al, 2009). Later the data on alpha phase and amplitude was presented in more concrete terms as the theory of gated inhibition by Jensen and Mazaheri in 2010. This theory postulated the phase and amplitude of the alpha oscillation served as a method for controlling the propagation of parcellated information through the gamma oscillation and providing a mechanistic theory on how information flow was controlled around the brain (at least in this context).

Alpha oscillations and 'reactive processing'

However, the above studies and reviews all focused on the "proactive" use of alpha inhibition to control attentional resources prior to the presentation of an anticipated task/target stimulus.

To clarify, the participants in these experiments (Thut et al, 2006, Gould et al, 2011; Worden et al, 2000; Rihs, Michel, and Thut, 2007 to name but a sample) were cued that a stimulus and distractor were upcoming with spatial and/or temporal information (e.g., left arrow cue indicating upcoming left-sided target). There was then an attend period of ~100-300ms during which alpha power was measured as the subject prepared to perform the task using cognitive mechanisms such as deploying spatial attention. There has been very little research into the role of alpha (and other frequencies) studying how we "reactively" inhibit ongoing distraction or interfering information e.g., during (reactive) the performance of a task (Marini et al, 2016; Sauseng et al, 2009; Vissers et al, 2016; Janssen et al, 2017) as opposed to before (proactive) the task (Kizuk and Matthewson, 2017; Van Diepen et al, 2015; Samaha et al, 2015). To be clear, by proactive we refer to anticipatory inhibitory mechanisms that occur prior to a subsequent task; and by reactive we refer to more spontaneous inhibitory mechanisms that occur concurrently with another task. This could include suppression of either: a) locations within a sensory field; or b) competing sensory modalities. In this chapter proactive will mean when the prior cue before the presentation of the stimuli is correct, reactive will be where stimuli are presented which were not properly cued for i.e., a visual/auditory presentation which only had a visual cue presented beforehand.

The value of research in alpha and reaction to distractors in ecologically valid scenarios is very clear. Distractors present themselves regularly throughout everyday life and ubiquitously in the presence of modern electronic devices i.e., maintain your attention on a visual presentation while your phone makes a notification sound. We know with adequate cues the neural response to the presentation of a tone, or a visual distractor can be inhibited but that is only with an appropriately timed proactive cue (Posner, 1980; Kizuk and Matthewson, 2017). The current literature, discussed above, on alpha inhibitory mechanisms however is not able to explain the inhibitory alpha responses that inform the functional

inhibition and control of distractors with no prior cues (reactive) to the same degree we can when a prior cue is given (proactive). One of the aims of this chapter is to begin exploring whether the alpha mechanisms, so well understood in proactive scenarios, also apply to reactive scenarios. This would aid understanding of alpha in more general behavioural circumstances.

To date, there is limited evidence in how the brain processes distractors both immediately and over a short period in a reactive manner using NBRs or alpha oscillations. This is closer to how a person in the 'real world' would use inhibition, by selectively focusing on a task, being distracted by, often unexpected, external stimuli and then managing to reorient and maintain attention on the desired stimulus until the task is complete. Kelly et al in 2006 showed that during a visual task with 8 seconds of sustained distraction of random letter sequences there was an interaction between the direction of visual attention and hemispheric alpha power with higher alpha power occurring in the opposite locale to the attention spotlight (Kelly et al, 2006). The stimulus was a presentation of bilateral flickering stimuli as distractors presented simultaneously and continuously alongside random visually presented letter sequences the participants had to react to. This is analogous to a Posner task discussed in the introduction and chapter 3 where cues before stimulus presentation are used to generate top-down attentional control (Posner, 1980). The authors concluded that over a sustained period alpha synchronisation occurred in non-task relevant visual regions as an active suppression system due to the difficulty of the task. In this study the presence of a distractor in every trial was certain, meaning subjects were anticipating it and cognitively prepared to suppress it and making it difficult to ascribes the results to fully reactive mechanisms, but it does highlight that the alpha inhibition hypothesis relates to sustained distraction suppression and not just post-cue lateralisation. Sauseng et al in 2009 looked at the presence of distractors and found that alpha power positively scaled with the number of distractors in non-relevant regions,

even when the number was not known prior to display (Sauseng et al, 2009). However, the presence of some distraction in every trial was known, meaning the study did not look at purely reactive processing of distractors but the reaction to the scale of expected distraction.

Janssen et al 2017 used a flanker task where 50% of the stimuli showed incongruent flankers which were used as distractors in an identification task (Janssen et al, 2017). There was no way to predict prior to the presentation if a trial would show congruent or non-congruent stimuli, effectively meaning that processing was reactive. A significant difference in lateralised occipital alpha was found between -100ms to 600ms relative to presentation, with the contralateral side showing higher alpha power during incongruent trials than congruent trials. Frontal theta power followed a similar pattern of showing a significant synchronisation at 150ms on incongruent trials which was not found in congruent trials. The authors saying by using a linear mixed effect model there was evidence for 'a direction influence of theta power on alpha power modulations' (Janssen et al, 2017, pg. 7). This suggests that in reactive processing the role of selective attention regulation is not limited to just the alpha oscillation, but that theta may play either a controlling or supporting role.

Furthermore, using fMRI, not EEG or MEG, Marini et al (2016) showed that compared to a baseline of pure tasks with no distractors there were differences in brain activity during a flanker task where the participants had to determine the direction of an arrow visually and respond with a button press. There were trial blocks with either 20% or 60% likelihood of distractors. In the 60% likelihood blocks, where the optimal strategy was to presume distractors proactively, they found activation of the dorsal frontoparietal attention network with positive correlations between middle frontal gyrus and positive behavioural scores in distraction filtering. This proactive mechanism was also shown to result in less activity in V1/V2/V3 during visual processing over distractor locations. In the 20% trials, where the optimal strategy was to process reactively s brain activation was found in the insula and

anterior cingulate but also the inferior parietal cortex bilaterally suggesting increased attention recruitment during this task, likely to monitor for trials to react and respond to but the evidence is only correlational. As mentioned, while found in a different imaging modality it presents evidence that the neural pattern of activation in response to unpredictable distractors is different from proactive congruent distractors.

The closest study to the particular question of whether similar or different mechanisms underlie the use of alpha in reactive vs proactive distractor processing was performed by Vissers, van Driel and Slagter in 2016. Vissers, van Driel and Slagter (2016) studied proactive vs reactive visual distractor processing using Sauseng's 2009 paper as a model. In their paper, they replicated the finding of proactive suppression of the irrelevant hemifield with a significant increase in prestimulus alpha power compared to baseline. However, this change in alpha power did not relate to a change in performance even after controlling for visual short-term memory. There was no significant change in alpha power which predicted behavioural responses. This was measured through the number of distractors in either the cued or un-cued hemifield. The authors concluded that as alpha power did not change as a function of performance or to the effect of distractors the findings 'do not provide evidence for a role of lateralized alpha oscillatory activity' in processing reactive distractors instead of proactively cued distractors.

There were some methodological problems with the Vissers' experiment which need analysis and argue towards the need for an experiment to test reactive vs proactive inhibition with a greater level of controls. Firstly, their analysis focused on the one-second period between the stimuli display and the recall and response period. As the participants were not being stimulated during this period and were required to maintain the stimuli/target array the primary function of this period is memory maintenance instead of isolating reactive processing of a distracting stimulus. As such any analysis during this period is not looking at

the processes for effectively filtering an ongoing and distracting stimulus in another modality. Furthermore, during a personal correspondence, Vissers informed us that the participants were able to predict when an irrelevant distractor would be coming up, and in what location, which suggests the task contained an element of proactive stimulation during these periods.

The current experiment will address this by contrasting trials featuring a target stimulus (non-reactive) with trials where a second, distracting, stimulus in a different modality is added at an unpredictable interval. Good task performance, therefore, requires reactive suppression of distraction. The reactive and non-reactive trials will begin in the same manner so at the start of the trial just the target modality stimulus is presented. The cue for the dual trials was a presentation of a capital letter (V or A) representing the dominant modality and the one to attend and respond to when vowels were presented, a lower-case letter (v or a) after the capital letter identified the inferior modality which was to be ignored. In the reactive trials, the cues were presented as a single capital letter which was the same as the single modality trials to trick the participant into thinking the upcoming presentation was only a single modality presentation. During the dual trials, both modalities were presented at once for the duration of the trial but only the dominant modality had to be attended to and required responses. In the reactive trial, the dominant modality would be presented from the onset of the stimulation presentation and continue alone until 40-60%, randomised, through the presentation at which point the inferior modality would also be presented to the participant, but they had to ignore this other presentation and focus only on the dominant modality. Only 30% of trials will be ‘reactive’ to ensure that the optimal behavioural strategy is not to prepare for a reactive trial on any given stimulation. A key feature of our approach is not just studying suppression of distractors during task performance, but also when they aren’t expected or predictable, simulating as close to a truly reactive scenario as possible. The intended analysis was comparing posterior visual alpha power during the stimulus period

comparing both the reactive and nonreactive trials. We decided to use a different modality distractor as it better matched our work and understanding of multi-sensory inhibition and regulation as seen in the previous chapters. It is possible to do this experiment with distractors in a different spatial area or just left vs right hemisphere and that will be discussed in the future experiments section at the end of this chapter.

Rationale and hypothesis

Rationale

Our rationale is that given the majority of the literature has focused on studying alpha mechanisms following proactive cues, the use of alpha in more ecologically valid, reactive protocols has been left unexplored. If the regulation of distractors in a reactive scenario does not use alpha oscillations in a similar manner to that of proactive distractors the effect of the alpha inhibitory hypothesis would appear to primarily reflect a proactive inhibitory effect. This experiment will present reactive cues which are both only present in 30% of the trials in a given run and also unpredictable as to the length of the distractor during the stimulus presentation in-trial. This will allow us to measure the different alpha responses when comparing between dual-modality conditions where the secondary distractor modality was proactively cued vs reactively processed. We will be studying both the different responses in the distractor modality but also how non-task-relevant regions present alpha synchronisation. We are using a MEG system for this experiment, instead of EEG, because we want the best chance of extracting distinct neural responses from multiple concurrently active cortical areas and we want to reduce the effects of spatial smearing of neural activity that we observed in chapter 3. This would have been the ideal setup for Chapter 3 also, but a MEG system was not present at BUIC during the time the experiment was run.

Research Questions

Our research questions for this experiment can therefore be laid out as:

RQ1: Is there a significant difference in the alpha power stimulus-response of the visual region when comparing proactively cued dual-modality tasks and reactively cued dual-modality tasks?

RQ2: Does the dominant modality the participants have to attend to during the task alter the alpha power in the visual system during the task? Or phrased another way, is there a significant difference in alpha power when the dominant modality is visual compared to auditory?

Methods

Nineteen (avg. age = 19.1 (years), M = 7) participants were recruited to take part in this MEG study. All were University of Birmingham students either in undergraduate or postgraduate study. Participants were all in good health, had normal hearing and required no assistive devices and had normal or corrected to normal with MEG compatible glasses to correct eyesight to normal. This study was conducted with the approval of the University of Birmingham local ethics committee and all subjects provided informed consent. We received ethical permission to conduct MEG data acquisition, psychophysics experiments and collect T1 anatomical scans. All participants were briefed on the procedures of the MEG, fMRI, and behavioural elements of the experiment.

Paradigm

The paradigm involved the detection of vowel letters presented amongst consonants. Letters were presented in either the visual or auditory modalities and often in both. In the visual modality, the letter was presented as a black letter on a grey screen which was 1m away from

the participant. The auditory modality had letters presented as single spoken letters through MEG compatible SoundPixx earphones using a pre-recorded custom mp3 file.

In each trial, six letters were presented, at a rate of 1Hz, throughout a six-second presentation period. The consonants ‘W’ and ‘H’ and the vowel ‘O’ were not included as the pronunciation time was longer than 500ms and did not fit into the presentation format. The letter ‘Y’ was also excluded because while it is formally a consonant it can function as a vowel and we did not want to confuse participants, particularly any non-native English speakers.

There were six conditions. In all cases, target vowel letters had to be identified amongst distractor consonants. The different conditions were these:

1. Single modality visual trial
2. Single modality auditory trial
3. Dual modality stimulation, both visual targets and auditory distractors throughout (Not reactive)
4. Dual modality stimulation, both auditory targets and visual distractors throughout (Not reactive)
5. Visual targets throughout with un-cued auditory distractors (Reactive: visual dominant, auditory inferior condition)
6. Auditory targets throughout with un-cued visual distractors (Reactive: auditory dominant, visual inferior condition)

In single trials (conditions 1 and 2) only one sensory modality was presented during the trial. In the dual-modality trials (conditions 3, 4, 5, and 6), the visual and auditory items were presented at precisely the same time to maximise interference. During dual-modality, non-

reactive, trials (conditions 3 and 4) the distractor stimuli were presented throughout the whole six-second stimulus duration. During reactive trials (conditions 5 and 6) the distraction, inferior, modality stimulation was commenced at a random interval between 1.5-2.5 seconds after the start of the target stimuli, meaning that the distraction was sustained for between 4.5 and 3.5 seconds respectively. Stimulus periods were separated by a 6-second resting fixation (baseline) period, meaning each trial takes 14.5 seconds and had a 1 second cue period and 1.5 second waiting period between the end of the cue and the presentation of the stimuli.

Trials were presented in a pseudo-randomised order in four separate runs, each lasting 13 minutes. Cues were presented before each condition to notify the subject of which sensory modality to attend to for target detection. In the single and dual-modality conditions, the cues were presented as 100% accurate information using the same cueing method as chapters 2 and 3 i.e., V for visual and Va for visual/auditory with visual being the dominant modality with targets. In the reactive trials, the cue period was presented as though the trial would be a single modality condition as to not inform the participant of the additional modality and thus make any response and inhibition of the competing information reactive. In a reactive trial with a visual dominant modality and an auditory set of distractors, only a V would be presented in the cue period before the stimulus presentation.

We conducted four runs of the task (9 minutes each) per participant and also collected two 3-minute visual and auditory localiser tasks, featuring unimodal stimulation (8Hz black-white checkerboard, 8Hz 1kHz auditory tones) to facilitate localisation of sensory cortex ROIs during analysis

The non-reactive trials (conditions 1-4), single visual stimulation, single auditory, visual-auditory dual, and auditory-visual dual were each presented 8 times in a single experimental run. The reactive trials (conditions 5 and 6), visual-auditory reactive and auditory visual

reactive, were presented 6 times per run so they were marginally less likely than the dual conditions, and as such, it was not optimal for subjects to expect that a given trial would be reactive. Over all four runs, the participant was presented with 32 trials of each non-reactive and 28 trials of each reactive condition in total.

Target vowels could be presented at any point in the 6-second stimulation and were equally distributed between all possible time-points in conditions 1-4. In the reactive trials, to maximise the effect of distraction, the target stimuli were always presented during the reactive stimulus period, rather than before it occurred.

Responses to the identification of a vowel were given through an immediate button press. This was to ensure there was no memory element involved but instead, response signals would be limited to the somatosensory cortex which can be easily measured by MEG and isolated from occipital responses and therefore controlled using ROIs in the analysis. Research by Klimesch et al 1997, 1999; Huang et al 2013 have shown a phasic relationship during working memory tasks between the hippocampus and sensory cortices which would be a more confounding artifact through all of the stimulation. This reasoning means we did not provide the response period after the trial presentation so there was no need for memory encoding, maintenance, and retrieval periods which would cause interference in the visual cortex.

An additional condition had two target vowels, which were included to ensure participants were sustaining attention throughout the whole six-second period to prevent them from switching off after a single target was presented. There were two each of these presentations in visual-only, auditory-only, visual-auditory dual, and auditory-visual dual. As such, these double-target trials accounted for 10% of all trials over the course of a run.

The paradigm was designed to look at the effect of reactive processing of distractors during the rapid presentation of two different, competing stimuli while providing the minimal level of neural excitability possible (see below). The stimuli were a serial presentation task of visual and auditory letters at 1Hz. Identification of targets could be completed even at 10Hz, Shapiro, Raymond, and Arnell (1994) but due to the attentional blink lasting 500ms following attending to a target vowel were spaced more than 500ms apart (Nieuwenstein & Potter (2006). Auditory letters were recorded spoken letters. The letter lists for both the auditory and visual presentations were the same. This paradigm required the processing of two simultaneous streams of competing information with the same qualia (English letters during a linguistic discrimination task) resulting in a highly interfering task, e.g., requiring suppression of auditory interference during the performance of a visual task, and vice versa.

For the dual-modality conditions where the visual modality was the distractor (inferior) to reduce the intensity of the stimuli (and cause a minimal change in the desynchronization of alpha during a period where we want to measure alpha synchronisation as that area is non-task relevant), low contrast grey target letters were used as to not cause unwanted excitation because of a stark contrast between foreground and background. The Michelson contrast was 4%. In the visual inferior condition, the visual stimulus had an increased Michelson contrast of 52% between the item and background to make it pronounced and noticeable, and hard to ignore. All visual letters including cues and stimuli were presented in the centre of the screen at the same location as a fixation cross. They were 2.5cm tall in size and viewed at a visual angle of 1.43 degrees.

When calculating responses, we calculated that a participant had correctly identified the target if they responded up to 1500ms after the presentation of the target. This was done because during pilot testing participants on average scored only 6.2% of the response was required while the letter was still on the screen (i.e., within 500ms). Once we expanded the

response period to include the next stimulus presentation (to a total of 1500ms) performance improved to near ceiling in some cases (see results table 4.1 below).

MEG data were continuously collected using the CHBH Elekta TRUIX system (306 channel, 102 triple sensor elements) with a sampling rate of 1000Hz and a lowpass filter at 330Hz. Subjects were seated in the upright position.

Protocol

Participants were screened for suitability to be recorded by a MEG machine. Participants were demetalled and briefed on the experiment. All participants gave their informed consent after reading the information sheet and agreed to be part of the MEG session as well as to have a T1 anatomical scan taken and informed of their rights during the experiment like confidentiality and right to withdraw. Participants had head coils placed on their scalp with one behind each ear as well as one on each side of the temple above the eyes with approximately 5cms apart and one placed on the clavicle bone which was not used to monitor head position but was placed there to avoid interference during the experimental trials. The coils were kept in place with medical tape that was non-reactive to the skin. Participants had a digitisation taken with a Polhemus which was used later to co-register the MEG sensors with a T1 anatomical.

Participants sat in an upright 90-degree position with MEG compatible Soundpixx earbuds, and a screen with a projected image presented using a Vpixx projector at 60Hz reflected with a mirror at 90 degrees from a projection port perpendicular to the sitting position of the participant.

Participants were debriefed at the end of the experiment. Participants were booked for a T1 however after the MEG experimental session nine participants used their right to withdraw to not have a T1 taken. For the sake of obtaining the best data 20 further hours were requested

from the CHBH to scan 10 more participants and obtain both MEG and T1 data from the same participant in order to have BEM models made for each participant. This was granted and participant attrition was seen as an unavoidable factor however the extra data collection was scheduled for April 2020 onwards with postgraduate students set as the ideal recruitment population but the COVID pandemic and UK lockdown from March 2020 to July 2021 made this not possible. This means we did not have the intended number of 20 participants with T1 anatomicals.

Data Analysis

The data were exported and analysed using in-house code and the Fieldtrip software package (http://fieldtriptoolbox.org/) (Oostenveld, R., Fries, P., Maris, E., Schoffelen, JM, 2011) in Matlab 2020b. The double target trials were not included in further analyses due to the small number of trials lacking statistical power and we did not want to include them into any other single target condition's data. The data for conditions 1-6 were segmented into single-trial intervals of twelve seconds, with t=0 representing stimulus onset and t=12 the end of the resting baseline period. The last three seconds from within the stimulus presentation period were taken to be used as the active period. Three seconds, taken from 2-5s of the six-second baseline period between trials were also used as the passive period for the beamformer analysis. We sampled three seconds from the middle of the period to reduce artifacts from the end of the previous trial or anticipation of the upcoming cue and trial. The data were visually inspected to remove any outliers trials or sensors (any channel corrupted with a signal over 100 Hz indicative of high impedance) or clear muscle artifacts and an independent component analysis was also used to remove any external noise components i.e. mains electrical signals, and eye blinks from the data (Bell & Sejnowski, 1995, Amari, Cichocki & Yang, 1996).

9 subjects did not have a BEM model made as they exercised their right to withdraw from the study during the T1 acquisition period and so single sphere models were constructed for all of the subjects and used for beamforming (Vrba, 2002; Henson et al, 2009). While BEM models have been identified as superior (Brookes et al, 2007) spherical models can provide adequate modelling for visual cortex studies (Vrba, 2002; Henson et al, 2009) and were deemed a suitable compromise given the COVID-19 quarantine and the inability to source more participants. Data were filtered into the alpha (7-13Hz) frequency band. An LCMV beamformer (Van Veen, Van Drongelen, Yuchtman, Suzuki, 1997) with a regularisation factor of 3 was used to localise alpha ERD in the primary visual cortex based on the localiser task participants completed at the beginning of the experiment.

The spherical headmodels were matched to ROIs that were defined in the left and right hemispheres of the visual cortices based on the peak ERD response to the visual localiser task. Sourcemodels were taken as the outputs of the analysis and used for the definition of VE locations in the right and left primary visual regions. Pseudo-t-statistic maps of differences in source power between active and passive periods were calculated which allowed identification of the peak (largest magnitude) alpha ERD and ERS responses. For each subject, the VE timecourses were then extracted from these locations across every run, epoched into single trials and the magnitude of the Hilbert transform was used to calculate the average alpha power for the stimulus period and the baseline period in each condition. The means were then baseline corrected for condition-to-condition comparison.

Firstly, we analysed the behavioural data by taking the means of each participants' performance across all the trials per condition and then by averaging per condition. We show the mean accuracy per condition as well as the standard deviation in Table 4.1 below. We did the same analysis on reaction time too showing the mean reaction times and standard deviation per condition also in Table 4.1 below.

As the main hypothesis tested whether there was a difference in alpha power between dual and reactive trials, we focused our analysis on comparing between dual trials and reactive trials with a corresponding dominant modality i.e., Va dual vs Va reactive, or Av dual vs Av reactive.

While we did sample VEs from both hemispheres the display was bilateral, so we took the alpha power from the left hemisphere and more specifically the left visual cortex. Additionally, we had originally intended to analyse the auditory region as another task-relevant region, the parietal region for its involvement in attention control particularly with distractors (Romei et al, 2011), and the somatosensory region as an accessible measurable NTTR. However, due to the lack of BEMs across participants, we could not confidently apply atlases to the sphere models created and focused solely on studying the visual cortex where the strong visual/parietal ERD to the visual stimuli provided greater confidence in identifying the posterior alpha response. Further discussion of this and other analyses we were unable to do is covered below in the Limitations and Future Research section in the Discussion.

Paired t-tests were conducted to compare each condition with the average of compiled baseline periods following the respective conditions. Paired t-tests were also conducted to analyse the conditions Va Dual, Va Reactive, Av Dual, and Av Reactive conditions against each other. Tests were run to compare Va and Av against each other both with the reactive conditions paired and the dual conditions paired to see if cue type resulted in a significant difference, see more in Table 4.1 below. Tests were also conducted comparing Va and Av against each other with Va_Dual and Av_Dual being compared and again for Va_Rec and Av_Rec to analyse for significant differences when the dominant modality was different, but the cue type was the same. The p values were corrected with the Holm Bonferroni method (Holm, 1979) when significant and can be found in Table 4.1 below.

Results

Behavioural results

The behavioural results show that the accuracy of the task was near ceiling and participants were easily capable of completing the task above chance level (Table 4.1 below). We also see that the hardest task was the Auditory/Visual Reactive condition with a reduction of accuracy to 68.45% for the Auditory/Visual Reactive condition which showed the lowest performance from 96.42% on average over the other conditions. This highlights how the distraction of the visual elements on the screen when not cued adequately was a more distracting event than the auditory presentation. Interestingly, while Av Reactive did have the longest reaction time at 0.6 seconds it was only differentiated from the fastest condition, Va Reactive, by a minimal difference of 0.06 seconds. In this case, we do not see a reduction in reaction time but a considerable reduction in accuracy.

Condition	Mean accuracy (%)	The standard deviation of accuracy scores (%)	Mean reaction time (s)	The standard deviation of reaction times (s)
Visual Only	99.2	2.12	0.55	0.04
Auditory Only	92.85	9.57	0.58	0.08
Visual/Auditory Dual	96.87	4.9	0.56	0.04
Auditory/Visual Dual	94.07	8.2	0.57	0.06

Visual/Auditory Reactive	99.13	2.28	0.54	0.04
Auditory/Visual Reactive	68.45	33.34	0.6	0.05

Table 4.1. Group average behavioural scores for each condition are presented as the accuracy of responses and standard deviation of responses and the reaction times for responses as well as the standard deviation for responses.

Single-sphere sourcemaps of visual region responses

The sourcemaps below were taken from 3 representative participants show spherical models of the participant's visual ERD to all conditions (1,3 and 4) that featured a visual stimulus throughout, providing an example of the beamformer's localisation of responses in this task. Although the t-tests shown in tables 4.3 and 4.5 do not show significant ERD from baseline the maps themselves do show the visual regions responded to stimulation with a decrease in posterior alpha power.

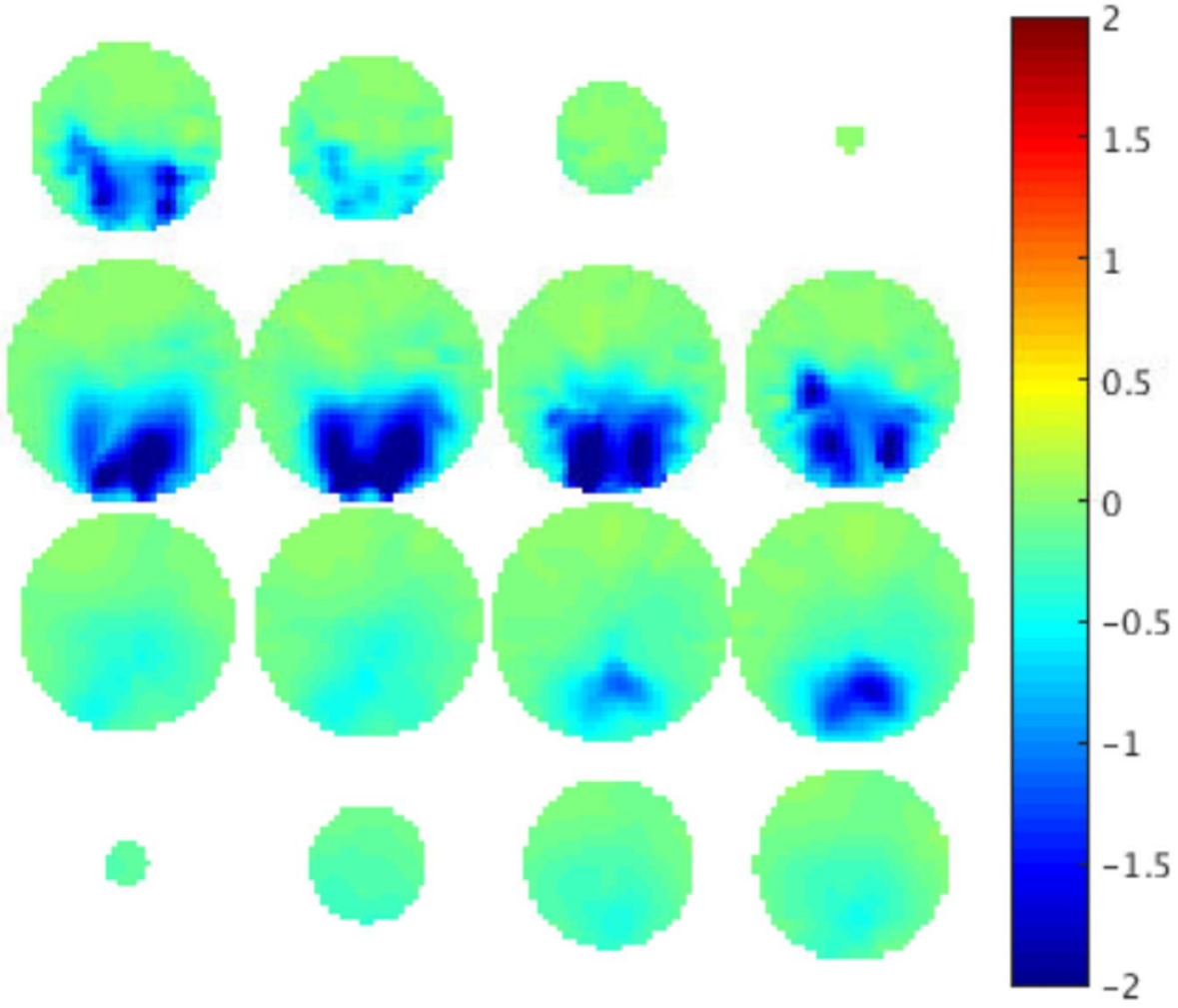

Figure 4.1. *Subject 9's visual response presented in a slice view. 16 slices were taken evenly spaced through the sphere. The lowest slice is bottom left and the highest slice is top right.*

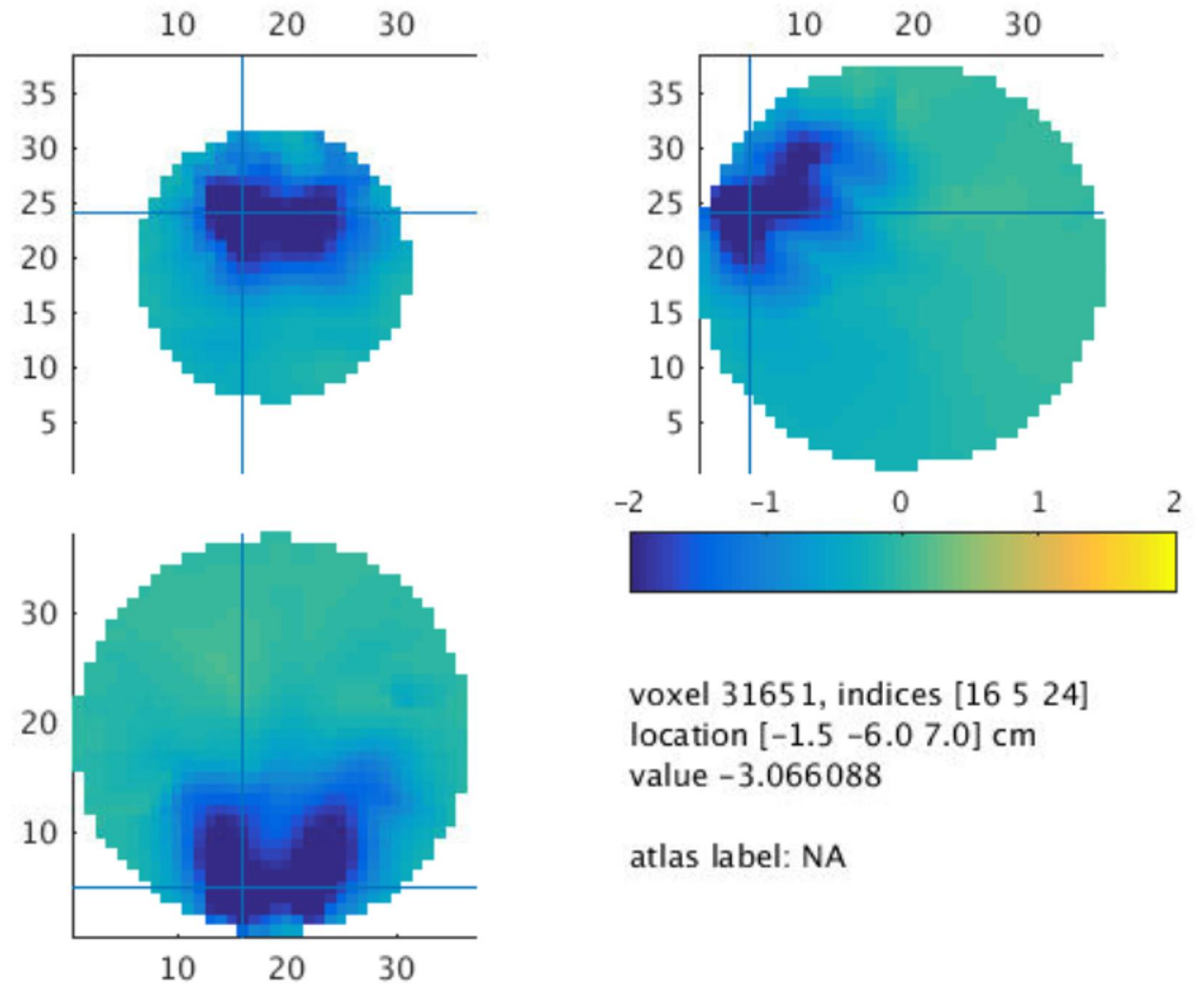

Figure 4.2. *Subject 9's sourcemap showing in the coronal view (top left), sagittal view (top right), and axial view (bottom left). The figure shows an alpha ERD in the upper posterior portion of the sphere over the visual/parietal cortex.*

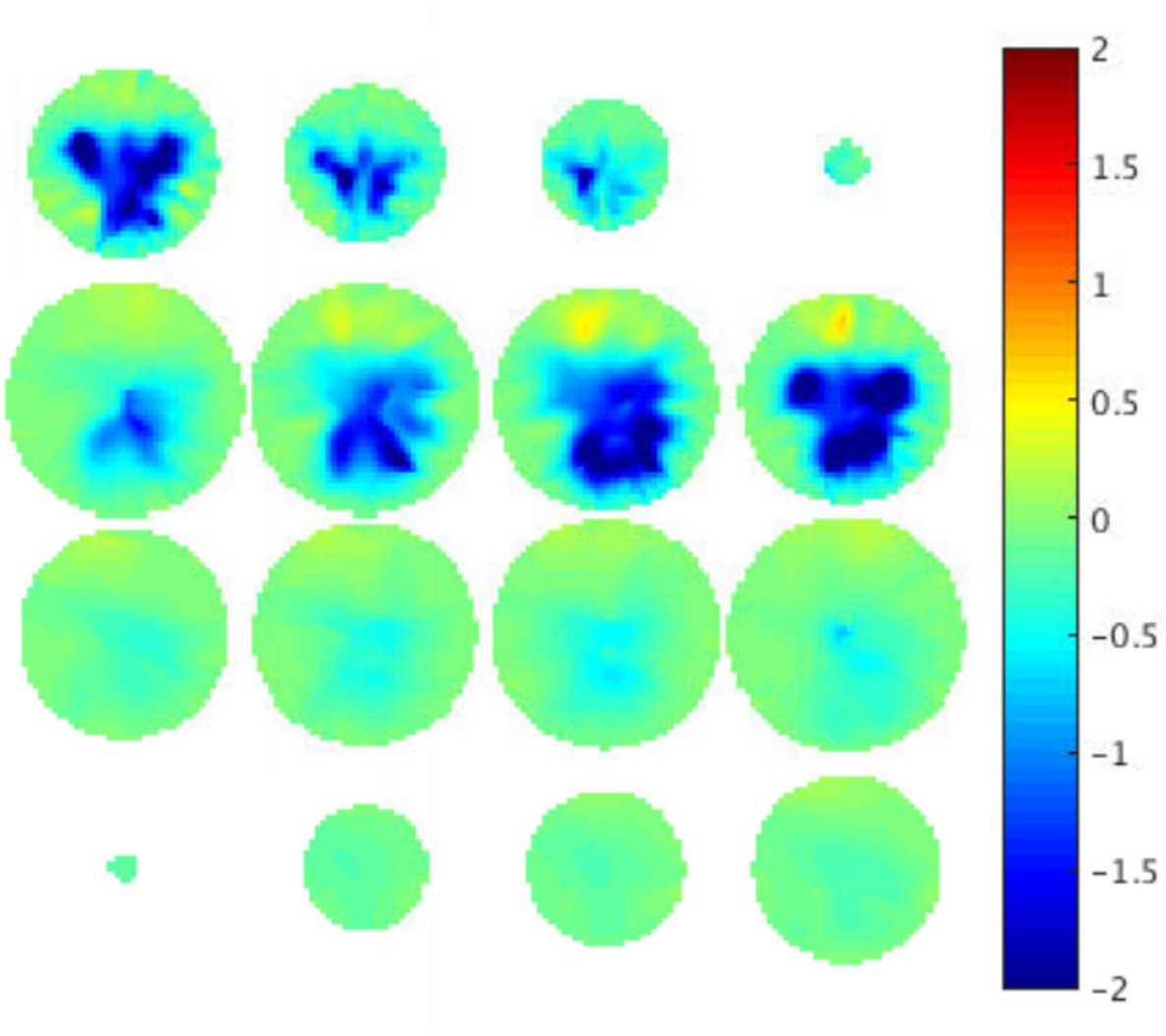

Figure 4.3. *Subject 14's sourcemap showing a visual and parietal region ERD with an ERS more anterior and dorsal. The scale to the right of the figure is the pseudo-tstat with a scale from -2 to +2.*

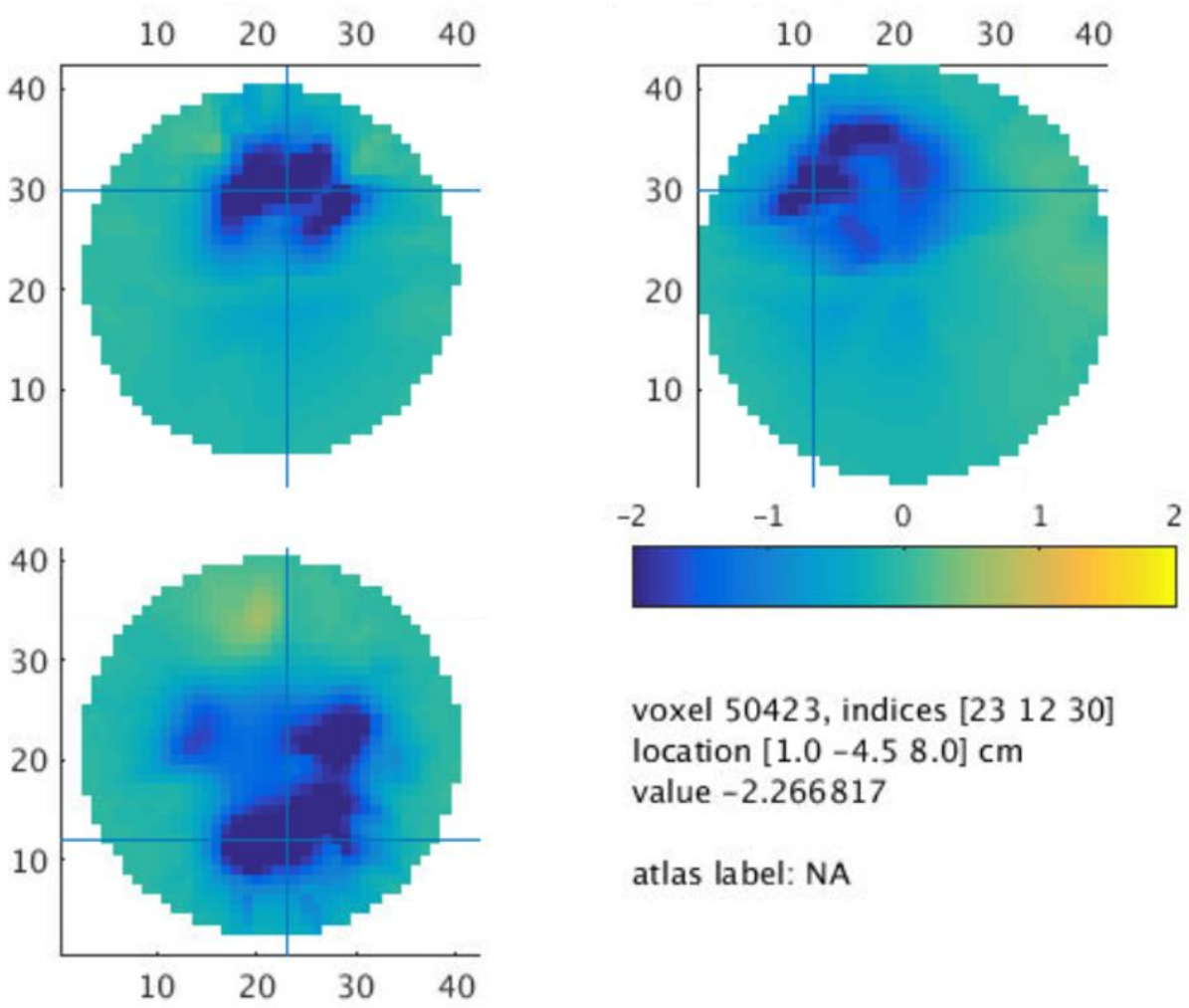

Figure 4.4. *Subject 14's sourcemap showing in the coronal view (top left), sagittal view (top right), and axial view (bottom left). The figure shows an alpha ERD in the upper posterior portion of the sphere over the visual/parietal cortex but more anterior and dorsal than subject 9 with an ERS again more anterior and dorsal than the visual/parietal regions' response.*

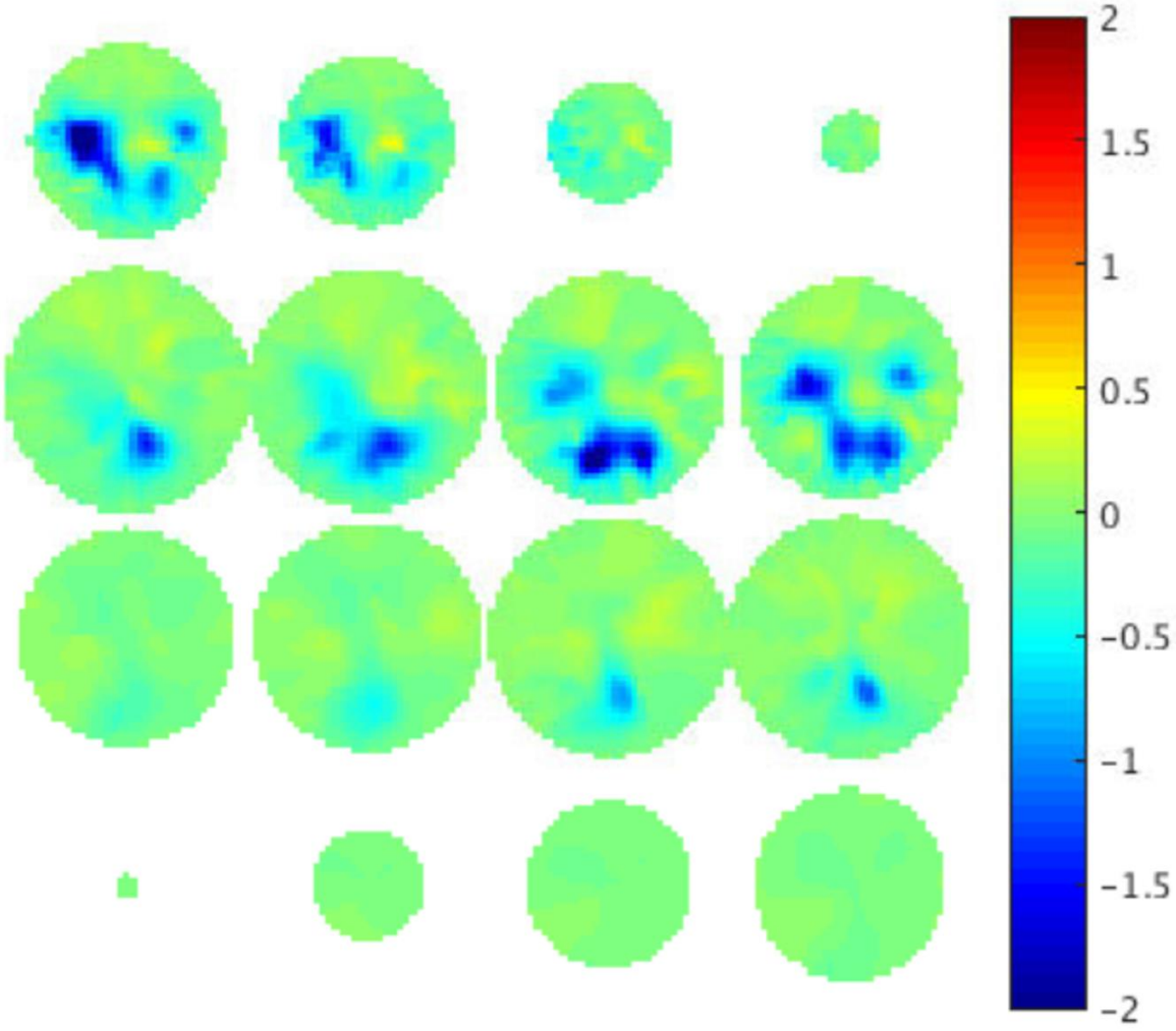

Figure 4.5. *Subject 16's sourcemap presenting a weaker visual ERD than participants 9 and 14 with the response centered more dorsally in the upper visual cortex. The scale to the right of the figure is the pseudo-tstat with a scale from -2 to +2.*

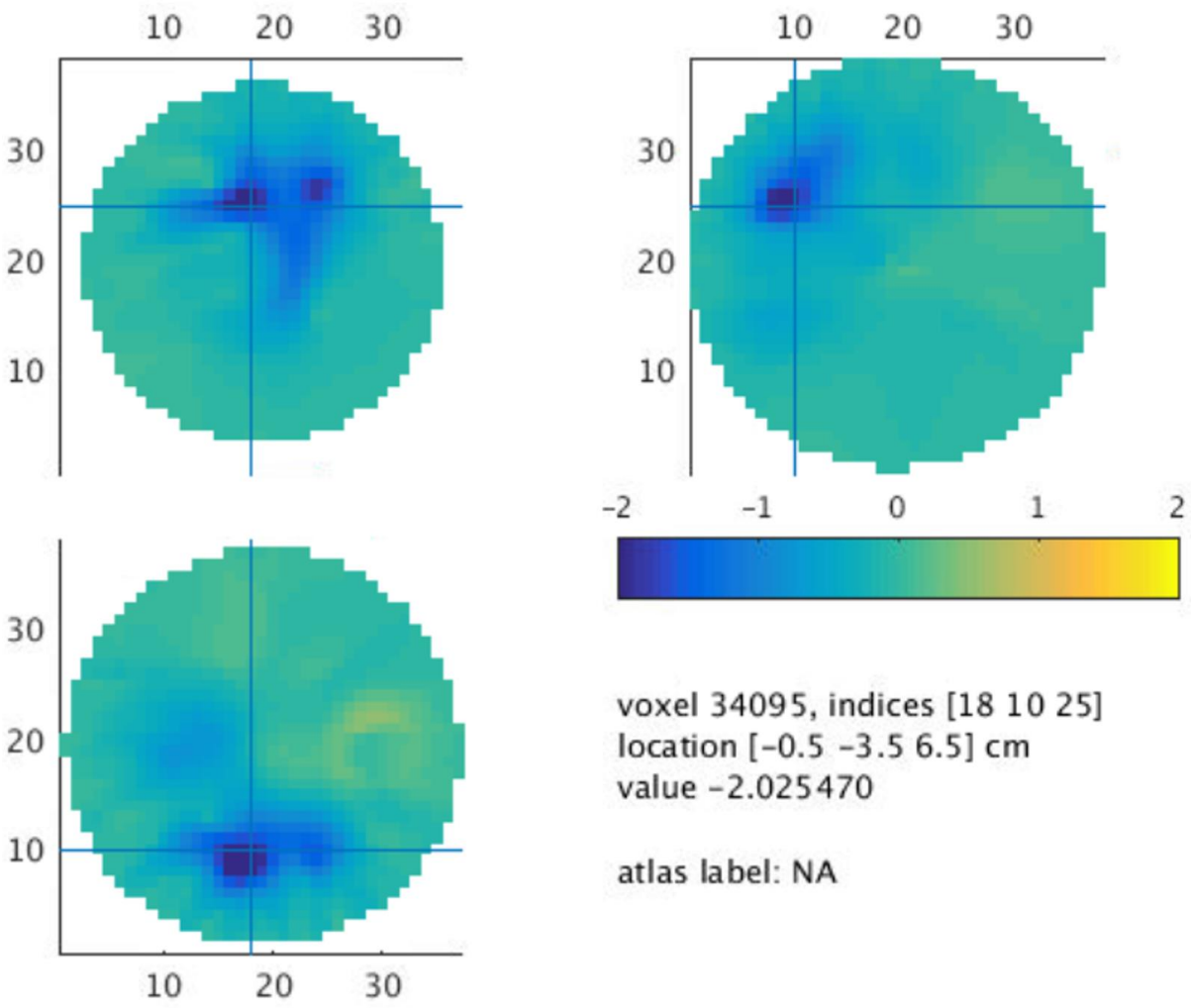

Figure 4.6. *Subject 16's sourcemap presented with the coronal view (top left), sagittal view (top right), and axial view (bottom left). The figure shows the same weaker visual ERD response as figure 4.6 above when compared to participants 9 and 14.*

Dual vs Reactive Visual Virtual Electrodes T-Tests

The results below in Table 4.2 show the alpha power in the visual cortex as the participants were in the baseline period suggesting a very minor effect of alpha desynchronisation during the stimulation. However, this decrease between the stimulation conditions and the baseline periods is also within the margin for standard deviation and the t-tests in Table 4.2 show the differences when comparing conditions to their respective baselines were not significant. The results in Table 4.4 show no significant difference between stimulus and baseline period for any

condition, after type 1 error correction. Since the paired t-tests in Table 4.5 for cue type and dominant type were all non-significant and above a p-value of 0.05 type 1 error correction has not been applied. The results show that alpha did not significantly vary between conditions and any differences in performance or the participant's ability to handle different cue types and distractors cannot be attributed to changes in visual alpha power.

Condition	Mean power (femtoteslas, fT^2)	Standard deviation (fT^2)
Visual Only	0.008	0.0046
Auditory Only	0.008	0.0036
Visual/Auditory Dual	0.01	0.0048
Auditory/Visual Dual	0.008	0.0039
Visual/Auditory Reactive	0.01	0.0058
Auditory/Visual Reactive	0.009	0.0048
Visual Only Baseline	0.009	0.0048
Auditory Only Baseline	0.011	0.0071

Visual/Auditory Dual Baseline	0.0105	0.0055
Auditory/Visual Dual Baseline	0.104	0.0058
Visual/Auditory Reactive Baseline	0.011	0.006
Auditory/Visual Reactive Baseline	0.012	0.007

Table 4.2. *This table shows the averages and standard deviations for the left V1 alpha response in femtoteslas. Both the response averages per condition and the corresponding baseline periods following the respective conditions.*

Condition/Comparison	P-value	FDR corrected P-value threshold	Significant?
Visual Only vs Baseline	0.089	0.016	No
Auditory Only vs Baseline	0.028	0.0125	No
Va_Dual vs Baseline	0.180	0.05	No
Av_Dual vs Baseline	0.011	0.008	No

Va_Rec vs Baseline	0.142	0.025	No
Av_Rec vs Baseline	0.21	0.01	No

Table 4.3. *Statistical significance (active vs baseline) of alpha power change in each condition using ERD-based VE's in the left V1 region. Baselines for each comparison are taken from the baseline periods following each respective condition.*

Condition/Comparison	Mean (fT^2)	Standard Deviation (fT^2)
Va_Dual – baseline corrected	0.0012	0.0041
Va_Rec - baseline corrected	0.0011	0.0041
Av_Dual – baseline corrected	0.0003	0.0048
Av_Rec – baseline corrected	0.0002	0.0044

Table 4.4. *The table below shows the average power per condition for Va_Dual, Va_Reactive, Av_Dual, and Av_Reactive after baseline correction. The standard deviation for each group has also been included.*

Condition/Comparison	P-value	Significant?
Va_Dual vs Va_Rec	.795	No
Av_Dual vs Av_Rec	0.887	No

Va_Dual vs Av_Dual	.243	No
Va_Rec vs Av_Rec	..296	No

Table 4.5. *Paired t-tests to analyse the statistical significance (active vs baseline) of alpha power change comparing Dual conditions against Reactive conditions and visual dominant conditions and Auditory dominant conditions. Baselines for each comparison are taken from the baseline periods following each respective condition.*

Discussion

This experiment studied whether there was a significant difference in the power of posterior alpha oscillations. We compared when participants were performing sensory target detection between conditions where subjects were accurately cued to proactively suppress distraction in a different sensory modality and conditions with inaccurate cues that meant participants had to reactively suppress distractors without warning. Our first research question was whether there was any significant difference in posterior alpha power when comparing proactive dual conditions and reactive dual conditions. We did not find any significant difference between conditions after type 1 error correction. The second research question was analysing if the dominant stimulus modality affected the power of the alpha oscillations and this was also not significant. The behavioural results show a ceiling effect with all conditions except Av_Rec having an average accuracy over 96.42% but Av_Rec's accuracy was at 68.45%. This difference in accuracy however was not reflected in any significant difference from either baseline or other conditions. The difference in performance scores seen here does therefore not reflect a change in the alpha power of the visual system and may be due to other factors not measured or analysed by this chapter i.e. theta or gamma waveforms which were

discussed by Visser's et al as being key components in reactive distractor processing which require further study (Visser's et al, 2016).

While it is disappointing to not have found any significant role of alpha in the visual system when comparing proactive and reactive processing this study does show, with a truly random and non-predictable paradigm, that the alpha inhibitory mechanism is not responsible for inhibitory control particularly during stimulation. The bulk of the literature on alpha inhibition is focused on pre-stimulation cueing effects and preparatory alpha however this thesis has focused on neural responses to stimulation and so the role of alpha during stimulation and its role as an inhibitory mechanism for sustained inhibition was studied here. As discussed in the introduction there is literature on both reactive distractor processing and the role of alpha during sustained stimulation (Marini et al, 2016; Sauseng et al, 2009; Vissers et al, 2016; Janssen et al, 2017) however these studies regularly contain an element of proactive cueing or at least predictability in the design which meant the participants could (and presumably did) prepare to handle the subsequent distraction. Our experiment presented a reactive distractor paradigm where participants could not predict when the need for reactive suppression of distractors would be required, because reactive trials were cued in the same manner as single stimulation trials. The reactive trials were the least likely to occur, so it was not optimal to prepare for them on any given trial but not impossible that participants did and this is discussed in the limitations section below. Regardless, this provides an understanding of where alpha is and is not used in inhibitory contexts. In the 2016 paper by Vissers et al, the authors discussed that theta oscillations were the key candidate oscillation for controlling and inhibiting the flow of information for distracting information (Vissers et al, 2016). Future experiments should focus on this area, but the goal of this experiment was to focus on alpha only after the restrictions caused by the COVID-19 outbreak.

Additionally, given there was a result that was initially significant and still only marginally non-significant after type 1 error correction, Av_Dual vs Av_Rec, which shows an increase in alpha power during the reactive trials while the visual regions were NTR this is an area which a large sample and further testing may reveal is controlled by alpha, but a clear significant finding was not possible with this sample.

In brief, this experiment provided further evidence against alpha as a primary control mechanism for sustained inhibition lasting over one second and does not appear to differentiate in this function when comparing proactively cued functional inhibition vs reactive functional inhibition.

Limitations

The first limitation of this study was that we were not able to use BEMs for each participant. Nine participants elected to use their right to withdraw after the MEG session and did not provide us with a chance to collect a T1 scan to form an accurate headmodel. This meant we had no ability to measure the anatomy of the brains or surrounding tissue of those individuals and so instead we used spherical models for all subjects. The visual localiser task and ERD from the visual dominant tasks themselves provided us with a way of localising the visual cortical areas responding to visual stimuli, but further localisation of the somatosensory, auditory and parietal regions was not possible to the same level of confidence. This means studying if the difference in alpha power between dual and reactive trials was in non-visual regions was limited in this study. We elected to focus on the visual cortex, and which is the area of the brain with the strongest alpha signals (Babiloni et al, 2006). Further research will be able to complete the intended additional recruitment of subjects, which was not possible due to the COVID-19 lockdown in the UK and subsequent CHBH imaging facilities shutdown. This will allow for a complete sample of participants with BEMs so the study of

the auditory, visual, somatosensory, and parietal regions can be completed as intended. The other intention will be to scan a larger population of people than was possible due to the COVID-19 lockdown and provide further clarification of if the Av_Dual vs Av_Reactive does present a true significant difference in alpha power when the visual regions are NTR.

Additionally, in the paper by Vissers the authors discussed that alpha-gamma communication and theta oscillations by themselves were areas of study they did not fully explore in their experiment and these were prime areas open to future research (Vissers' et al, 2016). This study of cross-region communication with phase-locked oscillations was another intended area for study however because we could only localise signals to the visual cortex with any level of confidence, we did not analyse the communication between different regions of the brain. Future studies, again with a sample willing to undergo T1 scanning, can use BEMs to properly localise multiple regions of the brain and conduct a full ROI analysis to study how oscillatory communication between regions is occurring differently between dual and reactive trials as set up in this paradigm.

There is one limitation that requires further inspection regarding if the paradigm truly held 'reactive' trials or if the participants could prepare in some way and as such even reactive trials may have been on some level proactive. To provide an example after a number of trials the participants will have learnt that the cue V could mean either that the cue was truthful and only a visual stimulus was going to be presented for the next few seconds or halfway through the presentation an auditory stimulus may occur and being prepared for that distractor is the optimal strategy even if it is less likely to occur than just preparing for a visual-only stimulus. In this experiment, we did weigh the probability to focus on the single modality conditions occurring more than the reactive so preparation for single only was the best solution. However, participants could have prepared, either consciously or unconsciously, for a reactive trial since the change to the dominant modality is nothing but in both cases, the

auditory modality is suppressed whether it is needed to or not. To date, there is no literature on if inhibiting NTRRs has a cost that would prohibit this unneeded behaviour. We could not measure the auditory cortex in this chapter as intended so this chapter can only provide speculation. It is unavoidable that participants in any paradigm where there is a possibility of a reactive trial that requires a sudden reaction may always prepare as though that would occur. However, if that is the case then it does mean that a paradigm with a clear separation between proactive and reactive trials is not possible. When the cost of inhibiting NTRRs is so low because it is either beneficial or non-costly in all conditions there is no way to clearly partial out that effect especially when it is unconscious and outside of direct participant control. The paradigm used in this experiment provided the best method provided so far in the reactive distractor alpha literature but cannot guarantee no proactive preparation.

A final limitation of the study is that we did not test any condition where the visual cortex was an NTRR. Somatosensory stimulation using a median nerve stimulator which is compatible with a MEG would provide an additional set of conditions to allow for studying how the visual region and the high alpha oscillation expression in the visual cortex alter during proactive vs reactive trials. We did not add somatosensory conditions in this experiment as the experiment already had eight separate conditions the participant had to be trained on and we wanted to reproduce an audio-visual paradigm that was more comparable to the experiments which had inspired this chapter, particularly Sauseng et al in 2009 and Vissers et al in 2016. It was deemed that the somatosensory stimuli could not be presented in a way that was compatible with the string of letters the other two modalities used.

Future Research

The primary future research projects proposed from this experiment are to cover the main weakness which was not being able to get T1 anatomical scans for most of the participants

and instead of having to use spherical models. A future experiment will be able to image participants to get a T1 scan and complete BEMs which was not possible in this experiment due to the COVID-19 lockdown. Future experiments will be able to study the effects of dual vs reactive conditions in the auditory, somatosensory, parietal, and frontal regions with a spatial resolution and confidence in localisation that we were not able to achieve with only spherical models.

Additionally, future experiments will be able to study the effects of cross-region communication using phase-locked oscillations as suggested in Vissers et al, 2016 but using the truly randomised paradigm we piloted in this study. This was an area we did not attempt to study without proper source localisation using only a spherical model, but it is a key area to study how multiple interactions between different oscillatory bands may compensate for real-time reactions to new stimuli instead of simply focusing on only the power of one oscillation band in the primary visual cortex.

To continue on this idea, it is not only alpha and gamma phase-locked interactions that are an area that needs future study. While alpha is the primary oscillation band studied with regards to functional inhibition, especially in the primary visual cortex, (Klimesch, Sauseng, Hanslmayr, 2007) other oscillations bands like theta have been implicated in controlling interference (Vissers et al, 2016). Another future experiment is to focus the analysis instead on theta oscillations which were identified in Vissers et al, 2016, to be a key oscillation that may be more involved in the control of functional inhibition to reactive distractors than alpha oscillations are.

Regarding the use of only audio-visual stimuli and the visual cortex never being an NTRR, future experiments would be able to incorporate a new somatosensory design, although with new stimuli for auditory and visual which is not a recognition task from a string of letters as

this is not readily possible with an MNS. This complication led to us not using MNS or other somatosensory stimuli as we could not incorporate this into the vowel recognition paradigm and wanted to primarily study audio-visual stimuli. However, we acknowledge this will have led to the visual cortex being in a state of alpha ERD and may have made it harder to measure differences in alpha when bottom-up neural responses are driving ERD regardless of any use of inhibition in a given circumstance.

Conclusion

In conclusion, this experiment set out to understand the role of alpha inhibition in a region which is being stimulated with distractors which a subject was not properly cued for. This experiment found no significant difference in the alpha power in the primary visual cortex regardless of whether the distractors were cued correctly before the trial or incorrectly and the participant had to react to the distractors in the moment. This experiment aimed to study this effect during the stimulation and understand the role of alpha not just in the few hundred milliseconds after a cue has been presented but during the stimulation when distractor inhibition is most important.

This study suggests that during a stimulation period with distractors alpha is not significantly different depending on cues or the modality being attended to (visual or auditory) during a visual/auditory display. We propose that other oscillations are responsible for the control of information as alpha has been ruled out by both this experiment and others (Sauseng et al, 2008; Vissers et al, 2016) and any necessary functional inhibition supporting work of others in the field who have studied pre-stimulation period effects (Sauseng et al, 2008; Vissers et al, 2016).

Chapter 5 -The expression of NBRs in non-task relevant non-modality-specific cognitive networks as examined through a cognitive battery of sensory modality-specific tasks and non-modality-specific cognitive tasks.

Introduction

As discussed in the introduction to this thesis, inhibition has been recorded and discussed widely, and primarily in sensory cortices (Sten et al, 2017; Harel et al, 2002; Bressler, Spotswood, and Whitney, 2007; Mozolic et al, 2008). However, inhibitory regulation is not exclusive to sensory modalities and inhibition has been reported in cognitive processing regions not dedicated to sensory processing i.e., during memory encoding and maintenance (Nilsson et al, 2013 in fMRI and Klimesch et al, 1999 in EEG). When engaged in a memory task, the literature suggests that the sensory modality by which information is given to the participant would show a PBR, whilst NBR would be observed in the other (unused) sensory modalities. Sensory regions are not the only areas to present deactivation during a task. The default mode network (DMN) has been classified as a network whose activity is anti-correlated with engaging in tasks (Knyazev, Slobodskoj-Plusnin, Bocharov, and Pylkova, 2011).

Also, the DMN shows inhibition regardless of if a task is simply sensory in nature or requires more complex cognitive processing i.e., language or memory. To provide a brief summary, the DMN was first studied by Shulman et al (1997) who noted a network of regions that

reduced their activity during non-self-referential tasks or put simply when subjects focussed on an external task. In 2001 Raichle used positron emission tomography to map a set of DMN regions particularly in the forebrain and posterior areas of the brain that were anti-task correlated and were activated during self-referential thinking or daydreaming (Raichle et al, 2001). The accepted regions of the DMN were laid out by Raichle in 2010 and 2011 and are the medial and ventral prefrontal cortex, the intra-parietal lobes bilaterally on either side of the PCC, the precuneus and posterior cingulate cortex (Raichle, 2010; Raichle, 2011). Secondary regions have also been identified including the medial temporal lobes and hippocampus (Raichle, 2015). The ventral and medial prefrontal cortex are associated with the manipulation of information but also the processing of that information to the hypothalamus, amygdala, and periaqueductal gray matter (Raichle, 2015) and damage to these areas has been shown to result in disturbances to emotion, mood, and personality (Damasio et al, 1994). The other two regions, the posterior cingulate cortex, and precuneus are understood to be recruited for the use of previously studied items or more simply the replaying of memories (Vincent et al, 2006). These areas present strong links to the hippocampus, the most well-studied region for memory recall, and Shannon et al 2013 presented a strong relationship, even affected by the time of day, between the hippocampus, the posterior cingulate cortex, and precuneus and self-referential thinking through the framing of prior memories. The DMN however is not simply an extension of the memory systems and has been understood to regularly be involved in spontaneous cognition as well as more concerted daydreaming (Raichle, 2015).

However, beyond the DMN and primary sensory regions, the question of whether inhibition and NBR are expressed in other areas of the brain has been the subject of very little study. In this chapter, I will address this by investigating whether the cognitive systems themselves systematically respond with NBR inhibition when they are non-task relevant, and another

cognitive system is stimulated. This can also be framed as asking does NBR-inhibition only occur in the sensory cortices and the DMN or can activation of cognitive systems result in inhibition of other cognitive systems, if they aren't clearly needed for the performance of that task?

As a point of clarification, a cognitive network in this chapter will refer to a network that is primarily responsible for higher-level processing, and that is not primarily responsible for the processing of low-level sensory information. Example cognitive systems are working memory, language, or the emotion systems (Baddeley, 1992), and is not specific in the sensory modality from which it receives its information. Both linguistic and memory tasks can be presented in a visual or an auditory form and are therefore not reliant on an individual sense. Throughout this chapter, the sensory systems are those primarily responsible for initial sensory processing, that send outputs to the parietal and temporal lobes for integration with other sensory information (Himmelbach and Karnath, 2005). Of importance is to note that in this chapter cognitive inhibition does not mean the stop/go-no-go forms of inhibition seen in the literature (Simmonds, Pekar, and Mostofsky, 2008). A stop/go-no-go paradigm is where a signal is presented to inform a participant to press a button but throughout the paradigm, after presenting a 'go' signal another signal will be presented shortly afterwards which informs the participant to now withdraw their response (Simmonds, Pekar and Mostofsky, 2008).

An immediate challenge, presented by the aims of this chapter, is that it is implicit in studying inhibition of a network that the activation of that network is minimised. However, it is very difficult to provide a complete experimental separation between cognitive systems, such that one can be recruited by a task without activation of another. As an example, a language task required working memory to process and recall information over the course of the task and a working memory task can be represented in language internally by the participant even when the experimenters avoid language whenever possible. In this experiment, while total separation

of cognitive systems is not possible, we will be using localiser tasks designed to generate the highest specific response in a given cognitive system i.e., language vs non-language presentation, working memory Sternberg/n-back tests, and the presentation of emotional faces/scenes. Because localiser tasks are used to identify statistically significant PBRs in select ROIs despite the cross-over between cognitive systems this solution is suitable when measuring how specific cognitive systems' PBRs and NBRs interact. All of these concerns are relevant to the methods below.

When investigating how non-sensory specific cognitive processing i.e. language (Sommer et al, 2004; Rapp et al, 2012; Luk et al, 2011; Indefrey, 2006), working memory (Svoboda et al, 2006; Spreng et al, 2008; Rottschy et al, 2012; Owen et al, 2005; Murty et al, 2010), social processing (Van Overwalle et al, 2014; Van Overwalle and Baetens, 2009; Van Overwalle, 2009), emotional processing (Stevens and Hamann, 2012; Thorsen et al, 2018; Murty et al, 2010; Gao et al, 2019; Fusar-Poli et al 2009) induces inhibition across the cortex it is important to remember the most studied networks are the memory systems and as such should be reviewed first. There is evidence from fMRI studies, measuring PBR and NBR, that memory encoding, maintenance, and retrieval have differential effects on the activation and inhibition signals across the brain (Nilsson et al, 2013). In their study, Nilsson et al found that the hippocampus showed no change in activity compared to resting baseline levels when retrieving spatial information from the original perspective that the information was received (Nilsson et al, 2013). However, when participants retrieved information from a different perspective of an environmental landmark the hippocampus showed an NBR. The explanation provided by the authors was that new visual information had to be processed and spatial processing was needed to understand where landmarks were from a new perspective. This resulted in a hippocampal NBR to suppress memory interference in visual processing as trying to encode visual information which was not yet fully spatially processed would be distracting. NBRs in the

hippocampus have been measured also during spatial memory tasks (Shipman and Astur, 2008; Astur et al 2005; Viard et al, 2011; Rekkas et al, 2005). There is further evidence in memory paradigms that inhibition is not just correlated to task load but also to performance with NBRs in the hippocampus resulting in worse performance (Rekkas et al, 2003; Shipman and Astur, 2008; Rodriguez, 2010; Lambrey et al 2012), as encoding and retrieval are inhibited. The authors do not provide an explanation for the paradoxical finding that NBRs did not result in greater performance. Although these studies highlight the inhibitory relationship that occurs between memory and the visual system, cross-cognitive network inhibition is yet to be studied in other cognitive domains or cortical regions.

Other evidence for cognitive tasks resulting in inhibition of sensory regions instead can be found from electrophysiological studies of Sternberg tasks. Jensen et al in 2002 found alpha ERS over posterior brain regions during the retention period which increased with memory load (number of items). This was taken to represent functional inhibition of the visual cortex to reduce task interference from non-task-relevant regions. In 2007, Tuladhar replicated Jensen's 2002 findings with a Sternberg task that involved the visual maintenance of faces instead of letters (Tuladhar et al, 2007). This shows how the memory regions have a relationship with sensory regions where inhibition is used to stop the flow of sensory information when maintenance needs to be prioritised over further perception. This provides evidence for cognitive systems, showing a correlation between positive activity (gamma ERD/alpha ERD or PBR) and alpha synchronization to reduce interference during a task in NTR sensory regions.

However, there is a limitation in the literature. The visual system is inhibited when its activity is not required during the maintenance period of a memory experiment. During this period many other cognitive elements, such as processing of semantics, language, and emotions are also all not task-relevant, as only the maintenance of the specific visual information matters.

As such the networks responsible for these other cognitive functions are also non-task-relevant and should also be suppressed to minimise interference and distraction, such that they exhibit cross-network inhibition. However, only the sensory systems and the interaction with the hippocampus have been systematically studied for inhibition responses. The following meta-analyses show the current best understanding of how the brain responds, in a network sense, to the recruitment of language (Sommer, Aleman, Bouma and Kahn, 2004; Rapp, Mutschler and Erb, 2012; Luk, Green, Aubtalebi and Grady, 2011; Indefrey, 2006); memory (Svoboda, McKinnon and Levine, 2006; Spreng, Mar, and Kim, 2008; Rottschy et al, 2012; Owen, McMillan, Laird, Bullmore 2005; Murty, Ritchey, Adcock and LaBar, 2010); social processing (Van Overwalle, Baetens, Marien and Vandekerckhove 2014; Van Overwalle and Baetens, 2009; Van Overwalle, 2009); and emotion (Stevens and Hamann, 2012; Thorsen et al, 2018; Murty, Ritchey, Adcock and LaBar, 2010; Gao, Weber and Shinhareva 2019; Fusar-Poli et al 2009;). However, across these meta-analyses, there is no analysis of the NBRs which occur in response to different cognitive tasks. This topic appears to have been mostly ignored when looking at cross-network communication. There are also studies/meta-analyses on more complex processing which requires the combination of multiple cognitive systems such as Theory of Mind and narrative processing, but these also do not discuss inhibition across the cortex (Spreng, Mar, and Kim, 2008; Schurz, Radua, Aichhorn, Richlan and Perner, 2014; Denny, Kober, Wager and Ochsner, 2012). This gap in the literature on inhibitory responses to cognitive network recruitment provides an area of interest to study which currently is simply absent from the literature. Further information on the role of cognitive systems engaging in cross-system inhibition is sparse and the current study aims to fill this gap in the literature.

In Chapter 2, we observed that despite the high demand for concurrent processing of multiple sensory streams of information (both relevant and irrelevant) one of our main findings was that we did not see deactivation of cognitive networks despite them being task-irrelevant. We

interpret this to mean that cognitive networks may have a different inhibitory interaction when non-task relevant than is shown by sensory regions.

Hypothesis and rationale

This experiment aims to study whether NTR cognitive networks are inhibited during a variety of cognitive tasks and if so, whether the spatial locations of NBR are comparable to those seen during activation of sensory networks. We investigate if a non-task relevant cognitive region, when not showing PBR, will instead show an NBR in the manner that non-task relevant sensory regions behave in Chapter 2 and the rest of the literature (Rapp et al, 2012, Rottschy et al, 2012, Van Overwalle et al, 2014, Thorsen et al, 2018). The current literature has shown limited evidence of non-sensory specific cognitive regions being inhibited when they are not relevant to the task (Knyazev, Slobodskoj-Plusnin, Bocharov and Pylkova, 2011) but there is little information on how cross-region inhibition in the cortex is initiated, whether by the activated sensory or cognitive regions. An open question remains how to establish whether this inhibition is a function of the sensory modalities being activated by the stimulus input or caused by the cognitive networks themselves being activated. We investigate this by using GLM analysis of fMRI data from the HCP dataset.

Our hypothesis for this experiment is that when a non-task relevant (NTR) cognitive network, is not stimulated as part of a task this will result in an NBR in an NTR cognitive network. A cognitive region will be identified by tasks specifically designed to activate a given network while reducing cross-activation in other networks (named localizers in this chapter). We also expect to see NBRs in the non-task relevant sensory regions replicating our findings from Chapter 2 as well as deactivation across the DMN as this is a highly replicated finding during any task-orientated activity (Knyazev, Slobodskoj-Plusnin, Bocharov and Pylkova, 2011). If we do not see deactivations in NTR cognitive regions, then we can infer only sensory systems

engage in cross-regional inhibition unless the cross-regional inhibition is involved in a task-relevant sensory region (Klimesch et al 1999; Nilsson et al 2013.).

Methods

Intended Research Methods

Due to the COVID-19 outbreak, we were unable to continue with the EEG-fMRI experiment in human subjects that we had designed. The intended paradigm was for participants to undertake two experimental sessions which would engage a number of cognitive domains. We planned to use the following paradigms:

1. Auditory and visual stimulation similar to that used in Chapter 2 to establish how NBRs occurred across the cortex in response to simple sensory stimulation, with no cognitive component, in each participant.
2. We also included an imagination condition where after experiencing the auditory and visual stimulation the participants had to just imagine the stimuli for 6 seconds. This was to contrast NBRs from internally generated stimulation i.e., by imagination, compared to externally generated stimulation from paradigm 1.
3. A Sternberg memory task where the participants viewed a stream of consonants and had to recall if a vowel was present. We planned a 6 item Sternberg task with both visual and auditory presentation as a string of letters. The paradigm had 4 seconds for encoding and maintenance, a 1-second probe was presented and then a 1.5-second retrieval and response period where the participant responded if the probe was present in the presentation array by presenting a button on a response pad.
4. An established fMRI language localiser based on Alice in Wonderland where the participants were presented interleaved displays of written text from Alice in Wonderland or nonsense words (Fedorenko et al, 2010).

5. An autobiographical planning task involving self-referential imaging of how certain goals could be achieved (e.g., Save Money, Lose Weight), then adapting those scenarios to three prompt items which would change the parameters or provide difficulties and then answering how hard the task was for them to plan. This was based on Spreng and Schacter's paradigm (Spreng and Schacter, 2010).
6. Watching Bang! You're Dead to measure the participant's PBRs and NBRs over the course of a short TV show which would involve multiple concurrent cognitive systems. This was based on Uri Hasson's work on neurocinematics (Hasson et al, 2008)
7. A resting baseline was taken for five minutes which also served as a break for participants during testing.

We intended to stimulate each cognitive network with separate auditory and visual information so we could separate sensory-specific responses from the cognitive recruitment of a given network. The EEG component would have allowed us to monitor alpha activity known for its involvement in functional inhibition (Klimesch et al, 2007) and has been tied to NBRs (Mullinger, Mayhew, Bagshaw, Bowtell and Francis, 2012; Mayhew, Ostwald, Porcaro, and Bagshaw, 2013; Mullinger, Mayhew, Bagshaw, Bowtell, and Francis, 2014) across the visual, somatosensory, motor, parietal, and frontal regions. This paradigm was piloted to test the paradigms but unfortunately, proper data acquisition for the study had not begun before the COVID-19 outbreak closed the CHBH. Due to the time constraints of my Ph.D. and the continued halt on scanning into 2021 it was not possible to wait to resume the study so we sought an alternative means of addressing our research question.

We, therefore, used the Human Connectome Project (http://www.humanconnectomeproject.org/data/) (Barch et al, 2013) which features recordings from a battery of fMRI data acquired during a range of different tasks. From Chapter 2 we have a good understanding of how single and multisensory sensory stimulation

affects the activations and deactivations across the sensory cortices of the brain. We can use this as a guide to the sensory-only activations on a population level in replacement of the comparison we intended to make between sensory vs cognitive tasks in the original paradigm.

Replacement Research Methods

As stated, we replaced our paradigm with an analysis of secondary data obtained from the HCP dataset detailed by Barch et al 2013. The HCP used a battery of short tasks across many cognitive domains as functional localisers to help them define nodes for connectivity analyses. They also provide the opportunity to study patterns of PBR and NBR between cognitive systems.

The benefit of using the HCP datasets is that we can see the activation and deactivation maps from a much larger selection of tasks. Full details of the HCP task-related functional imaging sessions can be found in Barch et al 2013; for this experiment, we will be using:

- Working memory – There is still the issue that the items presented in the n-back test can have linguistic representations and may have a small cross over with the language task activations, but this is unavoidable and as such we will factor in the relative strengths of activations/deactivations across networks instead of using an all or nothing approach.

  As described in Barch et al (2013) an N-back task was used to assess working memory/cognitive control based on (Drobyshevsky et al., 2006) as a functional localiser with evidence for reliability across subjects (Drobyshevsky et al., 2006) and time (Caceres et al., 2009). Within each run, the 4 different stimulus types are presented in separate blocks within the run. Within each run, ½ of the blocks use a 2-back working memory task (respond ‘target’ whenever the current stimulus is the same as the one-two back) and ½ use a 0-back working memory task (a target cue is presented at the

start of each block, and the person must respond ‘target’ to any presentation of that stimulus during the block). A 2.5 s cue indicates the task type (and target for 0-back) at the start of the block. Each of the two runs contains 8 task blocks (10 trials of 2.5 s each, for 25 s) and 4 fixation blocks (15 s each). On each trial, the stimulus is presented for 2 s, followed by a 500 ms ITI. Each block contains 10 trials, of which 2 are targets, and 2–3 are non-target lures (e.g., repeated items in the wrong n-back position, either 1-back or 3-back). We chose faces, places, tools, and body parts as the four categories of stimuli because of evidence that these stimuli reliably engage distinct cortical regions (Downing et al., 2001; Fox et al., 2009; Peelen and Downing, 2005; Taylor et al., 2007) and because the associated brain activations are reliable across subjects (Downing et al., 2001; Fox et al., 2009) and time (Kung et al., 2007; Peelen and Downing, 2005). The stimuli were obtained from a number of previous studies using face (Pinsk et al., 2009), place (Kanwisher, 2001; O’Craven and Kanwisher, 2000; Park and Chun, 2009), body parts (Bracci et al., 2010; Downing et al., 2001; Downing et al., 2006b; Peelen and Downing, 2005; Pinsk et al., 2009; Barch et al. et al., 2006) and tool (Downing et al., 2006a; Peelen and Downing, 2005; Wierenga et al., 2009) stimuli.

- Language –This task involved the presentation of two runs of story and math presentation blocks with 4 blocks per each condition type that were interleaved through the presentation. The mathematics tasks provided a cognitive demanding contrast to the language task, but which involves different regions of processing i.e. activating the parietal lobes but not the anterior temporal lobes. This task was based on Binder et al 2011’s work which was validated by those researchers. The story blocks presented audio with 5-9 sentences from Aesop’s fables followed by a forced-choice question between two options on a topic from the story. The math task was also presented

auditorily and presented addition or subtraction problems which the participant responded to by identifying which of two options was the correct answer that were again presented through headphones. This lasted 3.8 minutes per run with additional math tasks used to pad the run time once the story presentation was completed.

- Incentive/Gambling Processing – The HCP dataset also includes a gambling task to process incentive processing and was adapted from Delgado et al 2000 with testing by Delgado et al, 2000, Forbes et al, 2009, May et al 2004 and Tricomi et al 2004 that showed validity and reliability for this task in testing incentive processing across subjects. The task involved being presented with a '?' for 1.5 seconds on a card presented on a screen and the subject had to indicate if they thought the value on the card would be above or below 5. The subject won $1 for being correct, they lost $0.5 for being incorrect and if the number was 5 it was deemed a neutral trial with no effect on the subject's financial amount. The trial order involved presenting mostly loss or mostly reward blocks where the reward condition was presented 6 times and then 1 loss and 1 neutral trial or the number of reward and loss trials were reversed. The number of reward and block trials was matched at 2 each with 4 15 second fixation blocks also presented. The amount of money that was won over the trials was provided to the subject at the end of the trial ensuring the consequences of gambling were not abstract but had real-world implications improving the validity of the test. The inclusion of the gambling task allows us to look at how both the striatum, prefrontal cortex, and subcortical regions that are all involved in incentive processing can cause NBRs across the cortex (Barch et al, 2013). This task provides an interesting case where we would expect that the limbic system should have conflicting results on whether it will exhibit PBR/NBR. On the one hand, gaining incentives and gambling are known to be

emotionally charged and highly motivating scenarios, on the other hand, the desire to inhibit emotional processing and use only logical thought patterns is clear.

- Social Cognition – The HCP dataset allows us to look at social cognition processing through their social cognition localiser which measures the response to the 'behaviour' of a set of squares. This method has been validated from multiple experiments and shown to be reliable across different population groups (Castelli et al, 2000; Castelli et al 2002; Wheatley et al 2007; White et al, 2011). This condition required participants to watch 20s video clips watching objects (squares, circles, and triangles) move either in a random pattern or a pattern that involved interaction. Participants had to choose between three options after watching the clip: social interaction, no interaction, unsure between the two options. While anthropomorphizing the movements of squares is not a desirable proxy for actual social interactions the social cognition task does allow this experiment to have some measure of social cognition in its crudest forms. This task allows us to measure the PBRs and NBRs to social processing which is arguably ubiquitous in our daily lives and therefore greatly adds to the ability to speak about the larger population from the results of this study.
- Relational processing – The stimuli for this experiment were 6 different shapes filled with 1 of 6 textures; when the subject was required to do relational processing, the subject was presented with 2 pairs of objects on the top and bottom of the screen and told to detect if the shape or texture differed both on the top and bottom pair. The control condition required the same task but a cue for shape or texture was provided. The presentation of the stimuli in the relational processing condition lasted for 3.5s with a 500ms ITI and four trials per block. In the matching control condition, the presentation of the stimulus lasted 2.8 seconds and 400ms ITI and five trials per block. This experiment was modified from Smith et al 2007.

- Emotional Processing –The HCP data set includes a task on processing whether a face has a certain emotional trait more than a neutral face based on Hariri et al, 2002 and reliability testing confirmed by Manuck et al 2007a. Participants were presented trials with visual presentations that required matching two faces on the bottom of the screen to a probe face on the top of the screen. The participants were told to match the top and bottom face with the corresponding emotion. The emotions to match were either anger or fear. The contrasting condition was matching shapes that had no emotional information. In the analysis of the emotion condition, fear and anger were combined because it is only emotional processing that was being measured to study if emotional processing results in cross-cognitive system inhibition. It is an area for future study to understand if different emotional responses result in different cross-cognitive system inhibition patterns. The trial structure involved a 3s task cue to identify if the trial was shape or emotion processing and then 2s stimulus presentation followed by 1s inter-trial interval (ITI) and resting period in between trials. Each condition type (face vs shapes) was presented in 6 trial blocks. There is an arguably large difference between processing if a face is fearful or angry vs more complex tasks involving inferring the emotional state of a person through understanding their theory of mind. This would, like the social cognition point above, require a more ecologically valid paradigm that could involve discussing the emotional state of an actor in a video during an fMRI acquisition and focus on the actor's emotional state, what caused it, and any conflicts that may be occurring. This naturally would take longer for the subject to process and express which makes it more suited to later experiments once cognitive inhibition patterns are better understood.

Notable removals –

- We cannot test the auditory/visual processing in our participants as the HCP dataset does not have singular and multisensory focused processing paradigms as our original experiment did. This means we are not able to partial out the sensory processing from the cognitive tasks on a subject-by-subject basis as we intended originally, and we will need to infer generalisability between the populations in chapters 2 and 3 with this chapter. This is an accepted limitation of the new paradigm and the COVID-19 situation this chapter was written in.
- We do not have an 'imagination' task anymore as this is not part of the HCP dataset.
- The autobiographical planning task has been removed again due to it not being part of the HCP datasets.
- The removal of a narrative presentation is of importance because the HCP dataset did not contain a narrative task nor could we find a replacement that would allow for an analysis of the timecourses in a way that would match Hasson's experiment (Hasson, et al, 2008) both in the PBRs across networks and the NBRs.

MRI data

As described in Barch et al. 2013 the HCP fMRI data was acquired on a 3T Siemens Skyra with a 32-channel head coil using the scan parameters of: TR = 720ms, TE = 33.1 ms, BW = 2290Hz/Px, flip angle = 52 degrees and 2mm isotropic voxels with a multi-band factor of 8 (Feinberg et al, 2010; Moeller et al, 2010). For each of the conditions mentioned two runs were acquired with each run consisting of the full set of blocks discussed and left to right phase encoding on one run and right to left phase encoding on the other. From the Barch et al (2013)

paper we analysed the first 100 participants, mean age 29.1 years old, ± 3.67 (years) and 55 males.

Analysis

Pre-processing was completed by Barch et al (2013) with full details on page 14 of Barch et al (2013). The HCP pipeline was described as pre-processing the 4D time series with gradient unwarping, motion correction, brain boundary-based registration to a T1-weighted anatomical scan from each participant, and registration into MNI152 space. The data were spatially smoothed using a gaussian kernel of FWHM = 4mm.

We downloaded event timings and pre-processed data prepared for analysis by Barch et al 2013. GLMs were then implemented using FSL's FEAT. fMRI data were analysed in FSL v6.01 (http://www.fmrib.ox.ac.uk/fsl). Regressors were formed for each condition based on the timings of the stimuli and were convolved with a double gamma haemodynamic response function, with temporal derivatives included in the design matrix. Positive and negative contrasts were set on each regressor to respectively estimate PBR and NBR with respect to a resting baseline.

The first levels GLMs were made per condition using the following regressors:

1. Language – the language and mathematics conditions were modelled as two separate regressors.
2. Memory – The successful and incorrect responses for both the 2 and 0 back conditions were modelled as separate regressors, resulting in four regressors in total. This enabled the study of responses to success in responding as well as the number of n-back items.
3. Relational – The relational processing condition and the control condition were modelled as two separate regressors.

4. Social – The two conditions were identifying social interaction from purposeful square movement and square movement with random interaction were modelled as separate regressors.
5. Emotional - The fearful face and neutral angry face conditions were modelled as separate regressors
6. Gambling/Incentive – The reward and loss conditions were modelled as separate regressors.

For the second level GLMs, the resulting contrasts were compiled across both runs using fixed effects to give a mean response per subject. The group mean, third level analysis results, were calculated using FLAME 1 mixed effects with $Z > 3.1$. Additionally, for NBRs only a Z threshold of 2.3 was also used to allow a comparison for sensory NBRs to be compared with fMRI data from chapter 3 . All levels of the analyses were corrected to $p<0.05$ cluster corrected. In language conditions, only 93 participants were used and in the gambling condition only 96 participants were used due to data corruption on 4 participants. For each third level analysis, the second level GLM contrasts were also compiled into an analysis using FLAME 1 with $Z > 3.1$ comparing the NBRs across conditions to measure commonality between NBRs across the cortex and partial out sensory-specific effects.

We are primarily interested in contrasting the task conditions vs resting baseline to evaluate PBR and NBR. The comparisons between the task and the comparison condition used as the original HCP localisers have not been conducted here as localizing the various cognitive functions is not the aim of this paper but instead to measure the NBRs across the cortex to each task. As such the NBRs to both the localizer and comparison conditions are of equal interest since both require the recruitment of non-sensory specific cognitive systems.

The final NBR maps for each condition will then be compared against a map of the DMN (Przezdzik, Bagshaw and Mayhew, 2013). This will be done to assess the spatial locations of NBRs both inside and outside the DMN. The DMN's nature as an anti-task correlated network means clearly identifying NBRs occurring beyond the DMN is of great importance for understanding when cross cognitive network inhibition is occurring compared to where it is simply part of the DMN's expected NBR.

Results

PBRs

This section discusses the PBRs seen in each condition. An analysis of higher-level comparisons of PBRs between experimental and control conditions as well as between different cognitive tests was not conducted on the PBRs as differences in positive BOLD region recruitment are not the primary focus of this chapter and so for brevity have been left out. This section intends to inform the reader on the activated regions to provide greater context for which regions presented NBRs in the section below.

Figure 5.1 shows the PBR to the language task when the participants were processing an audio-delivered story. We observed activations in the bilateral auditory cortex as well as activation in the superior regions of the cerebellum indicating both listening to the auditory information and generating a motor action to respond. We also saw activation in the dorsal attention network with posterior parietal activations bilaterally and prefrontal cortex showing auditory processing of the linguistic stimuli as well as the frontoparietal attention network. Interestingly there was minimal temporal lobe activation as would be expected in a language task (Friederici and Gierhan, 2013). Figure 5.2 shows the PBR to the math condition. There was a stronger auditory response during the language task compared to baseline as indicated by the higher peak Z-stat (12.4 vs 11.7) in the primary auditory cortices. The activation also descended down

into the bilateral frontotemporal poles but compared to Figure 5.1 we did not see the same extent of parietal or frontal lobe activation.

Figure 5.3 shows the PBR to the emotion fearful faces task. We observed the widespread activation of the visual system as the participants were processing the stimulus faces images. PBRs were also observed in the cerebellum, amygdala, bilateral insula cortex, and the dorsal attentional network. For the angry condition, shown by Figure 5.4, we observed similar PBRs to Figure 3 in all visual regions, the superior regions of the cerebellum as well as activations in the right superior insula and dorsal attentional network (DAN) as well as the frontoparietal attention network, with slightly lower z scores and smaller PBRs than for emotional faces. DMN and DAN were identified using atlases based on previous findings from Khalsa et al (2014) and Wilson et al (2015). Responses in the amygdala and surrounding midbrain/limbic system regions were reduced or absent compared to Figure 5.3.

Figure 5.5 shows the PBR for when a participant had won a gambling session. We observed strong activation of the cerebellum as well as the main PBR showing bilateral activation of the whole visual cortex. Additionally, we observed bilateral insula activation in the superior insula but the PBR on the right side of the brain extended further into the midbrain than on the left insula. There was also activation across the frontoparietal attention network as seen with the activation of the frontal dorsolateral prefrontal cortex and bilateral posterior parietal network activation just posterior of the somatosensory regions. The dorsal lateral attention network shows heavy extended activation bilateral visual cortices extending into the parietal cortices and showing the highest activation around the intraparietal sulcus. In Figure 5.6 which shows the group PBR for when a participant had lost during the gambling task the map is almost identical to the win scenario but with the responses being marginally larger spatially in Figure 5.5. The activation maps do not show spatial differentiation suggesting the processing between reward and loss recruits the same locations.

Figure 5.7 shows the PBR to relational processing condition when the participant was processing shapes in relation to each other. The map in Figure 5.7 shows strong cerebellum activation along with the same recruitment of the visual systems bilaterally encompassing the entire occipital lobe as seen in Figures 5.5 and 5.6 for the gambling task. In Figure 5.7 only superior bilateral insula activation was seen with no hemispheric differences and greater recruitment in this condition of the midbrain regions bordering on the central ventricles around the caudate, putamen, and basal ganglia. Activation of the dorsal attention network can also be seen with heavy parietal lobe activation extending forward to the frontal regions. In Figure 5. .8 where the participants were conducting the relational processing control condition, we observed the same activation patterns as in Figure 5.7 with strong cerebellum, visual and dorsal attention networks as the participants were conducting a visual task involving a motor response to respond. There are no clear differences in spatial location of PBRs between the control and experimental relational processing.

Figures 5.9 and 5.10 show the PBR to the social processing task involving presenting shapes moving with purposeful action. The activation patterns here showed: bilateral cerebellum, bilateral visual cortex recruitment that extended into the superior temporal lobe, bilateral insula and midbrain activations bordering on the central ventricles, superior temporal and parietal activation involving the dorsal attention network with frontal activation extending except to the primary motor and somatosensory regions at the most superior part of the cortex.

Figures 5.11 and 5.12 show the PBRs for the n back memory task when n is 0 in Figure 5.11 and n is 2 in Figure 5.12. The Figures show activation of the visual systems corresponding to the task being visual in presentation. We also saw the activation of the DAN and frontal attention network as well as the posterior hippocampal regions as would be expected.

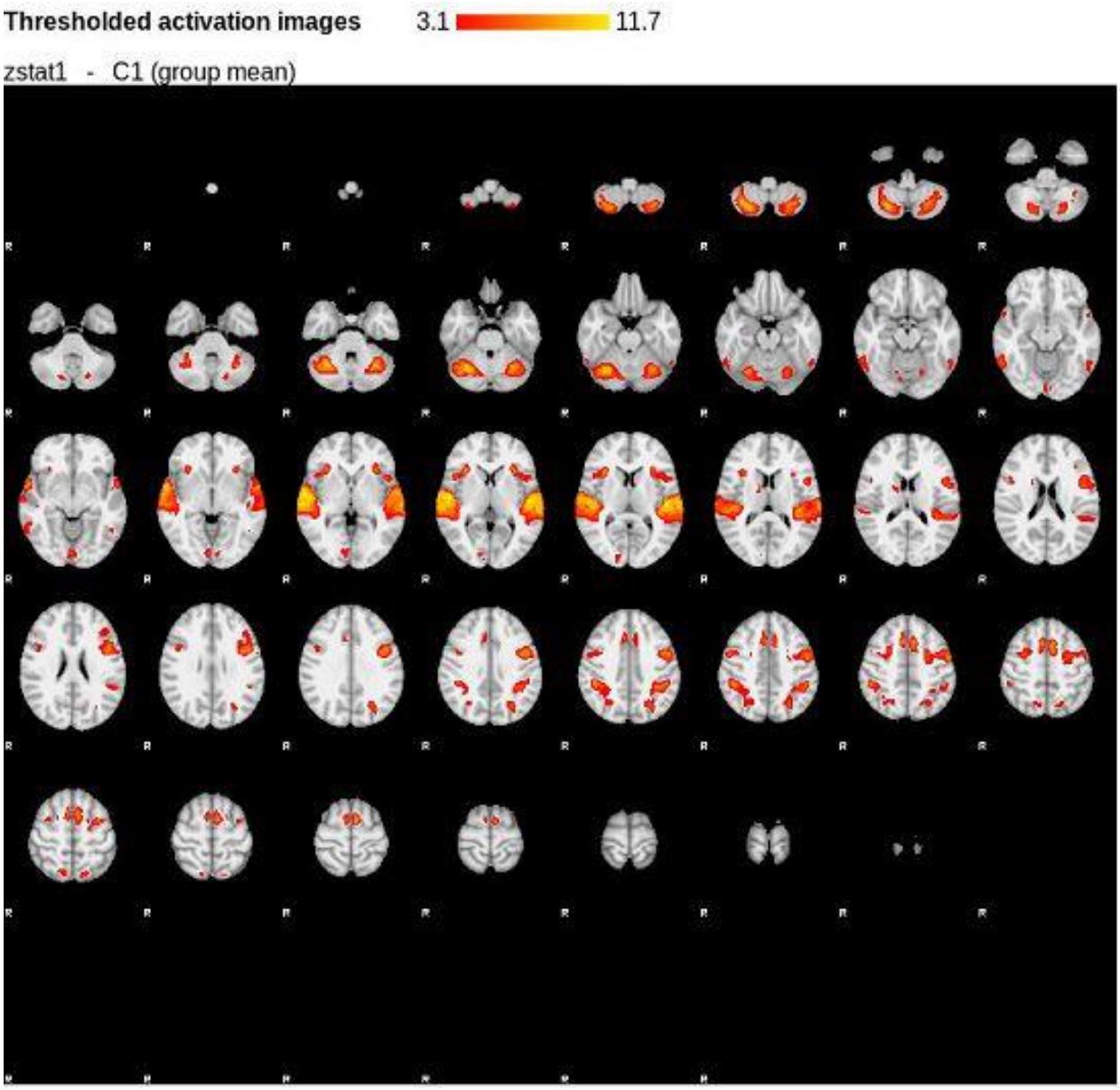

Figure 5.1 - *Language story > resting fixation baseline*

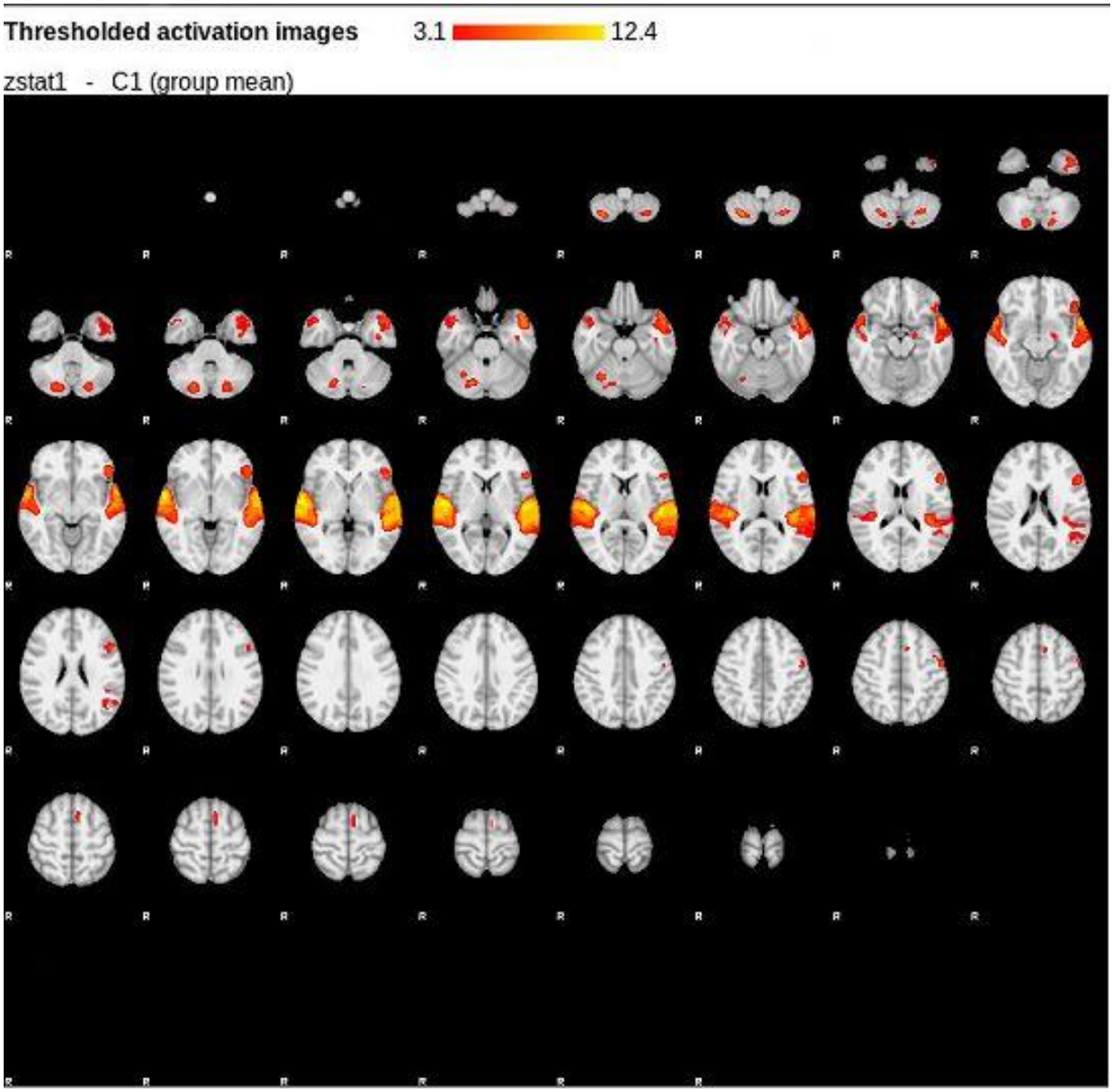

Figure 5.2 - *Langauge math > resting fixation baseline*

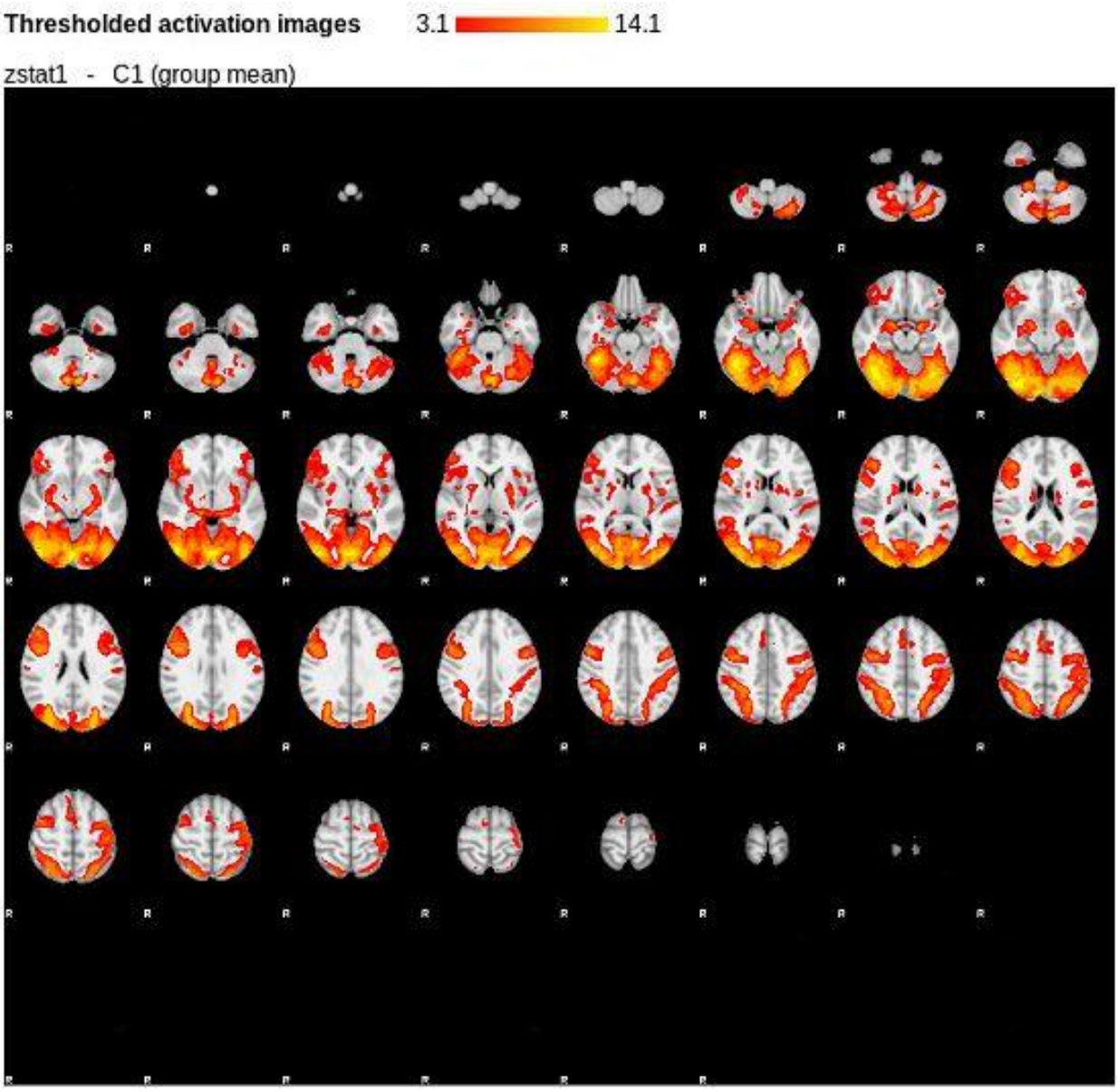

Figure 5.3 - *Emotion fearful face > resting fixation baseline*

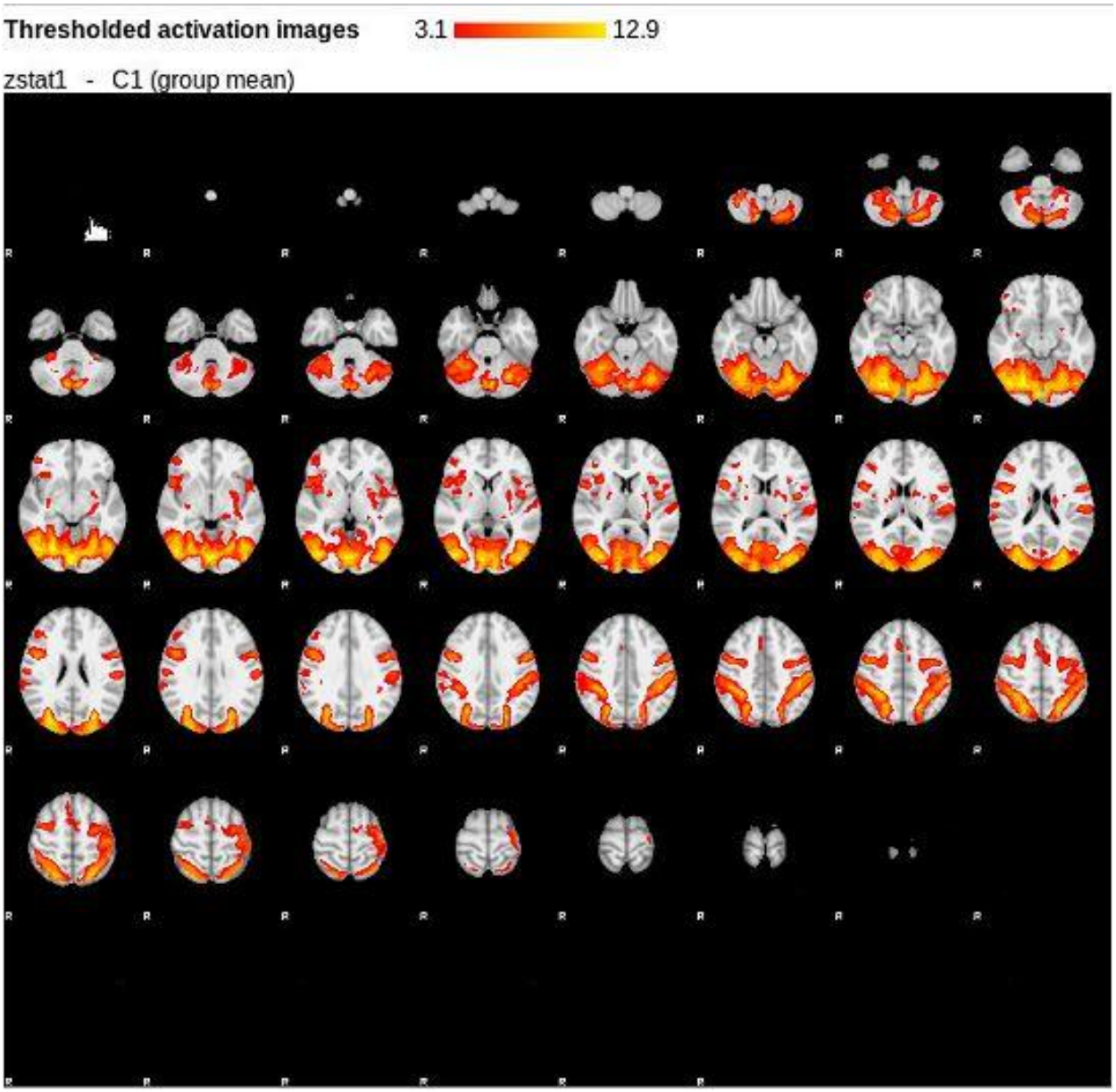

Figure 5.4 - *Emotion angry face > resting fixation baseline*

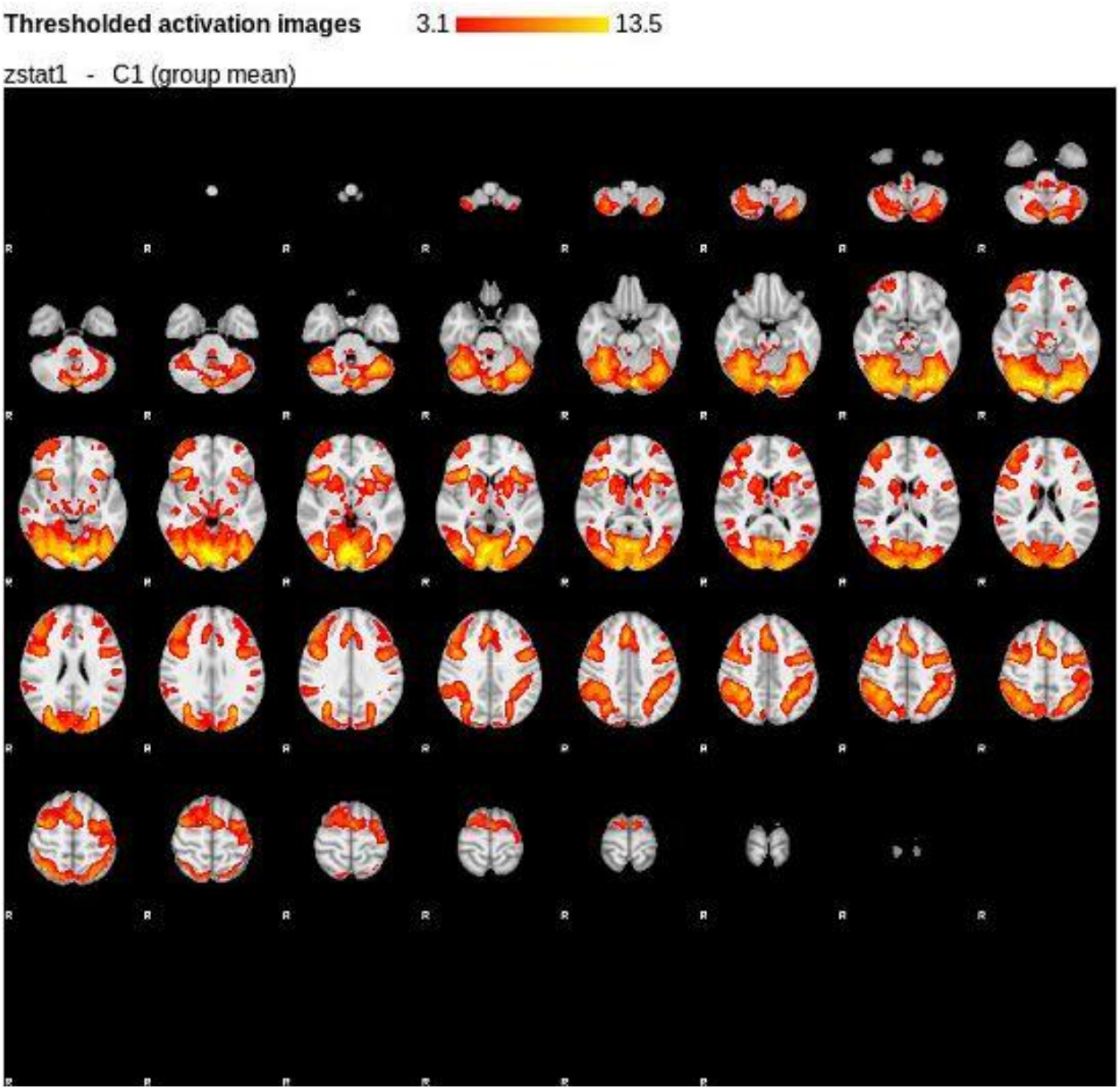

Figure 5.5 - *Gambling win > resting fixation baseline*

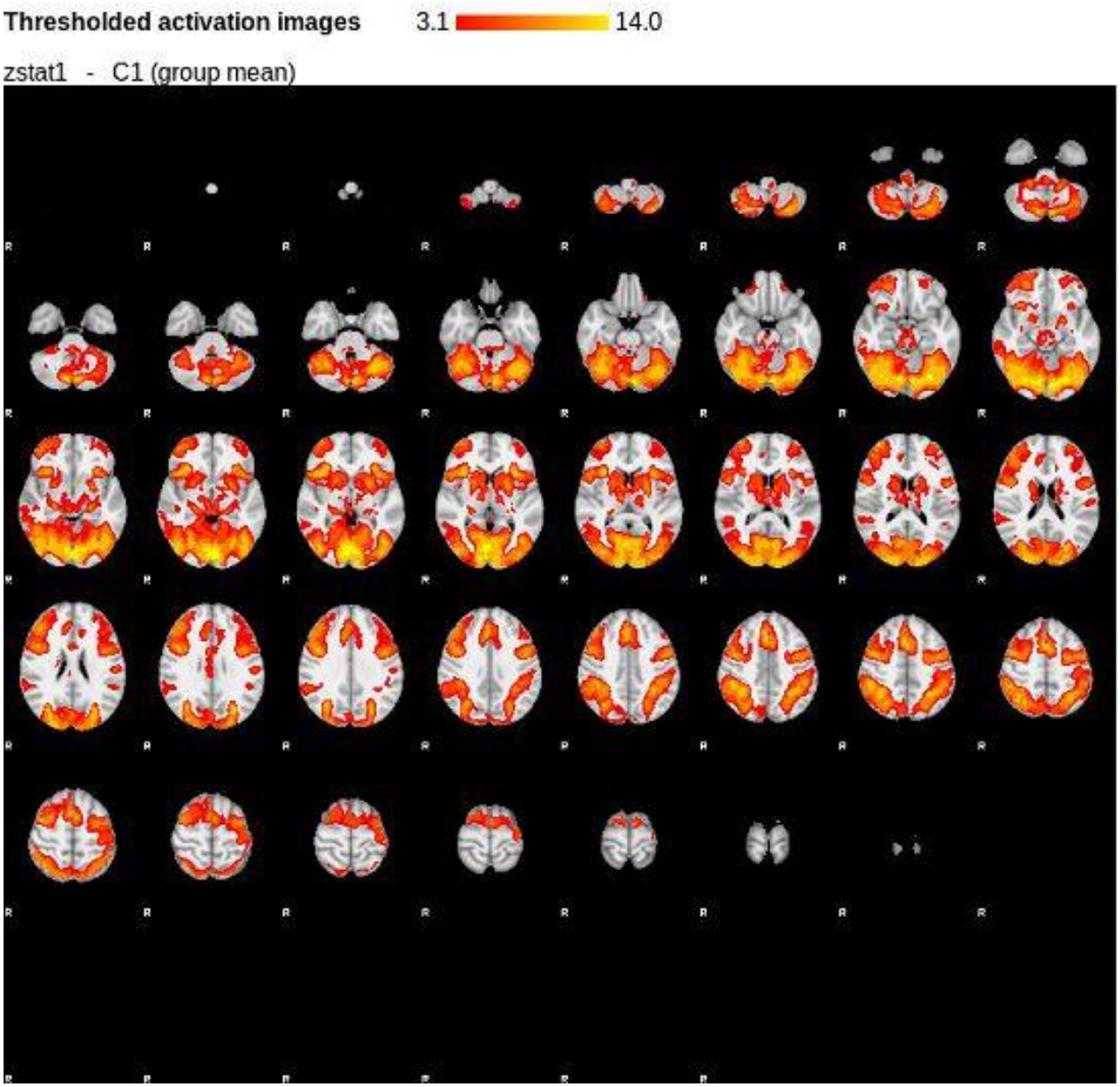

Figure 5.6 - *Gambling loss > resting fixation baseline*

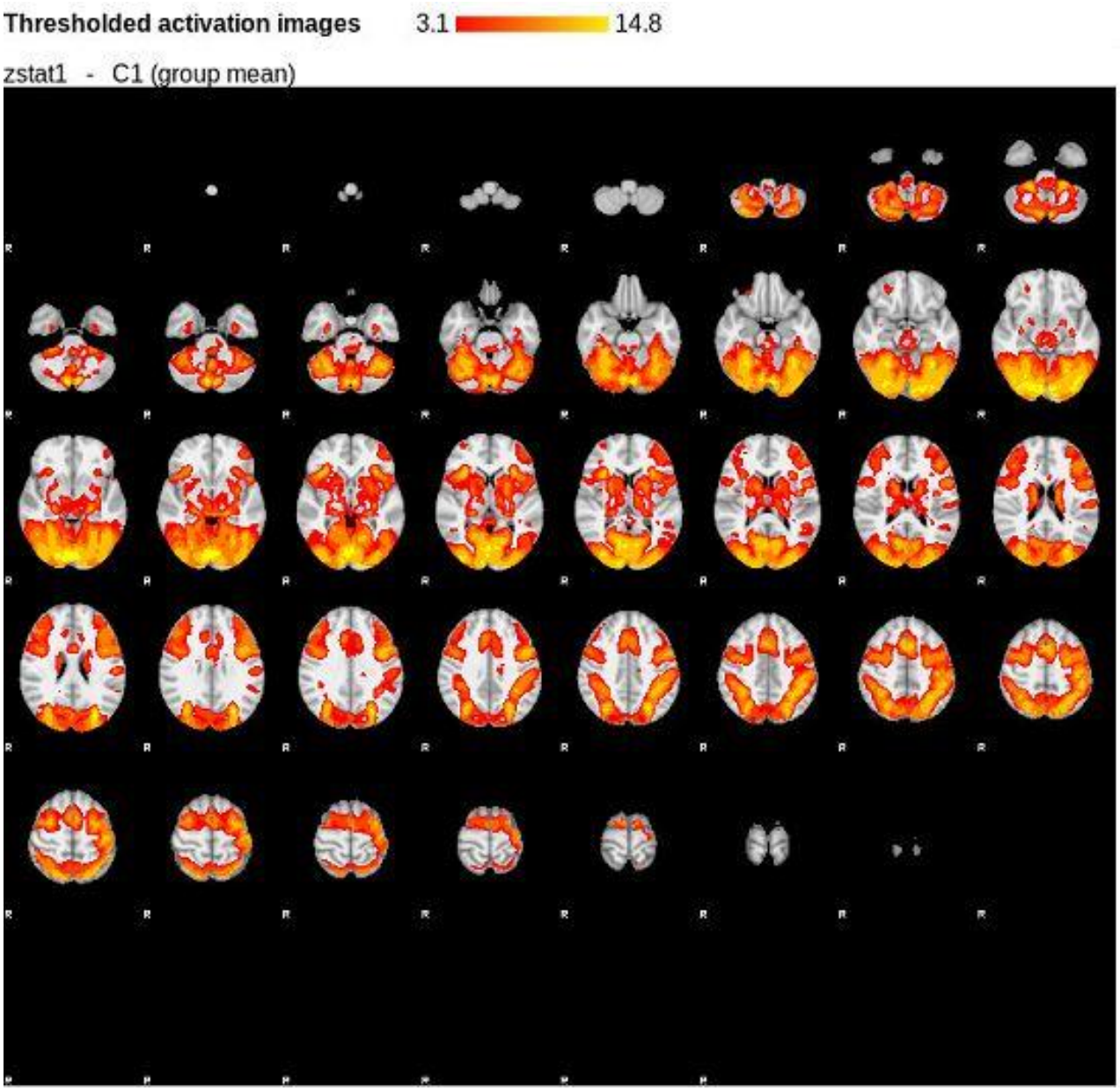

Figure 5.7 - *Relational processing > resting fixation baseline*

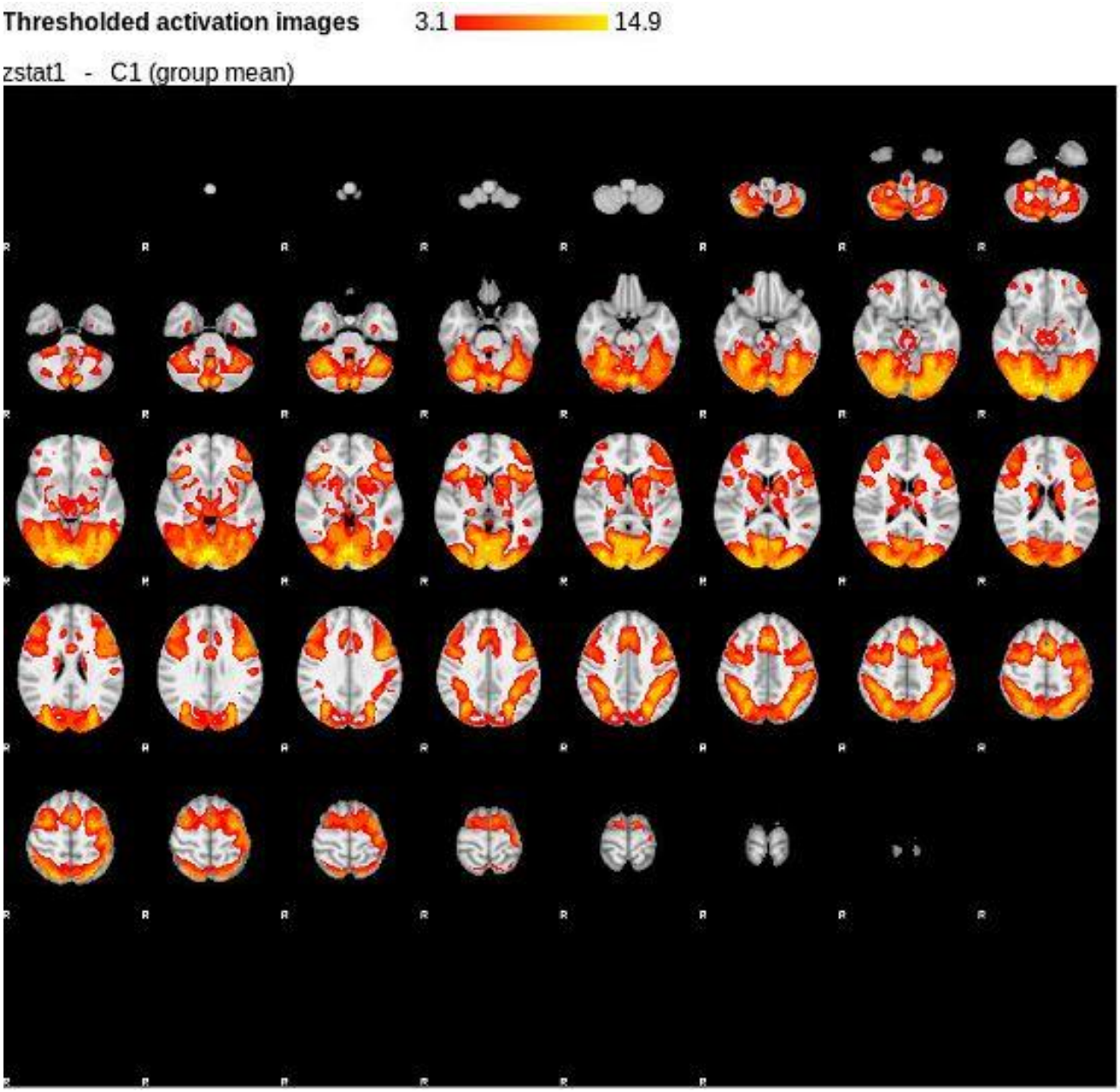

Figure 5.8 - *Relational control condition > resting fixation baseline*

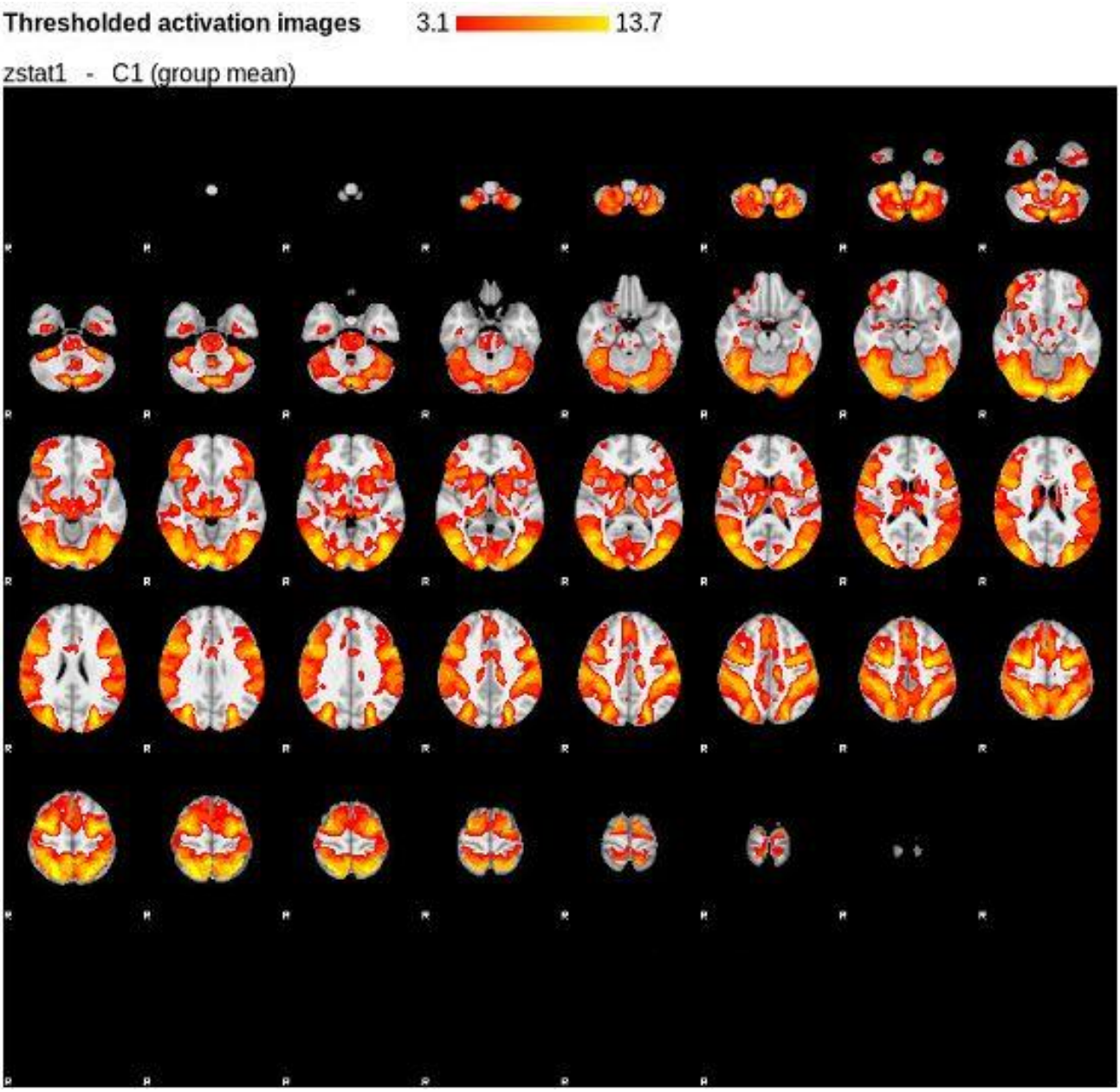

Figure 5.9 - *Social purposeful movement > resting fixation baseline*

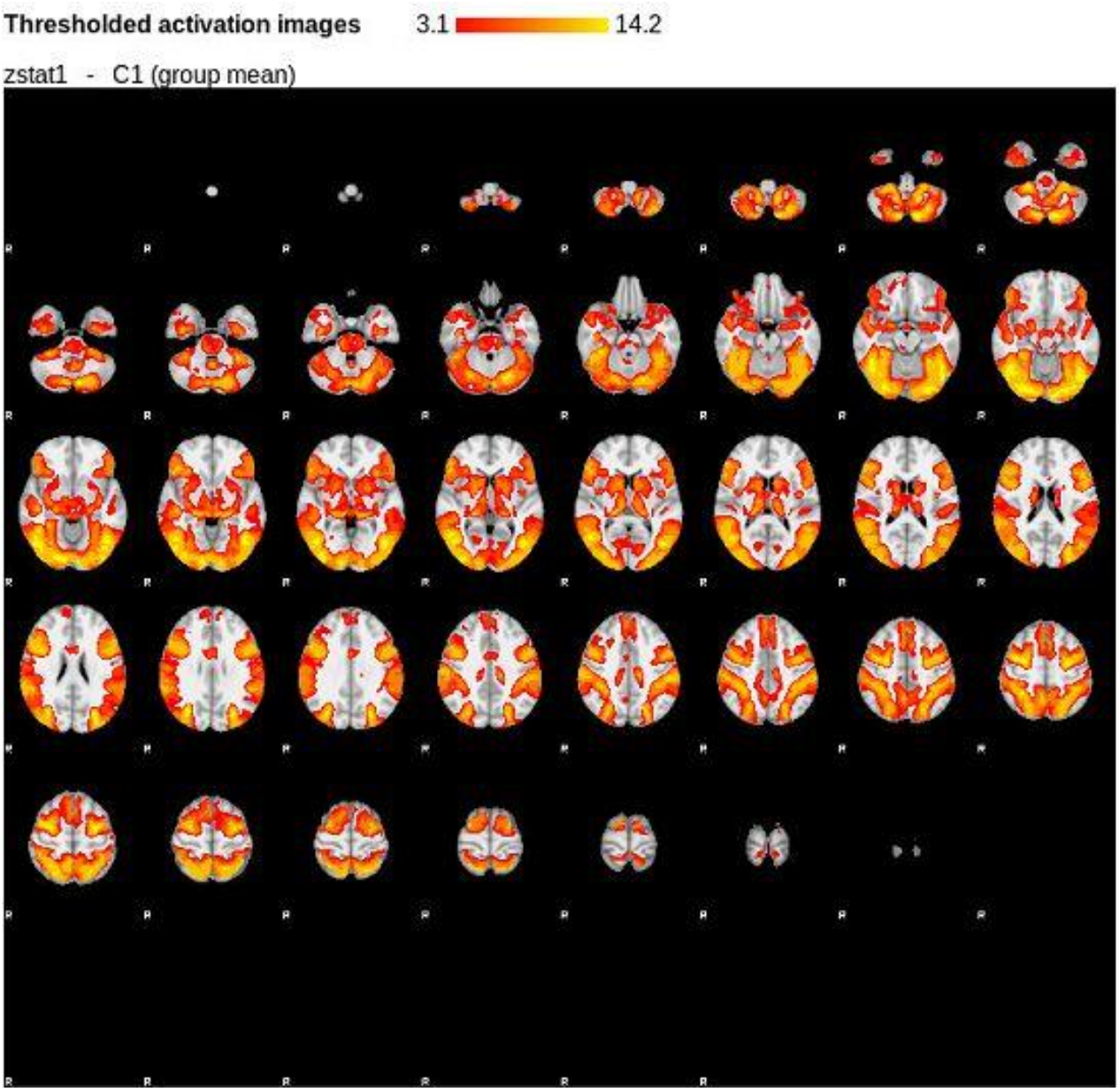

Figure 5.10 - *Social random movement > resting fixation baseline*

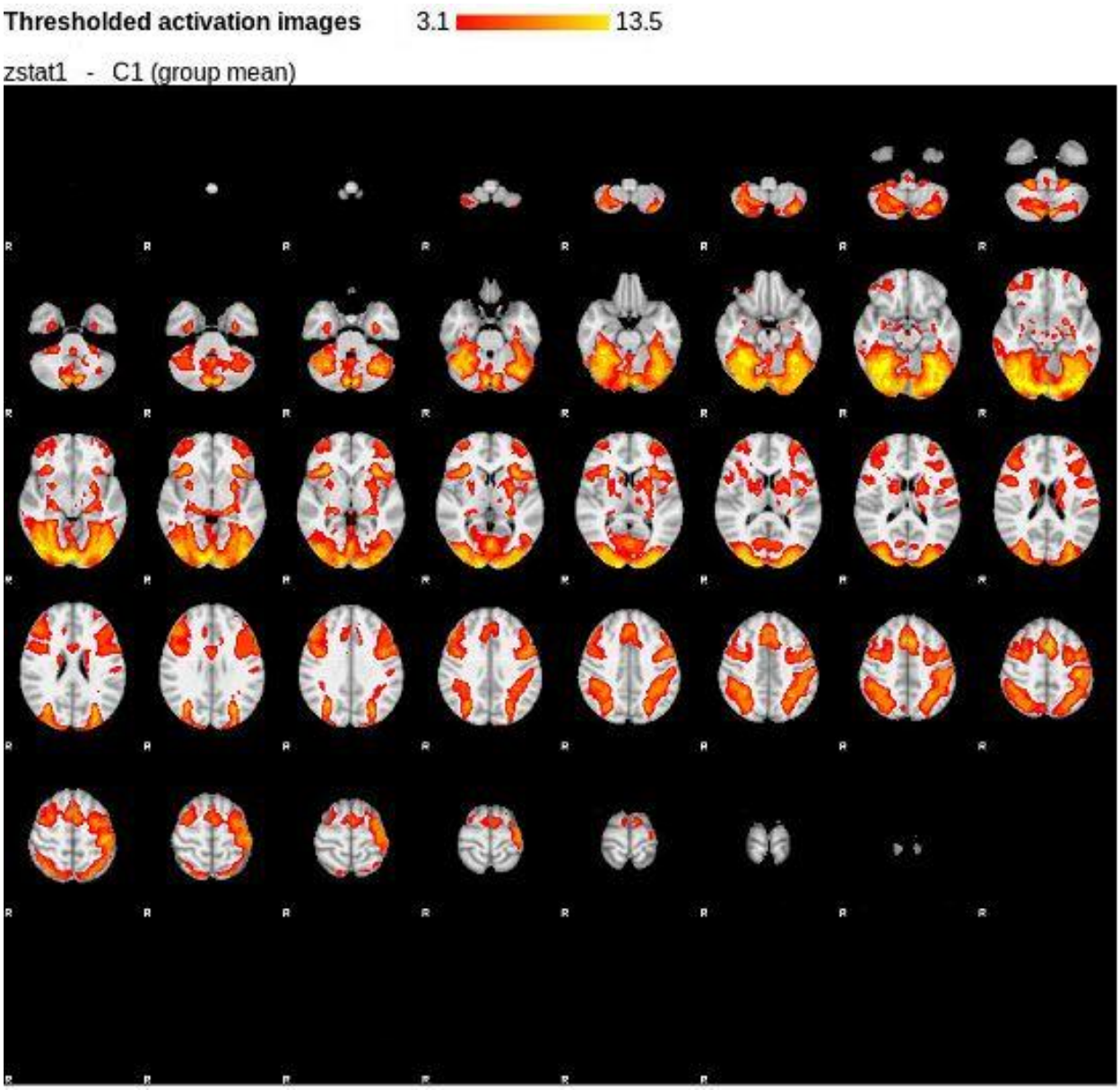

Figure 5.11 - *Memory 0 n-back > resting fixation baseline*

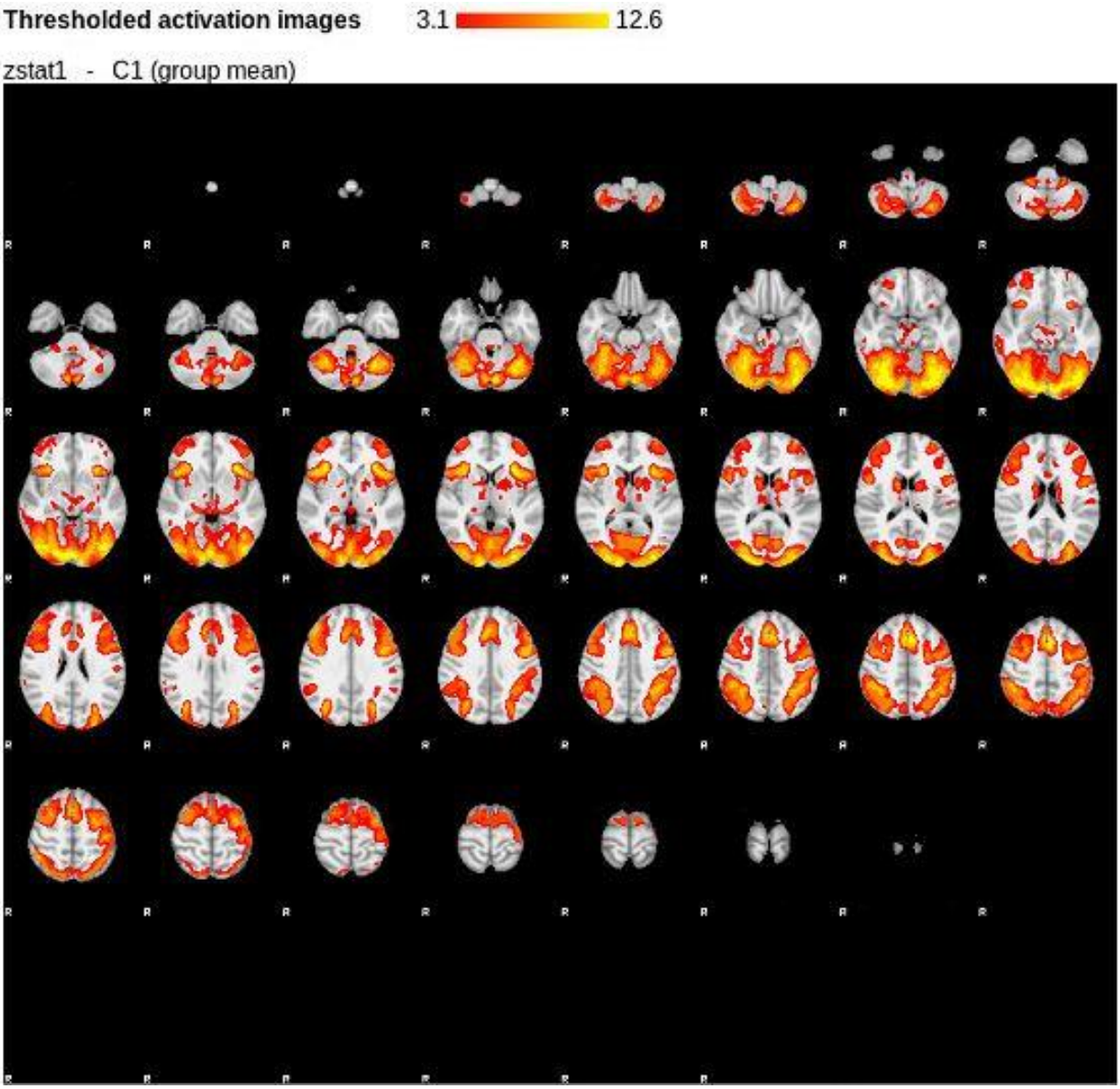

Figure 5.12 - *Memory 2nd back > resting fixation baseline*

NBRs

Figures 5.13 and 5.14 for the language task show large DMN, bilateral somatosensory, and visual deactivations; NBRs are more extensive but still contained to the DMN and NTR sensory regions. We hypothesise the NBRs are generated firstly by the PBRs for the task being mainly confined to the auditory cortex but also that the language task requires representation processing, understanding of semantics and salience meaning it was a highly engaging task and

non-task-relevant regions, in this case meaning all but the activated regions show NBRs. The NBRs however do primarily focus on the visual system extending into the dorsal attention network, the sensorimotor system extending into the parietal lobe, and the DMN network presenting frontal deactivation but that extends further into the orbitofrontal and dorsofrontal regions. While the deactivations are extensive, we conclude only NTR sensory and DMN regions are deactivated, and we do not see any evidence of NBRs in non-sensory regions responsible for cognitive processing in other conditions.

Figures 5.15 shows the NBR to the emotional processing task. When participants viewed fearful faces, we observed NBRs in the inferior cerebellum, right auditory cortex, and the right operculum as well as the somatosensory cortex primarily in the right S1 and S2 regions. We also saw deactivation in the middle and superior temporal gyrus, the medial prefrontal, and the posterior cingulate cortex regions corresponding to the DMN. Finally, we observed deactivations throughout the ventricles which likely represent artefactual responses, previously reported due to changes in blood volume (Thomas et al, 2013; Bright et al, 2014). Similar ventricle deactivations are observed in subsequent Figures but will not be further reported. Figure 5.16 shows NBR to processing angry faces and shows similar responses as in Figure 5.15 but with the addition of the bilateral hippocampus and bilateral deactivation of posterior visual cortex which was not seen in Figure 5.15. Additionally, the frontal node of the DMN has an extended deactivation going further into the inferior prefrontal cortex alongside deactivation in the orbitofrontal regions bordering on the frontal regions of the temporal lobe. In summary in the emotional copes, we see deactivation only in the NTR sensory regions and the DMN but with spatial smearing resulting in larger deactivations than seen in previous chapters.

Figures 5.17 and 5.18 show NBR to the gambling task and both show a pattern of somatosensory deactivation with a greater NBR on the right hemisphere, bilateral auditory

cortex again favouring the right hemisphere, bilateral hippocampus, and superior temporal gyrus right cerebellum deactivation. Default mode network deactivation is also present but additional right and left temporal pole deactivation along with deactivation from the DMN extending down into the anterior cingulate cortex, bilateral pars orbitalis, and anterior prefrontal cortex (Raichle, 2011; Raichle 2015) irrespective of the outcome of the gambling scenario. In this condition, we also only seen NTR sensory and DMN deactivation again with spatial smearing due to the large participant pool from the HCP dataset.

Figures 5.19 and 5.20 for the relational task show NBRs in the DMN, bilateral auditory cortices, and somatosensory regions with the greater response in the right somatosensory region. We also see the response of right and left temporal poles and the inferior dorsal to anterior prefrontal cortex deactivation adjacent to the deactivation in the frontal node of the DMN, as well as deactivation in the bilateral hippocampus and superior temporal gyrus. In contrast in Figure 5.20, we also see an extended NBR in the auditory cortices which encompasses the frontal temporal lobe and extends into the cerebellum. We also see a central deactivation which presents a smearing of the NBR in the posterior DMN and motor networks which is also seen in the gambling task and does not represent NBRs outside of the DMN or NTR sensory regions. We conclude that this shows only NTR sensory regions and DMN deactivation.

Figures 5.21 and 5.22 for the social task show standard DMN NBRs but also NBRs which have extended into the midbrain white matter and the central ventricles suggesting this does not represent true NBRs but instead noise in the data. In Figure 5.22 we see larger NBR responses than in Figure 5.21 but also bilateral deactivation of the superior temporal gyrus just anterior of the primary auditory regions which represents the temporal region of the DMN. In this condition, we see only evidence for NTR sensory and DMN deactivation.

Figures 5.23 and 5.24 for the memory task show NBRs in the auditory and somatosensory regions as is expected for a visually presented task. The default mode network also shows deactivation with the frontal-temporal pole showing particularly larger deactivation in the intensity of the response. In this condition, we also only see evidence for NTR sensory and DMN deactivation.

Finally, Figure 5.25 shows all the NBR analyses compiled into one fixed-effects flame 1 contrast to remove any sensory-specific effects due to stimulation occurring in different modalities. The results show DMN and right somatosensory NBR occurring consistently across all conditions. It is interesting that while bilateral inferior insula deactivation was seen in almost all conditions it is not seen in Figure 5.25. This is because bilateral inferior insula deactivation was not seen in the social condition.

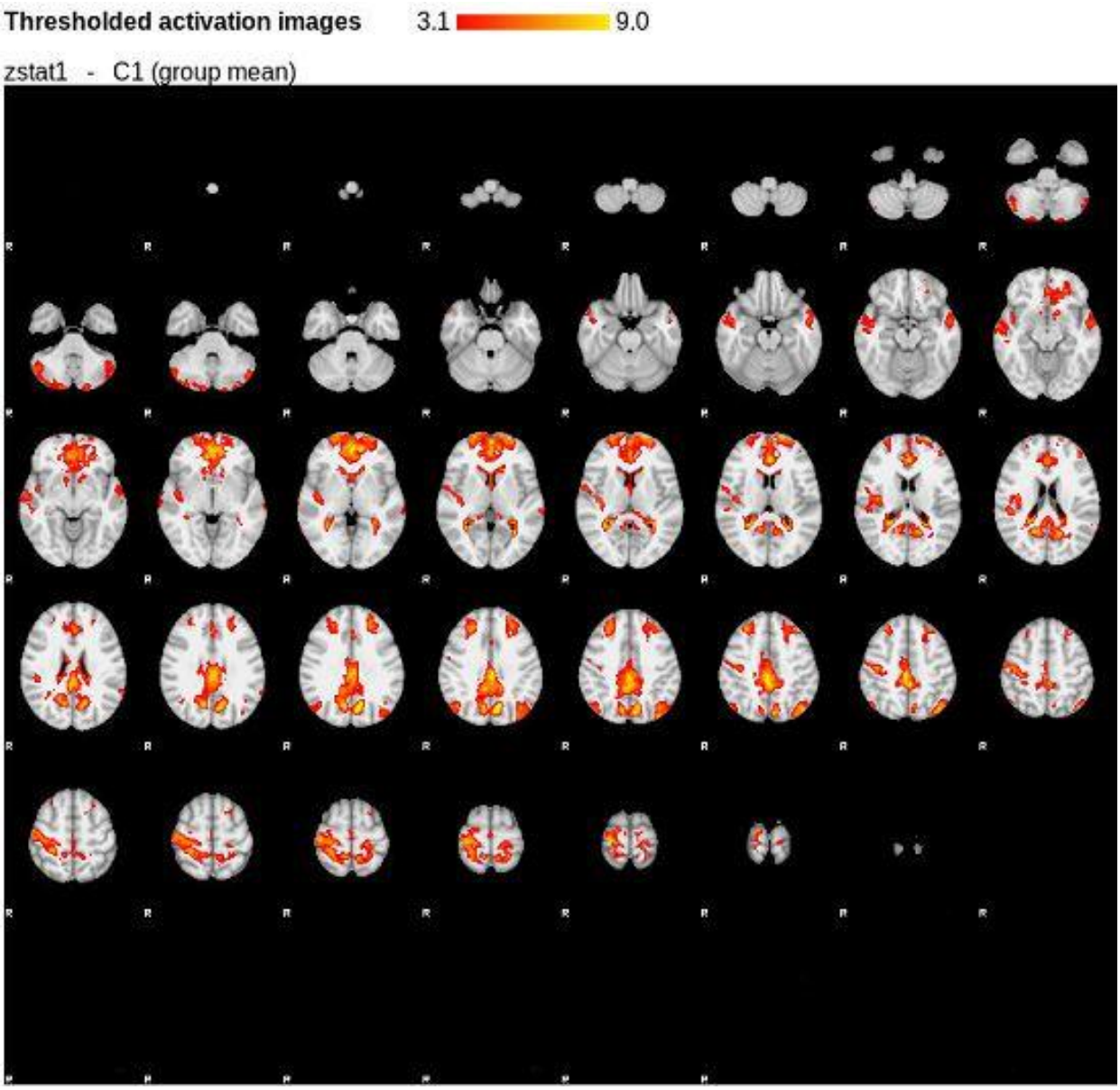

Figure 5.13 – *Emotion fearful faces < resting fixation baseline*

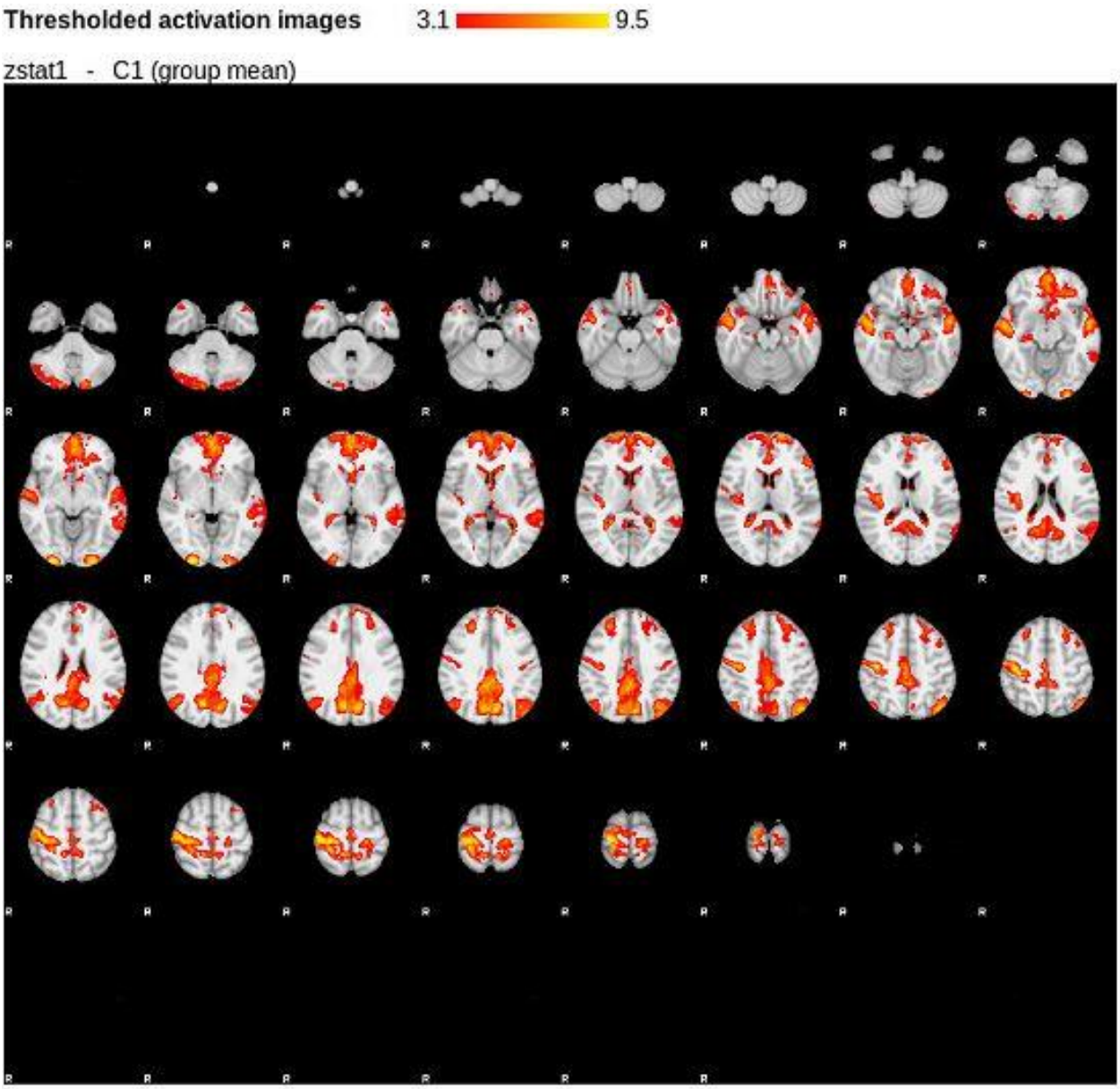

Figure 5.14 – *Emotion angry faces < resting fixation baseline*

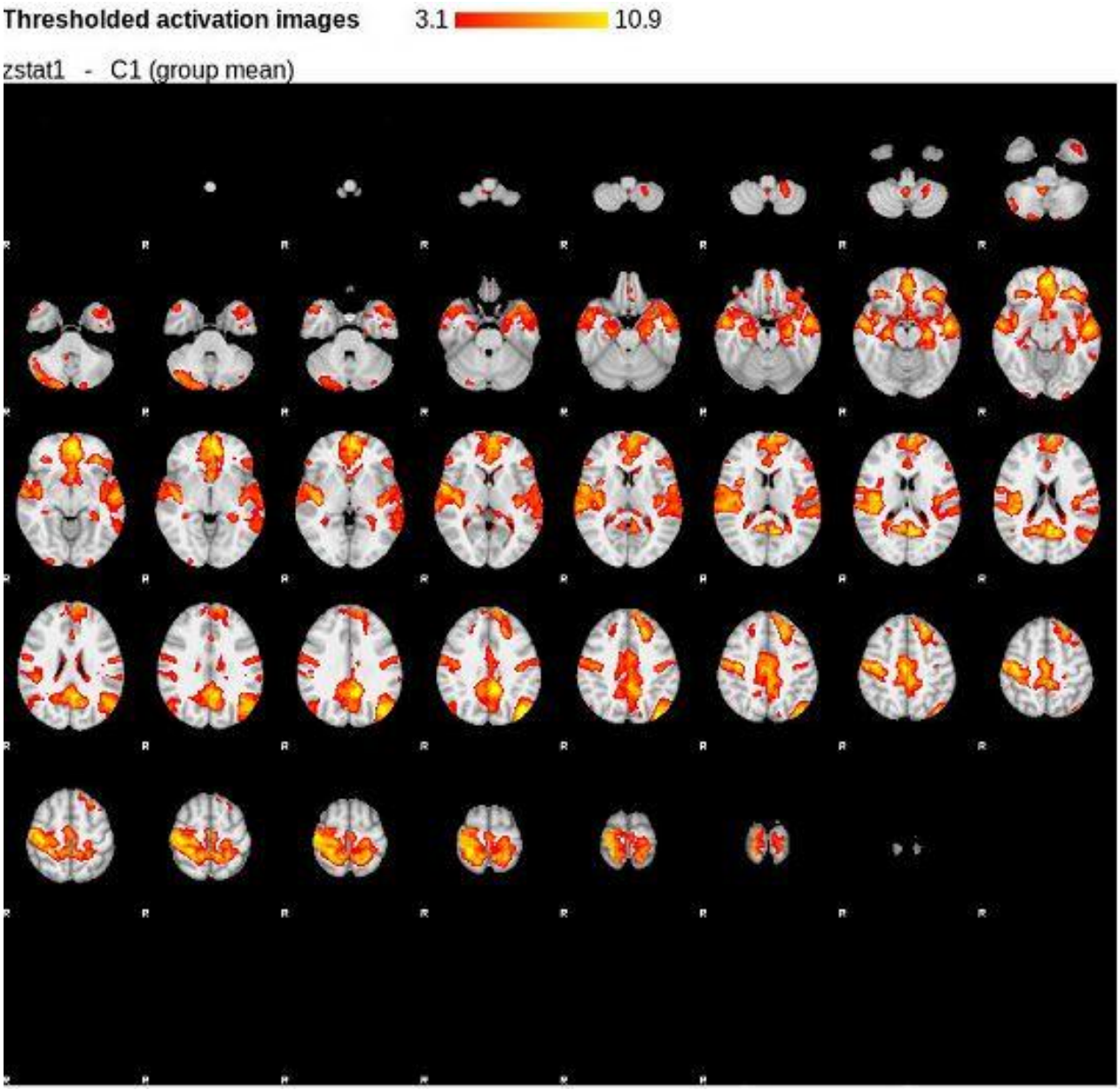

Figure 5.15 - *Gambling success < resting fixation baseline*

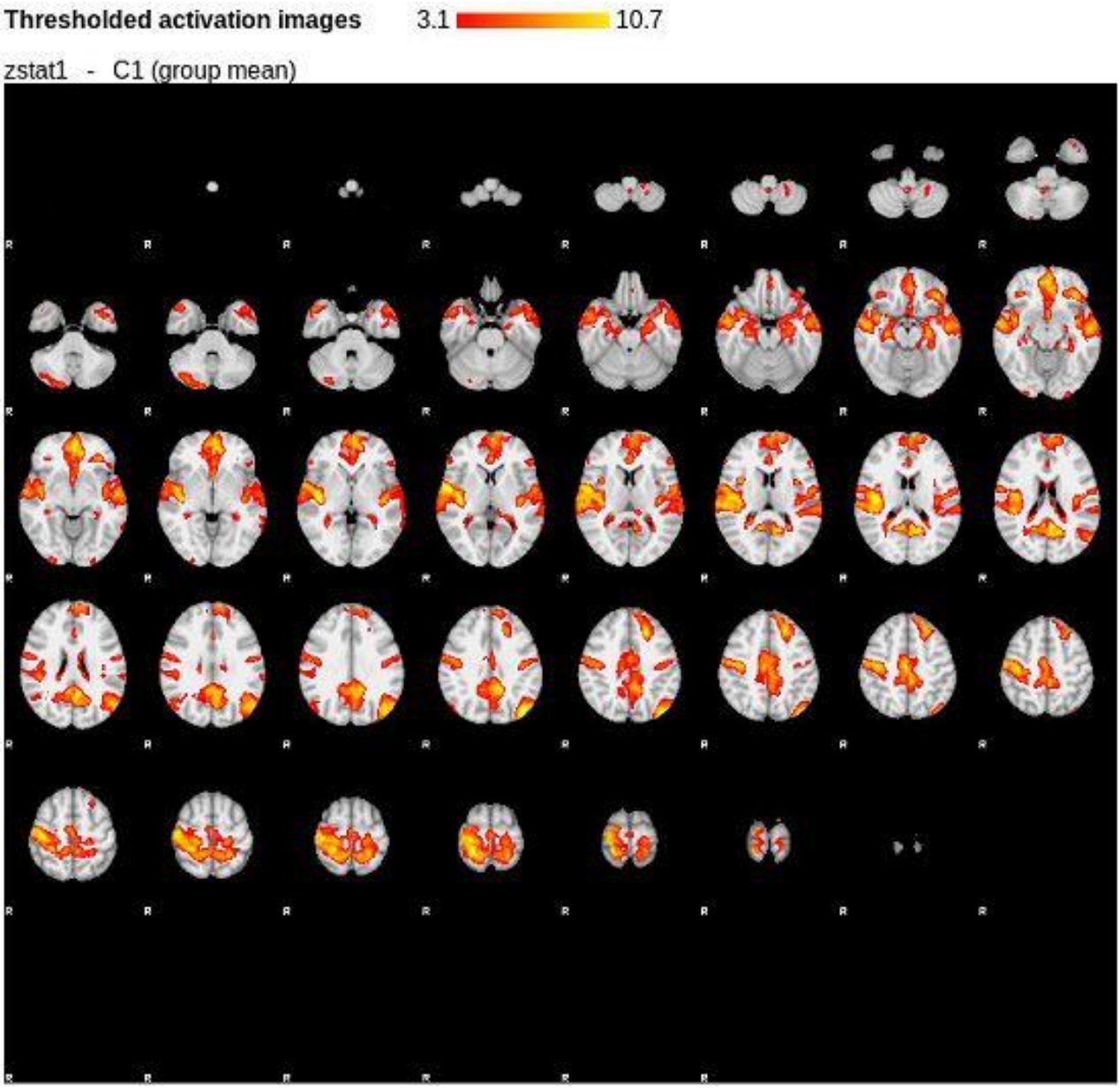

Figure 5.16 - *Gambling loss < resting fixation baseline*

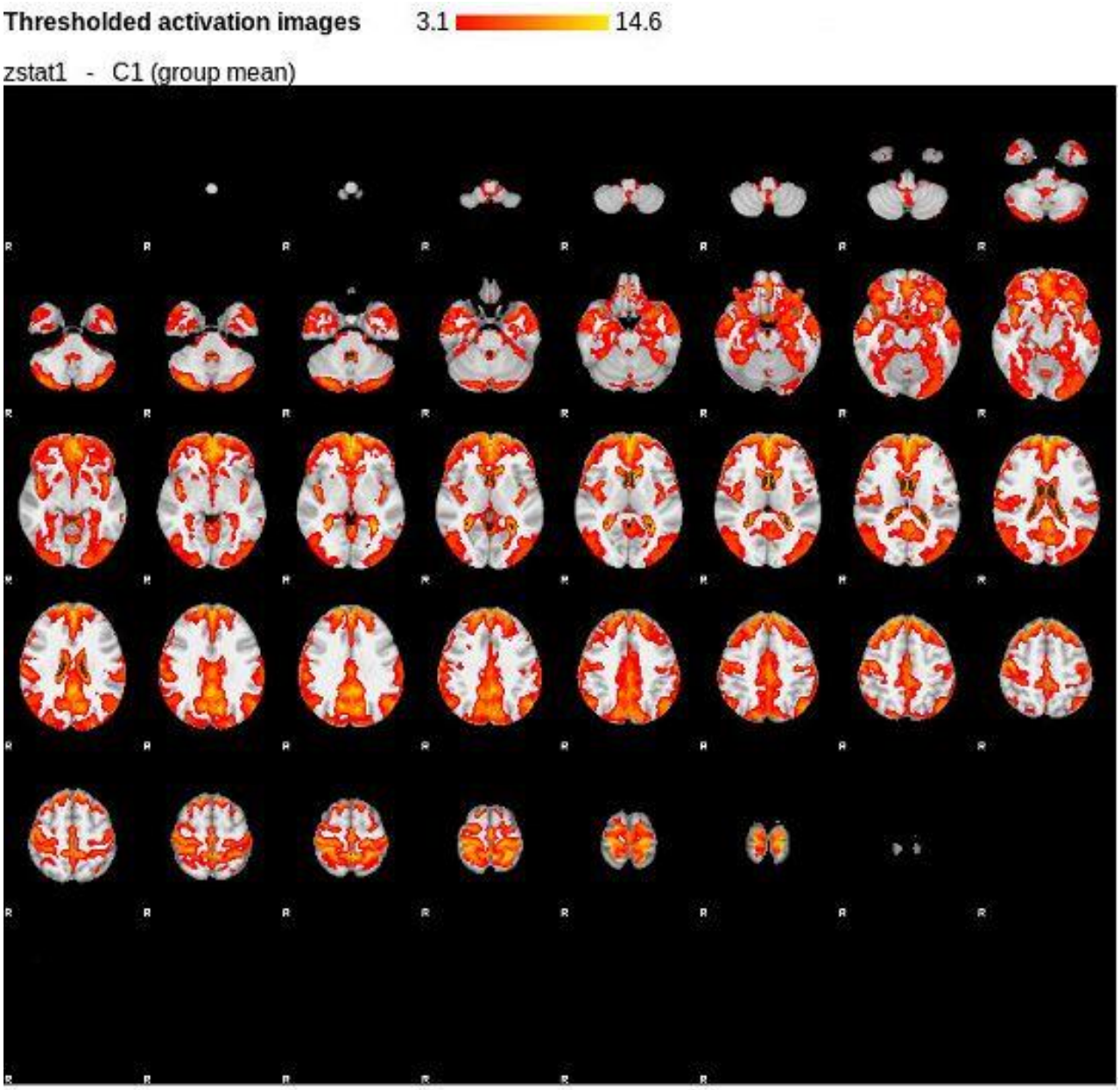

Figure 5.17 - *Language story < resting fixation baseline*

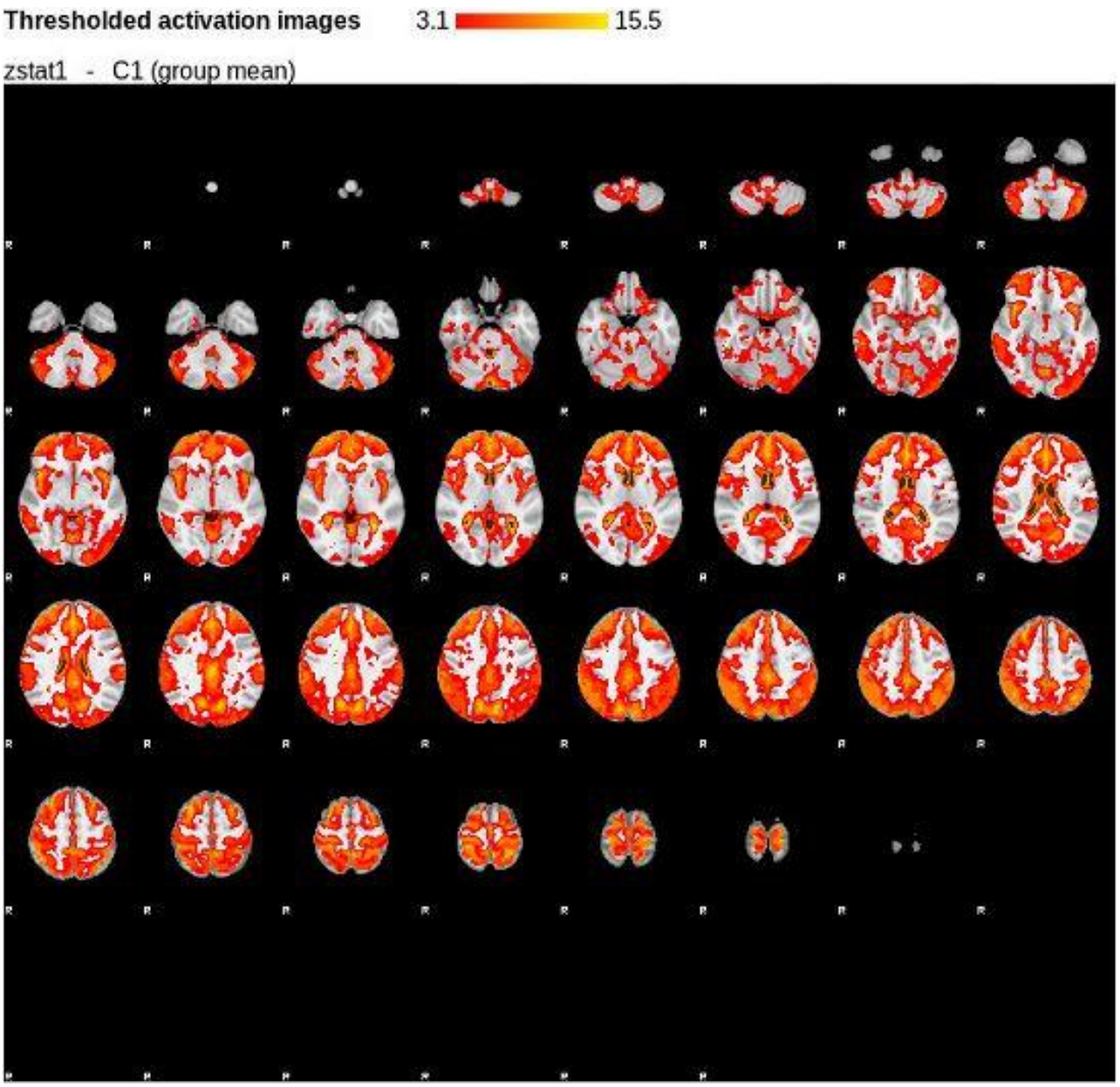

Figure 5.18 - *Language maths < resting fixation baseline*

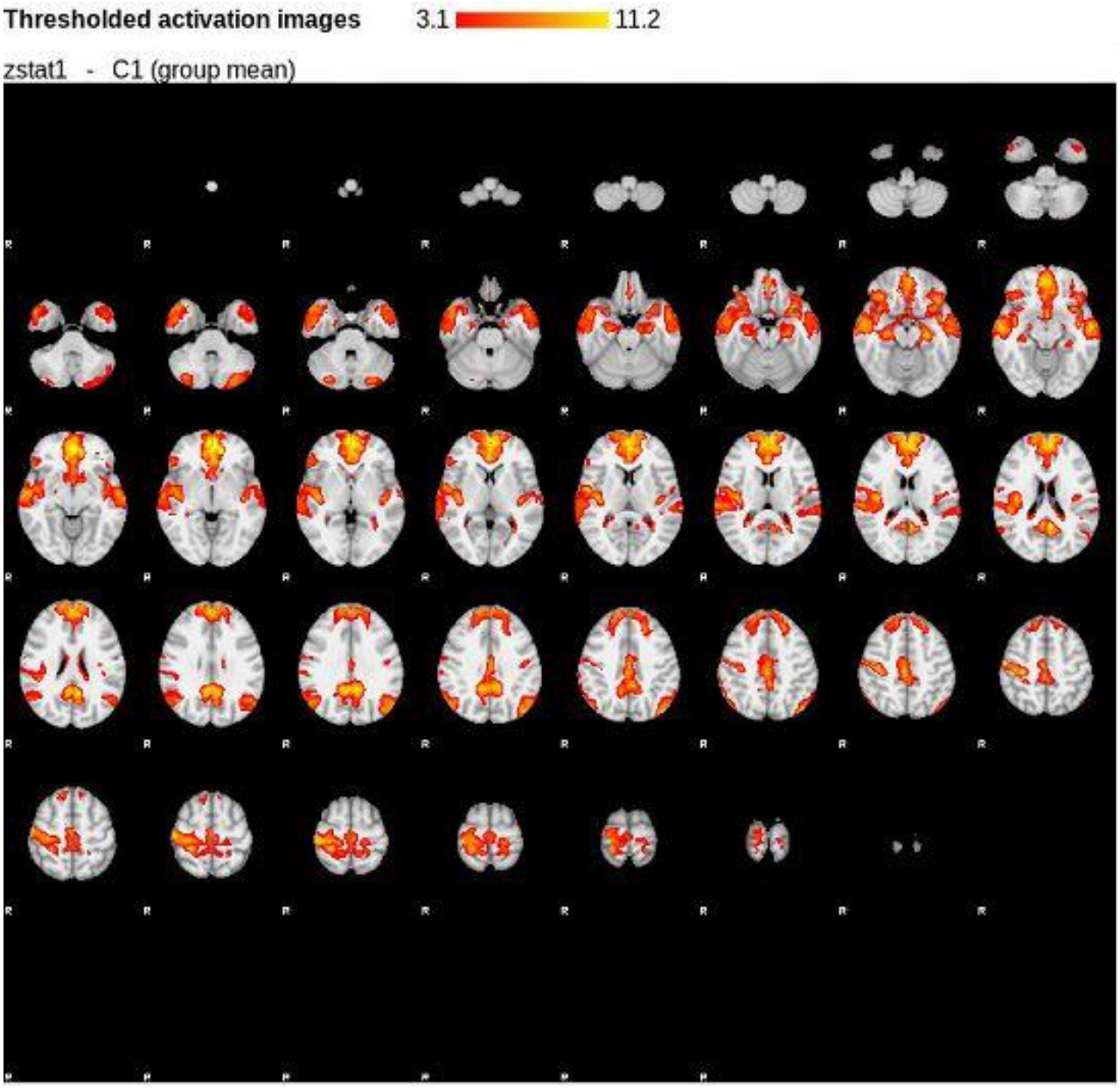

Figure 5.19 - *Relational paradigm relational movement condition < resting fixation baseline*

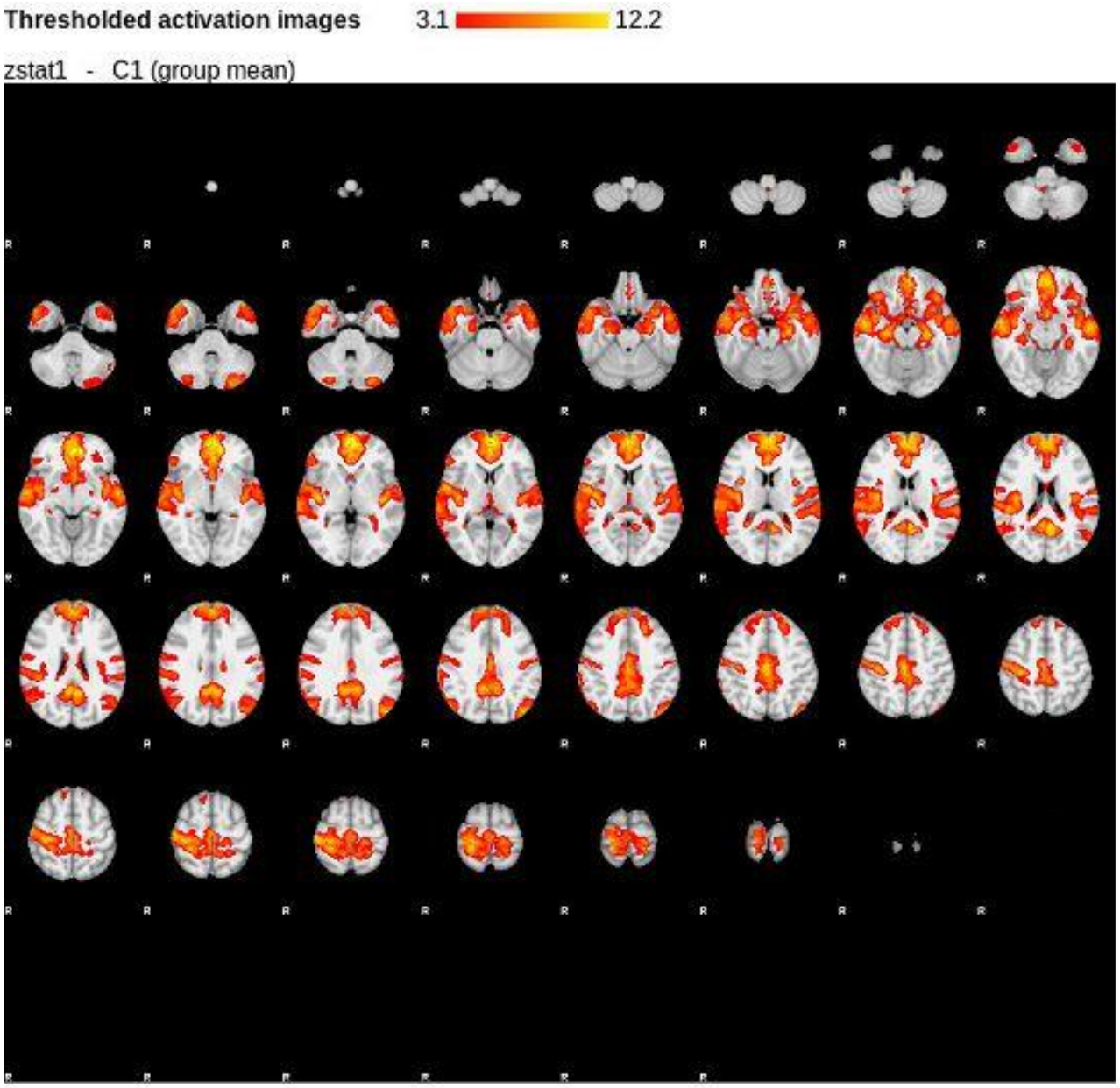

Figure 5.20 – *Relational random movement < resting fixation baseline*

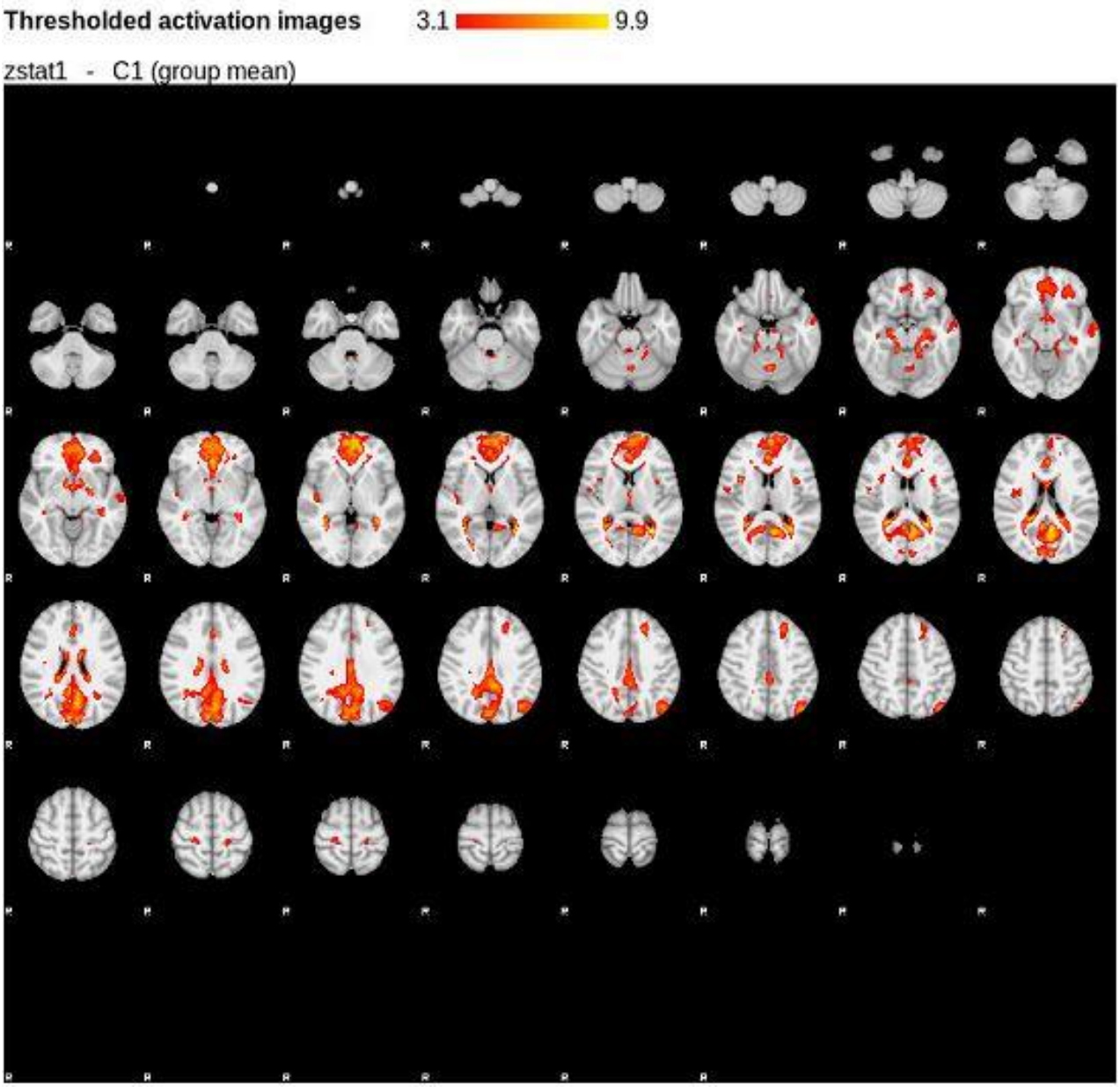

Figure 5.21 - *Social purposeful movement < resting fixation baseline*

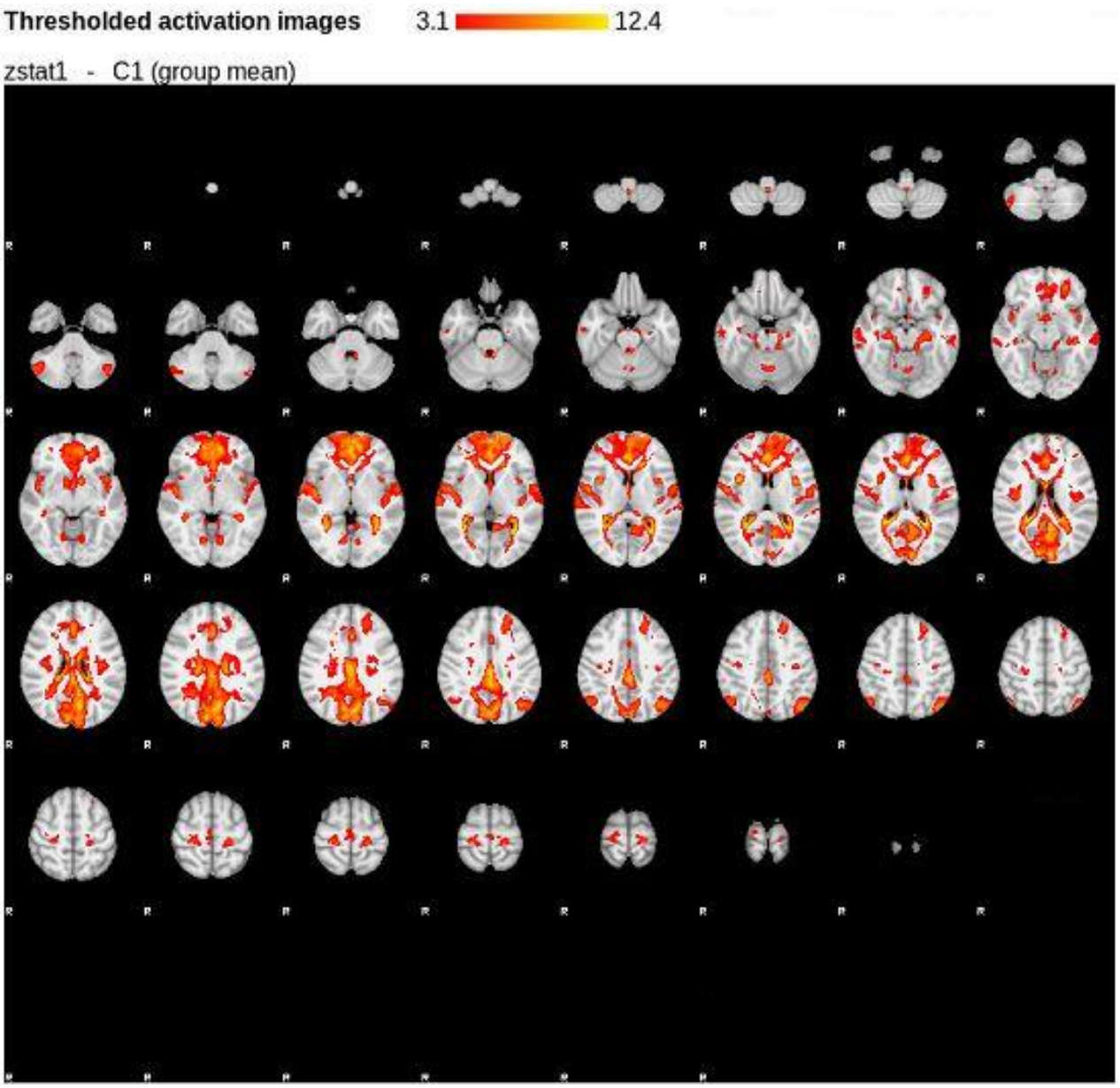

Figure 5.22 - *Social random movement < resting fixation baseline*

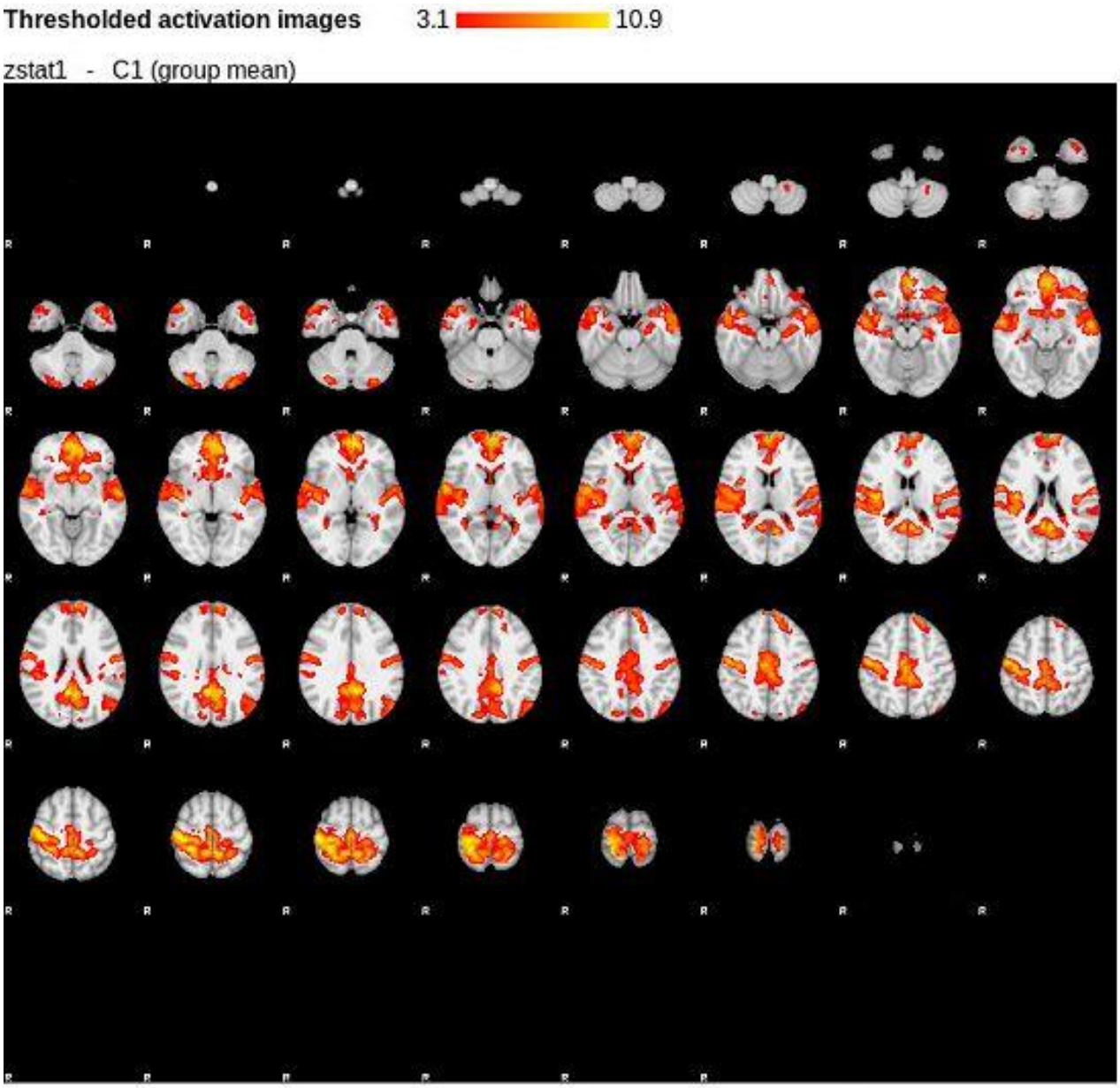

Figure 5.23 - *Memory 0 back < resting fixation baseline*

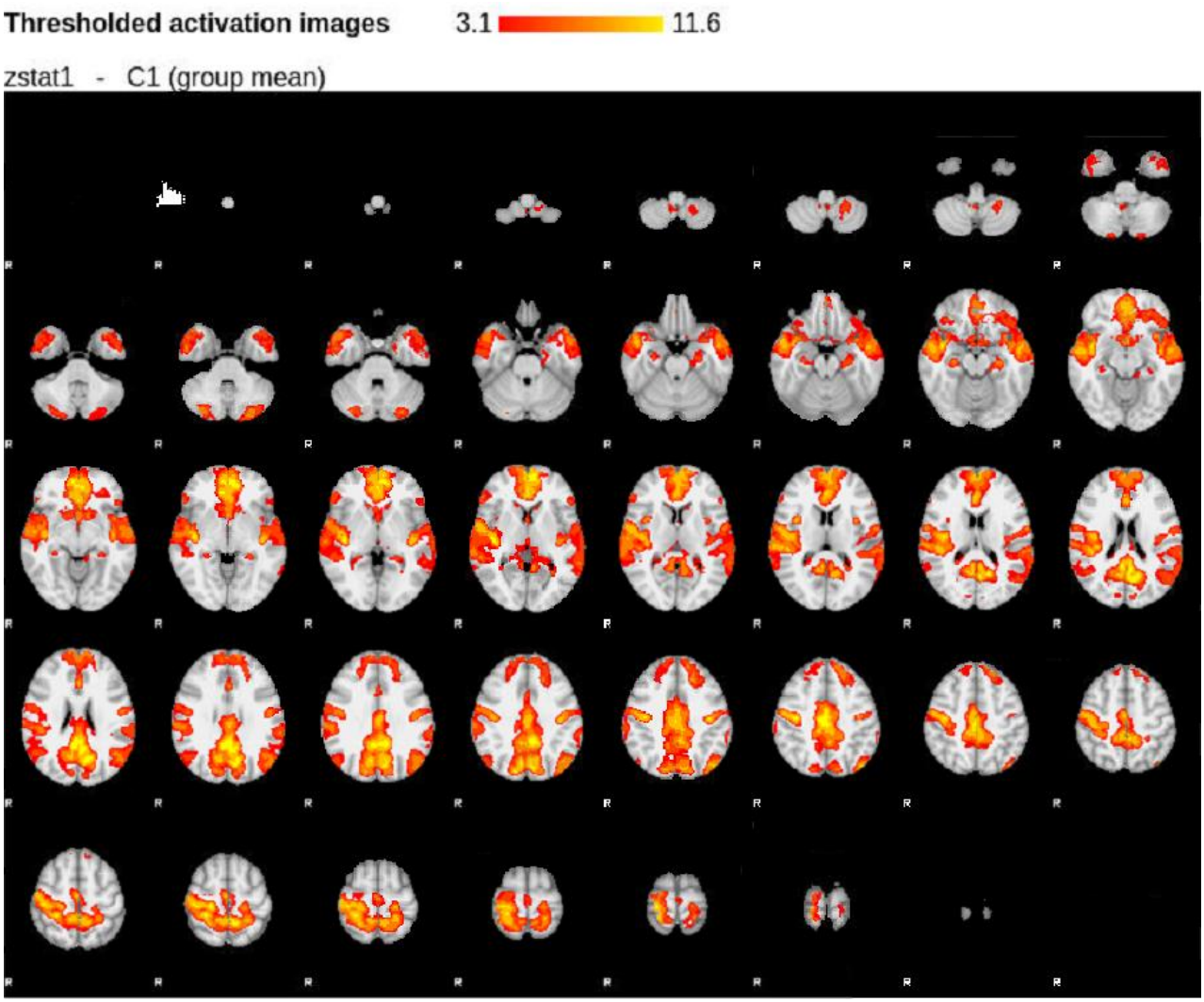

Figure 5.24 – *Memory 2 back < resting fixation baseline*

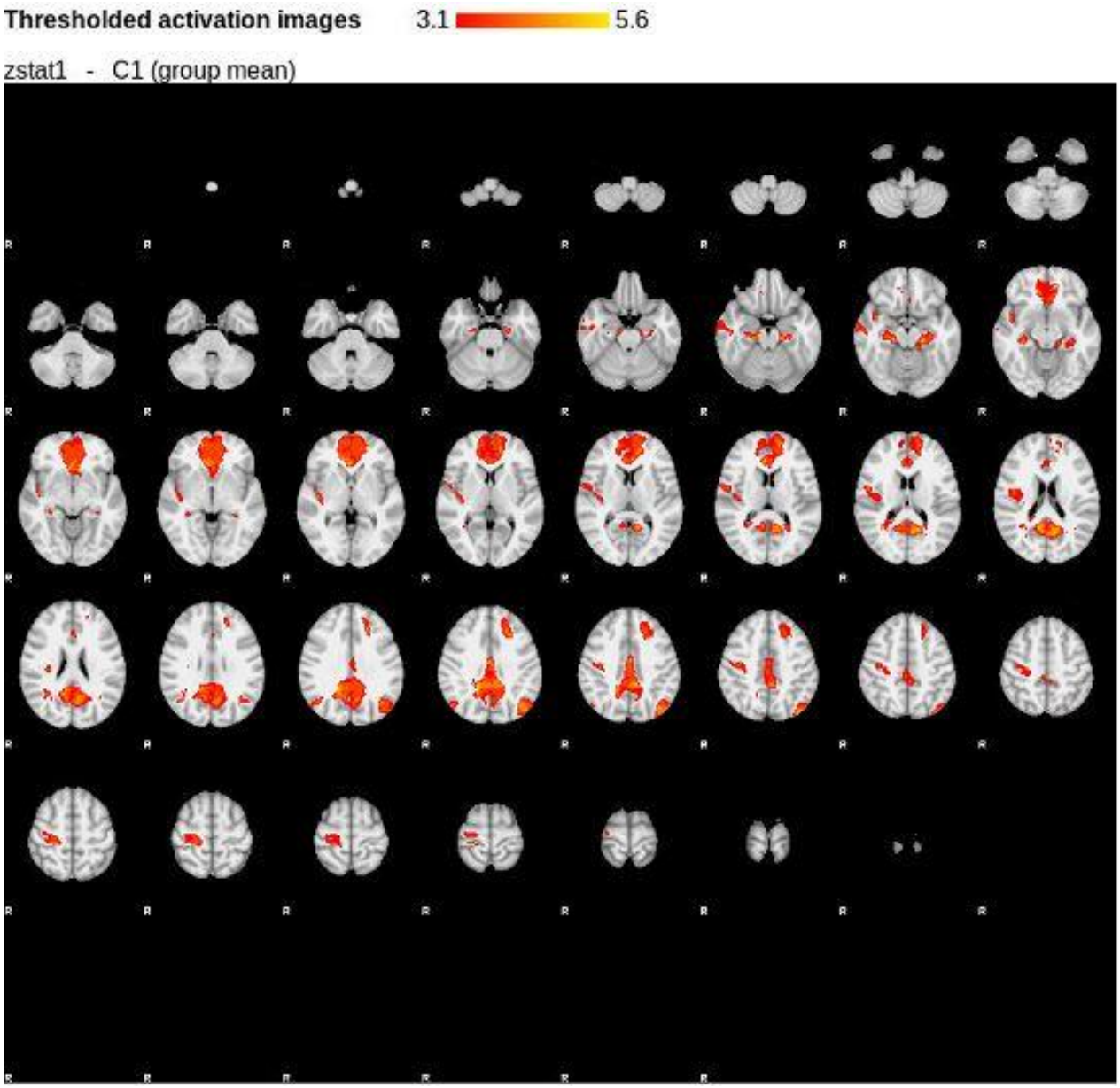

Figure 5.25 – *Fixed effect, all conditions < resting fixation baseline*

Discussion

The aim of this study was to investigate whether tasks involving cognitive recruitment of non-sensory specific functions i.e., language, memory, gambling, emotion, etc. presented the same inhibitory patterns as single and dual sensory stimulation. Our aim was to understand if inhibitory spatial maps across the cortex are a function of the cognitive systems being stimulated and as such if NBRs are tied only to the sensory stimulation for a task.

Firstly, our findings do show the main NBRs across each of the maps are in NTR sensory regions, primarily the auditory and somatosensory regions due to the experimental design of each of the conditions, and the default mode network although the extent of the NBRs did vary between conditions and this will be discussed in greater detail below. We also saw deactivations in the inferior cerebellum which we interpret as being linked to the S1/M1 deactivations seen in all of the conditions. We see regions of NBRs adjacent to the default mode network and the sensory regions. All of the conditions show somatosensory NBRs which, while they extend into the parietal lobe, are primarily ipsilateral M1, M2, S1, and S2 regions with NBRs indicative of a standard NBR during a visual or auditory task and the lateralisation we see if again due to the button box responses required for all the tasks. With regards to deactivations in the temporal poles, frontal lobe, and superior/media temporal gyrus we have identified these as DMN deactivations with a larger spatial extent which we attribute this spatial smearing to the effect of a group analysis on 100 participants. As such in this case, we must accept the null hypothesis. This finding of cross-sensory inhibition is in keeping with the literature (Mozolic et al 2008; Bressler and Spotswood, 2008, Mayhew et al 2013a and 2013b, Wilson et al 2019).

One of the hypotheses for this experiment was if NBRs could be measured in cognitive tasks outside of the DMN and the NTR sensory regions and in this regard, the hypothesis must not

be accepted. However, the other aim of the study was to see if cross-system inhibition was a repeatable pattern across cognitive networks and we did not see clear deactivation of NTR cognitive regions during conditions i.e., the hippocampus did not show deactivation during language tasks and Broca's and Wernicke's area did not show deactivation in the memory tasks. The examples given are only limited to well-known nodes of the memory and language networks, but we will see not see a clear expression of PBRs and NBRs as a function of task-relevant as we see with the sensory regions. While the previous literature on cross cognitive-sensory inhibition (Klimesch et al, 1999; Shipman and Astur, 2008; Astur et al 2005; Viard et al, 2011; Rekkas et al, 2005) formed the foundation of our hypothesis that cognitive systems may be capable of cross-system inhibition these findings did only focus on memory and its interaction to the visual system. Those papers did not show cross-memory inhibition and as such we are left without a greater depth of literature to analyse these findings with.

This leads to an immediate question which is that while the sensory systems are large complex systems in their own right the cognitive requirements to process language or remember large amounts of data are arguably larger than the sensory processing requirements which are automatic in neurotypical consciousness experience. The question then is why do NTR cognitive systems not show inhibition to a significantly greater degree than a sensory task of equal difficulty and engagement? Our current hypothesis is that while sensory systems are inhibited when non-relevant for a task the inherent integration of cognitive tasks means cross-system inhibition may not be as useful. To expand on this argument experimental manipulations to separate stimulation of the senses are very easy, purely visual checkerboards or highly stimulating auditory trains are presented throughout this thesis and allow for stimulation of one modality without activating others. Cognitive stimulation is far less delineated. During any task the use of working memory is automatic and the creation of episodic memories in neurotypical populations is also expected. Even if a subject would have

trouble recalling specific details of an experiment days later the creation of episodic memories did occur. This means that while we may not see the recruitment of hippocampal regions which is extensive enough to pass statistical thresholding during analysis the memory systems are constantly working and directly inhibiting them is, therefore, counter-intuitive to both being able to handle any task that requires working memory or in creating a coherent autobiographical line of consciousness. Additionally, with other tasks, the use of any given cognitive system cannot be predicted as unnecessary. In a reading task the use of the working memory, episodic memory, and semantic networks are immediately clear, but any given sentence may require relational processing, have automatically salient emotional content to a given reader, or any other given cognitive system. As such cognitive systems, given the variety of activities humans can engage in, are not inhibited even when non-relevant to a task because they may become immediately relevant.

However, the argument that at any given time a cognitive system could be recruited and therefore none are inhibited has its faults when assuming a generalized theory of inhibition across the whole of the cortex. In more ecologically valid scenarios, the sensory systems are not separated to the same degree as in experimental conditions. This becomes relevant because even if you were to have an ecologically valid experience where only one modality is activated the introduction of information from other senses could occur at any time and are equally likely to provide relevant information as to be a distractor. Because of this, the same logic that answers cognitive systems inhibition patterns argues against the hypothesis that sensory systems inhibit to reduce competition and improve task performance. This discrepancy can effectively be answered by abandoning attempts to provide real-world rationalizations or pseudo- evolutionary arguments. Resolution is found in accepting the experimental evidence that shows that the sensory regions and non-sensory specific cognitive regions appear to simply inhibit/regulate their activity and the activity of other similarly classified regions differently.

Limitations

While we were not able to partial out the differences due to which sensory modality was being activated during a cognitive task the results match what we saw in chapter 3 and provide a clear view that it is the sensory modality driving the inhibition map. Our original experiment design would have allowed for direct comparability between the positive and negative BOLD responses to a sensory only task or cognitive task with a matching sensory component within a participant and then across the whole group, but this element was not possible with the HCP dataset (Barch et al, 2013). Future experiments may wish to replicate the intended methods which may present information that a purely visual task and a visual task with a cognitive element may show how NBRs differ in their z score if not in the spatial distribution.

While not immediately a limitation this experiment did intend for an EEG component to be able to measure the differences in alpha inhibition across the cortex. The alpha band has been strongly implicated in inhibition across the cortex and particularly in sensory regions (Klimesch et al, 2007; Jensen and Mazaheri, 2010) so studying it in tandem with NBR given their assumed common neural source (Mullinger et al, 2014) would have been ideal. This was not possible due to COVID-19 and a complete EEG-fMRI dataset with all of the conditions required like the HCP dataset was not available. Future research should look to complete the intended study to allow for a greater understanding of the neurological activity and not just the correlated neural activity from the BOLD signal.

We also aimed in our original paradigm to measure the NBRs during a movie/tv show and watch how the presentation changes the NBRs across the cortex with a series of sliding windows in the analysis. A movie would present not just each of the cognitive networks activated here (except for the gambling task and relational tasks) but also cognitive networks working in tandem. Uri Hasson's work on 'neurocinematics' has shown that narrative and

particularly movie displays have unique neural representations starting in the sensory areas and developing across the cortex throughout the presentation which remarkably synchronise with other participants watching the same display (Hasson et al, 2008). A narrative task would allow us to measure how much networks being active at once interact and also be able to measure the interaction of synchronisation between networks generating inhibition in NTR networks. Additionally, because a task as simple as watching a tv show would involve multiple cognitive and sensory networks at once it would give us more information about how inhibition is used to regular the cortex throughout the day of 'normal life'.

Future experiments

Future experiments will need to look at more ecologically valid paradigms whilst still being compatible with an fMRI e.g., watching a scene of real people and inferring what actions will occur after the video is paused. As cognitive systems in this chapter do not appear to show a need for inhibition in NTRs as sensory systems do the question is why? How are cognitive regions capable of processing immense amounts of data simultaneously and do not engage in proactive inhibition as has been detailed in-depth in both this thesis' introduction and this chapter's. To best understand this future research should therefore aim to look at activities such as watching movies or engaging in complex social events i.e., parties and social functions. These activities involve: working memory, language, social processing, relational processing, emotional processing, and executive function as well as using the motor systems to navigate around a space, audio-visual information which is entirely expected at any event and even background smells and tastes. This example naturally results in the imaging that the entire brain except for the DMN would be needed with an activated with constant communication and feedback across all networks. Since humans are capable of engaging in events like these for hours at a time and even consider movie-watching relaxation then this will provide an example study for testing how the brain handles information and metabolite regulation over a long

period. Methods like OPM are best suited for this method given the relative comfort and ease of mobility provided with a fitted helmet. Unfortunately, full brain neuroimaging coverage with full mobility and minimal intrusion on daily life is beyond the scope of modern neuroimaging so can be a challenge for future generations to come.

Beyond the scope of Cognitive Neuroscience, another question is left over from the analysis of this data. The evidence is that NBRs are a function of the sensory modalities stimulated in a task and not the cognitive networks required to process a task. This thesis however does not have the ability to provide a rationale for why in neurophysiological terms. The answer to why sensory regions show NBRs in the patterns described and cognitive regions do not means research into the neurons and glial is needed to specify understand how the energy and metabolite demands of these regions are handled. fMRI and EEG/MEG are ill-equipped to answer questions on neuronal inhibition/regulation from the standpoint of neurobiological signalling and other fields are invited to explore this question through single cell studies, genetic manipulations, and neurotransmitter recordings on the cellular level.

Finally, while each of the NBR maps presented for this study show repeated DMN deactivation as is expected during a task this chapter has not explored the patterns of activity. The spatial information of deactivations across the DMN has been studied in-depth and while the temporal information of the DMN was not the remit of this paper it is an area with a great deal left to investigate. Future research should look to investigate the differences in the spatio-temporal communication patterns across the nodes of the DMN using EEG-fMRI.

Chapter 6 – General thesis discussion

The aim of this thesis was to better understand how functional inhibition is represented across the cortex during stimulation, especially focussed on investigating the following areas:

1. During stimulation of multiple modalities with increases in cognitive load (Chapters 2 and 3)
2. To compare how different imaging modalities represent functional inhibition across the cortex using comparable experimental paradigms (Chapter 2 and 3)
3. During stimulation instead of just in the post-cue, pre-stimulation period (Chapters 2, 3, and 4)
4. Comparing dual stimulation trials where cues were correctly provided and that facilitated proactive inhibition of distraction to trials with inaccurate cues that required reactive processing of distractors (Chapter 4)
5. Across multiple cognitive systems to see if the same pattern of NTR functional inhibition observed in the sensory modalities was also present in networks responsible for cognitive tasks i.e., language, emotional processing, relational processing, and memory. (Chapter 5)

The other fundamental aim of the thesis has been to take the general theory laid out in the paper ‘Alpha Inhibition Hypothesis’ by Klimesch, Sauseng, and Hanslmayr, 2007, and to probe the limits of this theory. As discussed in the opening thought experiment the goal of the Psychology and Neuroscience fields is to obtain a comprehensive and ecologically valid understanding of neural activity and cognition. That means developing experimental paradigms with the appropriate level of control of variables and confounds while still providing insight into infinitely more complex everyday scenarios. On reflection, a key driving force throughout this thesis has been the criticism that some of the paradigms are so

stimulating as to leave little room for inhibition. Once I was presented with that idea a challenge came to mind ‘if something as mundane and simple as watching a TV show was so stimulating as to leave no room for inhibition across the cortex (except in the DMN), then what is the point of functional alpha/NBR inhibition?’. Now before going into that thought in more depth, it should be caveated with the acceptance that inhibition in many cases is passive, or the result of multiple sources of inequal intensity in real life, and there are many other forms of inhibition in the cortex outside of the purely alpha/NBR NTRR inhibition studied in this thesis. With that caveat firmly in place, the question remains.

This thesis also does not attempt to claim the alpha inhibition hypothesis, or any non-formalised version for NBRs, is not well-founded. The research which informs the theory is very well established and provided an excellent base for this thesis. However, it is primarily focused on single modality experiments with a focus on anticipatory processes using cue-based paradigms. The first two experiments of the thesis attempted to understand the effect of how concurrent stimulation of multiple modalities would affect NTRRs compared to single modality stimulation. In everyday life, it is difficult to find single modality environments unless a person deliberately attempts to. Chapter 2 and Chapter 3, therefore, probed this question using both fMRI and EEG respectively. The other fundamental question Chapter 3 approached (along with Chapter 4) was how alpha inhibition is relevant to functional inhibition that takes place during stimulation and that lasts at least a few seconds. Alpha inhibition is very well studied during bursts of a couple of hundred milliseconds usually following a cue and before a target stimulus (Thut et al, 2006 Rihs et al, 2007; Romei et al, 2008a; Romei et al, 2008 b; de Graaf et al, 2013; Marshall et al, 2015; Mazzetti et al, 2019) but is the alpha oscillation also responsible for performing more sustained functional inhibition?

In Chapter 2 we did not find any clear effect of single vs dual inhibition across the NTRRs, but we did see sustained NBRs throughout the stimulation period. In Chapter 3 we saw

instead that sustained alpha ERS was rare or difficult to measure due to a variety of factors including: between-subject variability in alpha synchronisation/desynchronisation, maintaining a sustained response, and spatial smearing of the visual ERD response to other NTRRs during visual stimulation conditions. These two experiments showed us firstly that at least regarding NBR the inhibition response seen in NTRRs was not modulated by the number of modalities active but there was evidence that it was modulated by the cognitive load in other experiments (Klimesch, Schimke and Pfurtscheller, 1993). Since the participants were only instructed to attend to one modality at a time it appears the NBRs in Chapter 2 were driven by where the attention was focused, rather than the overall cognitive load of the experiment. This provides valuable insight when theories of functional inhibition have to move away from single modality paradigms and into a world where dual or greater modality stimulation is the norm. Furthermore, looking into the findings of Chapter 3 we see that sustained functional inhibition if present is not controlled by alpha synchronisation and this begins to shape how we view the more general role of alpha oscillations. Even throughout a sustained (seated) conversation, certain brain regions e.g., motor areas controlling the feet are likely non-task relevant throughout, and automatic processing handles posture and moving the feet as to be comfortable without constant attention. However, our results, at least speculating from a stimulation period of a few seconds to longer periods, suggest that alpha oscillations in NTR are not clearly modulated during this type of task. The wider literature (Pfurtscheller, Stancak and Neuper, 1996) is filled with excellent examples of alpha's ability to control NTRRs for bursts of a few hundred milliseconds particularly in order to control the parcellation of information through gamma oscillations (Jensen and Mazaheri, 2010). However, for long periods when managing interference from NTRRs, it appears that alpha oscillations are not the primary mechanism by which this is achieved. This further clarification of the uses of alpha oscillations across the cortex and how they support

the enormous task of creating a coherent and useful attention network is very useful to researchers in many disciplines.

The other key element we wanted to investigate was how reactive distractors, that is those occurring concurrently with the target, were processed. We studied whether we could measure any difference in the use of alpha oscillations during reactive scenarios compared to proactive ones. The field has focused almost exclusively on using Posner-like tasks (Posner, 1980; Nobre et al, 2007; Doricchi et al, 2009), particularly visual lateralisation tasks, to prepare the participant for upcoming stimuli and focused heavily on understanding the period post cue but pre-stimulation (Thut et al, 2006 Rihs et al, 2007; Romei et al, 2008a; Romei et al, 2008 b; de Graaf et al, 2013; Marshall et al, 2015; Mazzetti et al, 2019). Chapter 4 studied how sustained reactive stimuli affected the alpha oscillations in the visual cortex following the studies of reactive and sustained distractors albeit with a relatively small amount of literature in this area compared to proactive alpha (Sauseng et al, 2009, Vissers et al, 2016, Marini et al, 2016, Janssen et al, 2017). Our work found no significant differences between proactive and reactive conditions, after type 1 correction, in the visual regions in the power of the alpha oscillations. While other work had studied the effect of distractors (Sauseng et al, 2009; Vissers et al, 2014) the paradigms used had not been truly random and preparation by participants was both possible and expected. Our paradigm provided a truly random set of conditions where reactive processing was the least likely option and participants were best suited to follow the cues provided. Still, in this paradigm, we confirmed the work of Vissers et al, 2014, and found that alpha oscillations lack any significant change in alpha power at all in those regions regardless of if the cue was correct or not.

Chapter 3 provides a picture of alpha oscillations being primarily absent in conditions that require sustained inhibition and having no clear differentiation, at least based on power, depending on if the condition was cued correctly or not during the sustained stimulation

period. Alpha's role is best understood during brief bursts following a cue to guide attention for periods in the range of hundreds of milliseconds, not seconds. However, as the paradigm measures 'during stimulation' the processing of the visual scenes results in a complex array of neural firing, not just in the alpha band, and not just limited to only EEG readable signals which would make measuring specific changes in alpha power harder to isolate. With that being said we do see large variability in the power of the alpha response and some participants showed stimulus period ERS, showing they were able to synchronise alpha for periods of longer than a few hundred milliseconds. However other subjects presented a visual alpha ERD despite the visual cortex being NTR in certain conditions i.e., somo alone and somo-auditory stimulation. In chapter 3 we saw a much greater variability in responses, (Figures 3.5 – 3.13) than the literature had previously discussed and while the average response was not significantly different from the baseline period this was due to a mixture of alpha ERS and ERD being exhibited across participants. Since we did not see consistent ERD or ERS responses across the trials it is possible our study lacked sufficient stimulation and may have been flawed but the same paradigm did produce consistent inhibitory responses in chapter 2 and as such subject variability in alpha power is more likely than simply the paradigm was incapable of generating an inhibitory response. As such this finding of limited sustained alpha synchronisation/desynchronisation is a key area for future study and brings forth the most interesting questions of this discussion:

1. Are there two or more populations of people with different expressions of alpha oscillations across the cortex?
2. Do these high and low alpha presentations affect behavioural/performance scores or how neural communication functions in any meaningful way? To clarify is the difference in alpha oscillation expression actually affecting anything or is it simply

two different ‘frameworks’ for how alpha oscillations can occur in the cortex but does not present any bearing on day-to-day functioning?

3. If the above point is correct and these differences in alpha oscillation power and the ERS/ERD response to sustained stimuli do not affect participant performance or other neural activity insignificant/meaningful ways how does that reflect on the role of alpha? In the case of low alpha subjects, are other oscillations or other neural systems compensating to allow for reductions in interference? Can the stimulated sensory modalities handle both processing incoming information and inhibiting interference through boosting other regions to provide increased gain in signal processing or simply not require suppressing interference in some participants due to better filtering at the point of multisensory integration?

The other key area from this thesis is the discussion in chapter 5 over how NBRs show the use of functional inhibition during cognitive tasks that only require half a minute to complete. The HCP has a full battery of cognitive tasks and controlled localisers that represent many tasks that people would complete in everyday life even if they are seemingly automatic i.e., social processing, emotional processing, and language to name a few. The analysis we conducted however showed across the battery of tasks that NBRs were driven by the sensory modality being stimulated i.e., visual stimulation, regardless of the cognitive domain focused on by the task, resulted in auditory and somatosensory NBRs in the same manner as a visual checkerboard only paradigm. The experiment highlighted that non-modality-specific cognitive tasks do not cause NBRs in other non-task relevant cognitive regions i.e., a memory task involving a series of numbers with no emotional content did not cause NBRs in the emotional processing regions highlighted in the HCP dataset.

Chapter 5 was originally intended to be an fMRI/EEG experiment that would study how alpha oscillations and NBRs combined informed the inhibition of NTRRs, where possible

with EEG's spatial resolution, but this was not possible due to the COVID 19 outbreak. The discussion will therefore be limited to imply that where NBRs are present we can assume functional inhibition is occurring and speculate that alpha synchronisation and functional inhibition are also occurring given prior literature which provides a correlation between the two (Mullinger, Mayhew, Bagshaw, Bowtell and Francis, 2012); Mayhew, Ostwald, Porcaro, and Bagshaw, 2013); Mullinger, Mayhew, Bagshaw, Bowtell, and Francis, 2014). The presentation of NBRs as a function of the stimulated modality instead of the cognitive regions leads to another very interesting question:

- During paradigms without auditory or somatosensory stimulation we see inhibition in the auditory and somatosensory regions, so why do we not see inhibition in networks responsible for emotional processing and memory consolidation during tasks with no emotional or memory component?

The most obvious question to ask following that question is:

- is inhibition as measured in this thesis only a sensory/DMN phenomenon?

This question naturally comes with a complication immediately which is that in chapters 3 and 4 we see evidence that sustained alpha responses are rare and difficult to analyse due to high variability in alpha power across the population. On the other hand, chapters 2 and 5 present NBRs which are slow in their temporal resolution but robust and easily measurable throughout the entire stimulation. This incompatibility is unavoidable when comparing EEG/MEG and fMRI experiments and hampers attempts at speculation on the more general cognitive control systems in the brain. fMRI and NBRs are driven by changes in the local metabolic activity of a given region (Logothetis, 2001) but alpha ERS is due to changes in neural synchrony of ongoing firing. The required change for an alpha ERS is not that more or fewer metabolites are demanded, only that neurons already firing fire in phase. As such it is

theoretically possible for no sudden metabolic change to be required that would result in either an NBR or PBR but an alpha ERS/ERD could occur.

Overall, this thesis has worked to produce a series of challenges and clarifications to the idea of functional inhibition across the cortex. This discussion has come to the conclusion that functional inhibition measured through dual-modality stimulation does not appear to generate significantly greater inhibition in NTRRs than single modality or that alpha inhibition is the primary mode of reducing interference from NTRRs for sustained periods longer than a second. The role of alpha then appears to be closer to a binary switch that sets a region to either be inhibited or not and only for a short period of a few hundred milliseconds as preparation for incoming stimuli that are not desired.

To conclude this thesis the areas for future research I suggest are developing a better understanding of the greater levels of variability in inhibitory responses than I was initially prepared for when starting this body of work. This variability represents an opportunity to better understand how inhibition is being used by different people and different brains and why in some scenarios we see no inhibition and in others, we see overwhelming responses that make measuring other signals almost impossible. The other area I suggest for study in is why the various non-sensory specific cognitive systems we studied do not appear to engage in competitive functional inhibition and instead the inhibition measured in this thesis at least is restricted to only the sensory networks and DMN. Those two areas provide some of the most fertile ground for continuing to study how our brains inhibit, regulate and control information and most importantly why brains do not do so across all networks, neural populations, or people uniformly.

Bibliography

Adrian, E. D., & Matthews, B. H. (1934). The Berger rhythm: potential changes from the occipital lobes in man. *Brain*, *57*(4), 355-385.

Allison, J. D., Meador, K. J., Loring, D. W., Figueroa, R. E., & Wright, J. C. (2000). Functional MRI cerebral activation and deactivation during finger movement. *Neurology*, *54*(1), 135-135.

Amari, S. I., Cichocki, A., & Yang, H. H. (1996). A new learning algorithm for blind signal separation. In Advances in neural information processing systems (pp. 757-763).

Arthurs, O. J., Williams, E. J., Carpenter, T. A., Pickard, J. D., & Boniface, S. J. (2000). Linear coupling between functional magnetic resonance imaging and evoked potential amplitude in human somatosensory cortex. *Neuroscience*, *101*(4), 803-806.

Arthurs, O. J., & Boniface, S. (2002). How well do we understand the neural origins of the fMRI BOLD signal? *TRENDS in Neurosciences*, *25*(1), 27-31.

Astur, R. S., Germain, S. A. S., Baker, E. K., Calhoun, V., Pearlson, G. D., & Constable, R. T. (2005). fMRI hippocampal activity during a virtual radial arm maze. *Applied psychophysiology and biofeedback*, *30*(3), 307-317.

Babiloni, C., Vecchio, F., Bultrini, A., Luca Romani, G., & Rossini, P. M. (2006). Pre-and poststimulus alpha rhythms are related to conscious visual perception: a high-resolution EEG study. *Cerebral cortex*, *16*(12), 1690-1700.

Babiloni, C., Pizzella, V., Del Gratta, C., Ferretti, A., & Romani, G. L. (2009). Fundamentals of electroencephalography, magnetoencephalography, and functional magnetic resonance imaging. *International review of neurobiology*, *86*, 67-80.

Baddeley, A. (1992). Working memory. *Science*, *255*(5044), 556-559.

Barch, D. M., Burgess, G. C., Harms, M. P., Petersen, S. E., Schlaggar, B. L., Corbetta, M., ... & Van Essen, D. C. (2013). Function in the human connectome: task-fMRI and individual differences in behavior. *Neuroimage*, *80*, 169-189.

Bell, A. J., & Sejnowski, T. J. (1995). An information-maximization approach to blind separation and blind deconvolution. Neural computation, 7(6), 1129-1159.

Bengson, J. J., Mangun, G. R., & Mazaheri, A. (2012). The neural markers of an imminent failure of response inhibition. *Neuroimage*, *59*(2), 1534-1539.

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal statistical society: series B (Methodological)*, *57*(1), 289-300.

Berger, H. (1929). On the EEG in humans. *Arch. Psychiatr. Nervenkr*, *87*, 527-570.

Boorman, L., Kennerley, A. J., Johnston, D., Jones, M., Zheng, Y., Redgrave, P., & Berwick, J. (2010). Negative blood oxygen level dependence in the rat: a model for investigating the role of suppression in neurovascular coupling. *Journal of Neuroscience*, *30*(12), 4285-4294.

Boorman, L., Harris, S., Bruyns-Haylett, M., Kennerley, A., Zheng, Y., Martin, C., ... & Berwick, J. (2015). Long-latency reductions in gamma power predict hemodynamic changes that underlie the negative BOLD signal. *Journal of Neuroscience*, *35*(11), 4641-4656.

Bressler, D., Spotswood, N., & Whitney, D. (2007). Negative BOLD fMRI response in the visual cortex carries precise stimulus-specific information. *PLoS One*, *2*(5), e410.

Bressler, S. L., Tang, W., Sylvester, C. M., Shulman, G. L., & Corbetta, M. (2008). Top-down control of human visual cortex by frontal and parietal cortex in anticipatory visual spatial attention. *Journal of Neuroscience*, *28*(40), 10056-10061.

Bright, M. G., Bianciardi, M., de Zwart, J. A., Murphy, K., & Duyn, J. H. (2014). Early anti-correlated BOLD signal changes of physiologic origin. *NeuroImage*, *87*, 287-296.

Brinker, G., Bock, C., Busch, E., Krep, H., Hossmann, K. A., & Hoehn-Berlage, M. (1999). Simultaneous recording of evoked potentials and T-weighted MR images during somatosensory stimulation of rat. *Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine*, *41*(3), 469-473.

Brookes, M. J., Stevenson, C. M., Barnes, G. R., Hillebrand, A., Simpson, M. I., Francis, S. T., & Morris, P. G. (2007). Beamformer reconstruction of correlated sources using a modified source model. *Neuroimage*, *34*(4), 1454-1465.

Busch, N. A., Dubois, J., & VanRullen, R. (2009). The phase of ongoing EEG oscillations predicts visual perception. *Journal of Neuroscience*, *29*(24), 7869-7876.

Buschman, T. J., & Kastner, S. (2015). From behavior to neural dynamics: an integrated theory of attention. *Neuron*, *88*(1), 127-144.

Buschman, T. J., & Miller, E. K. (2007). Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. *science*, *315*(5820), 1860-1862.

Buzsáki, G., Anastassiou, C. A., & Koch, C. (2012). The origin of extracellular fields and currents—EEG, ECoG, LFP and spikes. *Nature reviews neuroscience*, *13*(6), 407-420.

Buzsáki, G., & Draguhn, A. (2004). Neuronal oscillations in cortical networks. *science*, *304*(5679), 1926-1929.

Capotosto, P., Babiloni, C., Romani, G. L., & Corbetta, M. (2009). Frontoparietal cortex controls spatial attention through modulation of anticipatory alpha rhythms. *Journal of Neuroscience*, *29*(18), 5863-5872.

https://dev.twitch.tv/docs/embed/everything

Chalmers, 2016, “The Combination Problem for Panpsychism”, in Brüntrup & Jaskolla 2016: 179–214. doi:10.1093/acprof:oso/9780199359943.003.0008

Chang, C., & Glover, G. H. (2009). Effects of model-based physiological noise correction on default mode network anti-correlations and correlations. *Neuroimage*, *47*(4), 1448-1459.

Corbetta, M. (1998). Frontoparietal cortical networks for directing attention and the eye to visual locations: identical, independent, or overlapping neural systems? *Proceedings of the National Academy of Sciences*, *95*(3), 831-838.

Corbetta, M., Kincade, J. M., Ollinger, J. M., McAvoy, M. P., & Shulman, G. L. (2000). Voluntary orienting is dissociated from target detection in human posterior parietal cortex. *Nature neuroscience*, *3*(3), 292-297.

Corr, P. J., & Mobbs, D. (2018). From epiphenomenon to biologically important phenomena. *Personality Neuroscience*, *1*.

Da Costa, S., van der Zwaag, W., Marques, J. P., Frackowiak, R. S., Clarke, S., & Saenz, M. (2011). Human primary auditory cortex follows the shape of Heschl's gyrus. *Journal of Neuroscience*, *31*(40), 14067-14075.

da Silva, F. L. (2013). EEG and MEG: relevance to neuroscience. *Neuron*, *80*(5), 1112-1128.

da Silva, F. L., & Van Leeuwen, W. S. (1977). The cortical source of the alpha rhythm. *Neuroscience letters*, *6*(2-3), 237-241.

de Graaf, T. A., Thomson, A., Janssens, S. E., Van Bree, S., Ten Oever, S., & Sack, A. T. (2020). Does alpha phase modulate visual target detection? Three experiments with tACS-phase-based stimulus presentation. *European Journal of Neuroscience*.

de Graaf, T. A., Duecker, F., Fernholz, M. H., & Sack, A. T. (2015). Spatially specific vs. unspecific disruption of visual orientation perception using chronometric pre-stimulus TMS. *Frontiers in behavioral neuroscience*, *9*, 5.

de Graaf, T. A., Koivisto, M., Jacobs, C., & Sack, A. T. (2014). The chronometry of visual perception: review of occipital TMS masking studies. *Neuroscience & Biobehavioral Reviews*, *45*, 295-304.

de Graaf, T. A., Gross, J., Paterson, G., Rusch, T., Sack, A. T., & Thut, G. (2013). Alpha-band rhythms in visual task performance: phase-locking by rhythmic sensory stimulation. *PloS one*, *8*(3), e60035.

Devor, A., Tian, P., Nishimura, N., Teng, I. C., Hillman, E. M., Narayanan, S. N., ... & Dale, A. M. (2007). Suppressed neuronal activity and concurrent arteriolar vasoconstriction may explain negative blood oxygenation level-dependent signal. *Journal of Neuroscience*, *27*(16), 4452-4459.

Ding, N., Melloni, L., Yang, A., Wang, Y., Zhang, W., & Poeppel, D. (2017). Characterizing neural entrainment to hierarchical linguistic units using electroencephalography (EEG). *Frontiers in human neuroscience*, *11*, 481.

Doricchi, F., Macci, E., Silvetti, M., & Macaluso, E. (2010). Neural correlates of the spatial and expectancy components of endogenous and stimulus-driven orienting of attention in the Posner task. *Cerebral Cortex*, *20*(7), 1574-1585.

Doty, R. W. (1975). Consciousness from neurons. *Acta neurobiologiae experimentalis*, *35*(5-6), 791-804.

Dugué, L., Marque, P., & VanRullen, R. (2011). The phase of ongoing oscillations mediates the causal relation between brain excitation and visual perception. *Journal of neuroscience*, *31*(33), 11889-11893.

Denny, B. T., Kober, H., Wager, T. D., & Ochsner, K. N. (2012). A meta-analysis of functional neuroimaging studies of self-and other judgments reveals a spatial gradient for mentalizing in medial prefrontal cortex. *Journal of cognitive Neuroscience*, *24*(8), 1742-1752.

Ekstrom, A. (2010). How and when the fMRI BOLD signal relates to underlying neural activity: the danger in dissociation. *Brain research reviews*, *62*(2), 233-244.

Eimer, M. (1994). "Sensory gating" as a mechanism for visuospatial orienting: electrophysiological evidence from trial-by-trial cuing experiments. *Perception & Psychophysics*, *55*(6), 667-675.

Emrich, S. M., Johnson, J. S., Sutterer, D. W., & Postle, B. R. (2017). Comparing the effects of 10-Hz repetitive TMS on tasks of visual STM and attention. *Journal of cognitive neuroscience*, *29*(2), 286-297.

Ferbert, A., Priori, A., Rothwell, J. C., Day, B. L., Colebatch, J. G., & Marsden, C. D. (1992). Interhemispheric inhibition of the human motor cortex. *The Journal of physiology*, *453*(1), 525-546.

Foster, J. J., Sutterer, D. W., Serences, J. T., Vogel, E. K., & Awh, E. (2017). Alpha-band oscillations enable spatially and temporally resolved tracking of covert spatial attention. *Psychological science*, *28*(7), 929-941.

Fox, P. T., Mintun, M. A., Reiman, E. M., & Raichle, M. E. (1988). Enhanced detection of focal brain responses using intersubject averaging and change-distribution analysis of subtracted PET images. *Journal of Cerebral Blood Flow & Metabolism*, *8*(5), 642-653.

Fox, P. T., & Raichle, M. E. (1986). Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. *Proceedings of the National Academy of Sciences*, *83*(4), 1140-1144.

Foxe, J. J., Simpson, G. V., & Ahlfors, S. P. (1998). Parieto-occipital~ 1 0Hz activity reflects anticipatory state of visual attention mechanisms. *Neuroreport*, *9*(17), 3929-3933.

Friederici, A. D., & Gierhan, S. M. (2013). The language network. *Current opinion in neurobiology*, *23*(2), 250-254.

Frey, J. N., Mainy, N., Lachaux, J. P., Müller, N., Bertrand, O., & Weisz, N. (2014). Selective modulation of auditory cortical alpha activity in an audiovisual spatial attention task. *Journal of Neuroscience*, *34*(19), 6634-6639.

Fuchs, M., Wagner, M., & Kastner, J. (2001). Boundary element method volume conductor models for EEG source reconstruction. *Clinical neurophysiology*, *112*(8), 1400-1407.

Fusar-Poli, P., Placentino, A., Carletti, F., Landi, P., Allen, P., Surguladze, S., ... & Perez, J. (2009). Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. *Journal of psychiatry & neuroscience*.

Gao, C., Weber, C. E., & Shinkareva, S. V. (2019). The brain basis of audiovisual affective processing: Evidence from a coordinate-based activation likelihood estimation meta-analysis. *Cortex*, *120*, 66-77.

Gilbert, S. J., Dumontheil, I., Simons, J. S., Frith, C. D., & Burgess, P. W. (2007). Comment on" Wandering minds: the default network and stimulus-independent thought". *Science*, *317*(5834), 43-43.

Goense, J. B., & Logothetis, N. K. (2008). Neurophysiology of the BOLD fMRI signal in awake monkeys. *Current Biology*, *18*(9), 631-640.

Goff, 2017, *Consciousness and Fundamental Reality*, New York: Oxford University Press.

Gould, I. C., Rushworth, M. F., & Nobre, A. C. (2011). Indexing the graded allocation of visuospatial attention using anticipatory alpha oscillations. *Journal of neurophysiology*, *105*(3), 1318-1326.

Greicius, M. D., Supekar, K., Menon, V., & Dougherty, R. F. (2009). Resting-state functional connectivity reflects structural connectivity in the default mode network. *Cerebral cortex*, *19*(1), 72-78.

Gulbinaite, R., van Viegen, T., Wieling, M., Cohen, M. X., & VanRullen, R. (2017). Individual alpha peak frequency predicts 10 Hz flicker effects on selective attention. *Journal of Neuroscience*, *37*(42), 10173-10184.

Gusnard, D. A., & Raichle, M. E. (2001). Searching for a baseline: functional imaging and the resting human brain. *Nature reviews neuroscience*, *2*(10), 685-694.

Haegens, S., Händel, B. F., & Jensen, O. (2011). Top-down controlled alpha band activity in somatosensory areas determines behavioral performance in a discrimination task. *Journal of Neuroscience*, *31*(14), 5197-5204.

Haegens, S., Nácher, V., Luna, R., Romo, R., & Jensen, O. (2011). α-Oscillations in the monkey sensorimotor network influence discrimination performance by rhythmical inhibition of neuronal spiking. *Proceedings of the National Academy of Sciences*, *108*(48), 19377-19382.

Haegens, S., Luther, L., & Jensen, O. (2012). Somatosensory anticipatory alpha activity increases to suppress distracting input. *Journal of cognitive neuroscience*, *24*(3), 677-685.

Hairston, W. D., Hodges, D. A., Casanova, R., Hayasaka, S., Kraft, R., Maldjian, J. A., & Burdette, J. H. (2008). Closing the mind's eye: deactivation of visual cortex related to auditory task difficulty. *Neuroreport*, *19*(2), 151-154.

Halgren, M., Ulbert, I., Bastuji, H., Fabó, D., Erőss, L., Rey, M., ... & Cash, S. S. (2019). The generation and propagation of the human alpha rhythm. *Proceedings of the National Academy of Sciences*, *116*(47), 23772-23782.

Hall, S. D., Barnes, G. R., Furlong, P. L., Seri, S., & Hillebrand, A. (2010). Neuronal network pharmacodynamics of GABAergic modulation in the human cortex determined using pharmaco-magnetoencephalography. *Human brain mapping*, *31*(4), 581-594.

Hallez, H., Vanrumste, B., Grech, R., Muscat, J., De Clercq, W., Vergult, A., ... & Lemahieu, I. (2007). Review on solving the forward problem in EEG source analysis. *Journal of neuroengineering and rehabilitation*, *4*(1), 46.

Händel, B. F., Haarmeier, T., & Jensen, O. (2011). Alpha oscillations correlate with the successful inhibition of unattended stimuli. *Journal of cognitive neuroscience*, *23*(9), 2494-2502.

Hanouneh, S., Amin, H. U., Saad, N. M., & Malik, A. S. (2018). EEG power and functional connectivity correlates with semantic long-term memory retrieval. *Ieee Access*, *6*, 8695-8703.

Harel, N., Lee, S. P., Nagaoka, T., Kim, D. S., & Kim, S. G. (2002). Origin of negative blood oxygenation level—dependent fMRI signals. *Journal of cerebral blood flow & metabolism*, *22*(8), 908-917.

Hartmann, T., Schlee, W., & Weisz, N. (2012). It's only in your head: expectancy of aversive auditory stimulation modulates stimulus-induced auditory cortical alpha desynchronization. *Neuroimage*, *60*(1), 170-178.

Hasson, U., Landesman, O., Knappmeyer, B., Vallines, I., Rubin, N., & Heeger, D. J. (2008). Neurocinematics: The neuroscience of film. *Projections*, *2*(1), 1-26.

He, B. J., Snyder, A. Z., Vincent, J. L., Epstein, A., Shulman, G. L., & Corbetta, M. (2007). Breakdown of functional connectivity in frontoparietal networks underlies behavioral deficits in spatial neglect. *Neuron*, *53*(6), 905-918.

Heeger, D. J., Huk, A. C., Geisler, W. S., & Albrecht, D. G. (2000). Spikes versus BOLD: what does neuroimaging tell us about neuronal activity?. *Nature neuroscience*, *3*(7), 631-633.

Heinrichs-Graham, E., Arpin, D. J., & Wilson, T. W. (2016). Cue-related temporal factors modulate movement-related beta oscillatory activity in the human motor circuit. *Journal of cognitive neuroscience*, *28*(7), 1039-1051.

Herculano-Houzel, S. (2009). The human brain in numbers: a linearly scaled-up primate brain. *Frontiers in human neuroscience*, *3*, 31.

Heinrichs-Graham, E., & Wilson, T. W. (2012). Presence of strong harmonics during visual entrainment: a magnetoencephalography study. *Biological psychology*, *91*(1), 59-64.

Henson, R. N., Mattout, J., Phillips, C., & Friston, K. J. (2009). Selecting forward models for MEG source-reconstruction using model-evidence. *Neuroimage*, *46*(1), 168-176.

Himmelbach, M., & Karnath, H. O. (2005). Dorsal and ventral stream interaction: contributions from optic ataxia. *Journal of Cognitive Neuroscience*, *17*(4), 632-640.

Hlushchuk, Y., & Hari, R. (2006). Transient suppression of ipsilateral primary somatosensory cortex during tactile finger stimulation. *Journal of Neuroscience*, *26*(21), 5819-5824.

Holm, S. (1979). A simple sequentially rejective multiple test procedure. *Scandinavian journal of statistics*, 65-70.

Hopfinger, J. B., Buonocore, M. H., & Mangun, G. R. (2000). The neural mechanisms of top-down attentional control. *Nature neuroscience*, *3*(3), 284-291.

Hughes, S. W., & Crunelli, V. (2005). Thalamic mechanisms of EEG alpha rhythms and their pathological implications. *The Neuroscientist*, *11*(4), 357-372.

Iadecola, C., & Nedergaard, M. (2007). Glial regulation of the cerebral microvasculature. *Nature neuroscience*, *10*(11), 1369-1376.

Iadecola, C. (2017). The neurovascular unit coming of age: a journey through neurovascular coupling in health and disease. *Neuron*, *96*(1), 17-42.

Ikkai, A., Dandekar, S., & Curtis, C. E. (2016). Lateralization in alpha-band oscillations predicts the locus and spatial distribution of attention. *PLoS One*, *11*(5), e0154796.

Indefrey, P. (2006). A meta-analysis of hemodynamic studies on first and second language processing: Which suggested differences can we trust and what do they mean?. *Language learning*, *56*, 279-304.

Iurilli, G., Ghezzi, D., Olcese, U., Lassi, G., Nazzaro, C., Tonini, R., ... & Medini, P. (2012). Sound-driven synaptic inhibition in primary visual cortex. *Neuron*, *73*(4), 814-828.

Jackson, A. F., & Bolger, D. J. (2014). The neurophysiological bases of EEG and EEG measurement: A review for the rest of us. *Psychophysiology*, *51*(11), 1061-1071.

Jacobs, C., de Graaf, T. A., & Sack, A. T. (2014). Two distinct neural mechanisms in early visual cortex determine subsequent visual processing. *Cortex*, *59*, 1-11.

Jensen, O., Gelfand, J., Kounios, J., & Lisman, J. E. (2002). Oscillations in the alpha band (9–12 Hz) increase with memory load during retention in a short-term memory task. *Cerebral cortex*, *12*(8), 877-882.

Jensen, O., & Mazaheri, A. (2010). Shaping functional architecture by oscillatory alpha activity: gating by inhibition. *Frontiers in human neuroscience*, *4*, 186.

Jin, F., Jin, J., Li, Y., Wang, X., Liu, Z., & Yin, T. (2017). EEG under TMS-induced SP reveals inhibitory effects of low-frequency rTMS on the primary motor cortex. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, *10*(2), 372.

Jurkiewicz, M. T., Gaetz, W. C., Bostan, A. C., & Cheyne, D. (2006). Post-movement beta rebound is generated in motor cortex: evidence from neuromagnetic recordings. *Neuroimage*, *32*(3), 1281-1289.

Karakaş, S. (2020). A review of theta oscillation and its functional correlates. *International Journal of Psychophysiology*, *157*, 82-99.

Kastrup, A., Baudewig, J., Schnaudigel, S., Huonker, R., Becker, L., Sohns, J. M., ... & Witte, O. W. (2008). Behavioral correlates of negative BOLD signal changes in the primary somatosensory cortex. *Neuroimage*, *41*(4), 1364-1371.

Kelly, S. P., Lalor, E. C., Reilly, R. B., & Foxe, J. J. (2006). Increases in alpha oscillatory power reflect an active retinotopic mechanism for distracter suppression during sustained visuospatial attention. *Journal of neurophysiology*, *95*(6), 3844-3851.

Kevin, W., Doug, W., Matthias, S., & Gerhard, S. (2008). Correspondence of visual evoked potentials with FMRI signals in human visual cortex. *Brain topography*, *21*(2), 86-92.

Khalsa, S., Mayhew, S. D., Chechlacz, M., Bagary, M., & Bagshaw, A. P. (2014). The structural and functional connectivity of the posterior cingulate cortex: Comparison between

deterministic and probabilistic tractography for the investigation of structure–function relationships. *Neuroimage*, *102*, 118-127.

Kirschstein, T., & Köhling, R. (2009). What is the source of the EEG?. *Clinical EEG and neuroscience*, *40*(3), 146-149.

Kizuk, S. A., & Mathewson, K. E. (2017). Power and phase of alpha oscillations reveal an interaction between spatial and temporal visual attention. *Journal of Cognitive Neuroscience*, *29*(3), 480-494.

Klatt, L. I., Getzmann, S., Wascher, E., & Schneider, D. (2018). The contribution of selective spatial attention to sound detection and sound localization: Evidence from event-related potentials and lateralized alpha oscillations. *Biological psychology*, *138*, 133-145.

Klimesch, W. (2012). Alpha-band oscillations, attention, and controlled access to stored information. *Trends in cognitive sciences*, *16*(12), 606-617.

Klimesch, W., Sauseng, P., & Hanslmayr, S. (2007). EEG alpha oscillations: the inhibition–timing hypothesis. *Brain research reviews*, *53*(1), 63-88.

Klimesch, W., Schimke, H. A. N. N. E. S., & Pfurtscheller, G. (1993). Alpha frequency, cognitive load and memory performance. *Brain topography*, *5*(3), 241-251.

Klimesch, W., Doppelmayr, M., Schwaiger, J., Auinger, P., & Winkler, T. (1999). Paradoxical'alpha synchronization in a memory task. *Cognitive Brain Research*, *7*(4), 493-501.

Klingner, C. M., Hasler, C., Brodoehl, S., & Witte, O. W. (2010). Dependence of the negative BOLD response on somatosensory stimulus intensity. *Neuroimage*, *53*(1), 189-195.

Knyazev, G. G., Slobodskoj-Plusnin, J. Y., Bocharov, A. V., & Pylkova, L. V. (2011). The default mode network and EEG alpha oscillations: an independent component analysis. *Brain research*, *1402*, 67-79.

Lapate, R. C., Samaha, J., Rokers, B., Hamzah, H., Postle, B. R., & Davidson, R. J. (2017). Inhibition of lateral prefrontal cortex produces emotionally biased first impressions: a transcranial magnetic stimulation and electroencephalography study. *Psychological science*, *28*(7), 942-953.

Laurienti, P. J., Burdette, J. H., Wallace, M. T., Yen, Y. F., Field, A. S., & Stein, B. E. (2002). Deactivation of sensory-specific cortex by cross-modal stimuli. *Journal of cognitive neuroscience*, *14*(3), 420-429.

Lee, A. K., & Wilson, M. A. (2002). Memory of sequential experience in the hippocampus during slow wave sleep. *Neuron*, *36*(6), 1183-1194.

Li, L., Gratton, C., Yao, D., & Knight, R. T. (2010). Role of frontal and parietal cortices in the control of bottom-up and top-down attention in humans. *Brain research*, *1344*, 173-184.

Liu, Y., Shen, H., Zhou, Z., & Hu, D. (2011). Sustained negative BOLD response in human fMRI finger tapping task. *PloS one*, *6*(8), e23839.

Liu, S., Wang, X., Liu, M., & Zhu, J. (2017). Towards better analysis of machine learning models: A visual analytics perspective. *Visual Informatics*, *1*(1), 48-56.

Liu, Z., de Zwart, J. A., Yao, B., van Gelderen, P., Kuo, L. W., & Duyn, J. H. (2012). Finding thalamic BOLD correlates to posterior alpha EEG. *Neuroimage*, *63*(3), 1060-1069.

Logothetis, N. K., Pauls, J., Augath, M., Trinath, T., & Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. *nature*, *412*(6843), 150-157.

Logothetis, N. K. (2003). The underpinnings of the BOLD functional magnetic resonance imaging signal. *Journal of Neuroscience*, *23*(10), 3963-3971.

Logothetis, N. K., & Wandell, B. A. (2004). Interpreting the BOLD signal. *Annu. Rev. Physiol.*, *66*, 735-769.

Logothetis, N. K. (2008). What we can do and what we cannot do with fMRI. *Nature*, *453*(7197), 869-878.

Lozano-Soldevilla, D., ter Huurne, N., Cools, R., & Jensen, O. (2014). GABAergic modulation of visual gamma and alpha oscillations and its consequences for working memory performance. *Current Biology*, *24*(24), 2878-2887.

Luk, G., Green, D. W., Abutalebi, J., & Grady, C. (2012). Cognitive control for language switching in bilinguals: A quantitative meta-analysis of functional neuroimaging studies. *Language and cognitive processes*, *27*(10), 1479-1488.

Luck, S. J. (2012). Electrophysiological correlates of the focusing of attention within complex visual scenes: N2pc and related ERP components.

Mathewson, K. E., Gratton, G., Fabiani, M., Beck, D. M., & Ro, T. (2009). To see or not to see: prestimulus α phase predicts visual awareness. *Journal of Neuroscience*, *29*(9), 2725-2732.

Mathewson, K. E., Lleras, A., Beck, D. M., Fabiani, M., Ro, T., & Gratton, G. (2011). Pulsed out of awareness: EEG alpha oscillations represent a pulsed-inhibition of ongoing cortical processing. *Frontiers in psychology*, *2*, 99.

Mathiesen, C., Caesar, K., Akgören, N., & Lauritzen, M. (1998). Modification of activity-dependent increases of cerebral blood flow by excitatory synaptic activity and spikes in rat cerebellar cortex. *The Journal of physiology*, *512*(2), 555-566.

Marini, F., Demeter, E., Roberts, K. C., Chelazzi, L., & Woldorff, M. G. (2016). Orchestrating proactive and reactive mechanisms for filtering distracting information: Brain-behavior relationships revealed by a mixed-design fMRI study. *Journal of Neuroscience*, *36*(3), 988-1000.

Marshall, T. R., Bergmann, T. O., & Jensen, O. (2015). Frontoparietal structural connectivity mediates the top-down control of neuronal synchronization associated with selective attention. *PLoS Biol*, *13*(10), e1002272.

Marshall, T. R., O'Shea, J., Jensen, O., & Bergmann, T. O. (2015). Frontal eye fields control attentional modulation of alpha and gamma oscillations in contralateral occipitoparietal cortex. *Journal of Neuroscience*, *35*(4), 1638-1647.

Mazzetti, C., Staudigl, T., Marshall, T. R., Zumer, J. M., Fallon, S. J., & Jensen, O. (2019). Hemispheric asymmetry of globus pallidus relates to alpha modulation in reward-related attentional tasks. *Journal of Neuroscience*, *39*(46), 9221-9236.

Mayhew, S. D., Ostwald, D., Porcaro, C., & Bagshaw, A. P. (2013). Spontaneous EEG alpha oscillation interacts with positive and negative BOLD responses in the visual–auditory cortices and default-mode network. *Neuroimage*, *76*, 362-372.

McCormick, D. A. (1989). GABA as an inhibitory neurotransmitter in human cerebral cortex. *Journal of neurophysiology*, *62*(5), 1018-1027.

Michalka, S. W., Rosen, M. L., Kong, L., Shinn-Cunningham, B. G., & Somers, D. C. (2016). Auditory spatial coding flexibly recruits anterior, but not posterior, visuotopic parietal cortex. *Cerebral Cortex*, *26*(3), 1302-1308.

Miltner, W. H., Braun, C., Arnold, M., Witte, H., & Taub, E. (1999). Coherence of gamma-band EEG activity as a basis for associative learning. *Nature*, *397*(6718), 434-436.

Mitchell, D. J., & Cusack, R. (2011). The temporal evolution of electromagnetic markers sensitive to the capacity limits of visual short-term memory. *Frontiers in human neuroscience*, *5*, 18.

Mozolic, J. L., Joyner, D., Hugenschmidt, C. E., Peiffer, A. M., Kraft, R. A., Maldjian, J. A., & Laurienti, P. J. (2008). Cross-modal deactivations during modality-specific selective attention. *BMC neurology*, *8*(1), 35.

Müller, N., & Weisz, N. (2012). Lateralized auditory cortical alpha band activity and interregional connectivity pattern reflect anticipation of target sounds. *Cerebral Cortex*, *22*(7), 1604-1613.

Mullinger, K. J., Mayhew, S. D., Bagshaw, A. P., Bowtell, R., & Francis, S. T. (2014). Evidence that the negative BOLD response is neuronal in origin: a simultaneous EEG–BOLD–CBF study in humans. *Neuroimage*, *94*, 263-274.

Mullinger, K. J., Mayhew, S. D., Bagshaw, A. P., Bowtell, R., & Francis, S. T. (2013). Poststimulus undershoots in cerebral blood flow and BOLD fMRI responses are modulated by poststimulus neuronal activity. *Proceedings of the National Academy of Sciences*, *110*(33), 13636-13641.

Murty, V. P., Ritchey, M., Adcock, R. A., & LaBar, K. S. (2010). fMRI studies of successful emotional memory encoding: A quantitative meta-analysis. *Neuropsychologia*, *48*(12), 3459-3469.

Muthuraman, M., Hellriegel, H., Hoogenboom, N., Anwar, A. R., Mideksa, K. G., Krause, H., ... & Raethjen, J. (2014). Beamformer source analysis and connectivity on concurrent EEG and MEG data during voluntary movements. *PloS one*, *9*(3), e91441.

Newton, J. M., Sunderland, A., & Gowland, P. A. (2005). fMRI signal decreases in ipsilateral primary motor cortex during unilateral hand movements are related to duration and side of movement. *Neuroimage*, *24*(4), 1080-1087.

Nielsen, A. N., & Lauritzen, M. (2001). Coupling and uncoupling of activity-dependent increases of neuronal activity and blood flow in rat somatosensory cortex. *The Journal of physiology*, *533*(3), 773-785.

Niessing, J., Ebisch, B., Schmidt, K. E., Niessing, M., Singer, W., & Galuske, R. A. (2005). Hemodynamic signals correlate tightly with synchronized gamma oscillations. *science*, *309*(5736), 948-951.

Ngai, A. C., Jolley, M. A., D'Ambrosio, R., Meno, J. R., & Winn, H. R. (1999). Frequency-dependent changes in cerebral blood flow and evoked potentials during somatosensory stimulation in the rat. *Brain research*, *837*(1-2), 221-228.

Nilsson, J., Ferrier, I. N., Coventry, K., Bester, A., & Finkelmeyer, A. (2013). Negative BOLD response in the hippocampus during short-term spatial memory retrieval. *Journal of cognitive neuroscience*, *25*(8), 1358-1371.

Nobre, A. C., Correa, A., & Coull, J. T. (2007). The hazards of time. *Current opinion in neurobiology*, *17*(4), 465-470.

Noyce, A. L., Cestero, N., Michalka, S. W., Shinn-Cunningham, B. G., & Somers, D. C. (2017). Sensory-biased and multiple-demand processing in human lateral frontal cortex. *Journal of Neuroscience*, *37*(36), 8755-8766.

Nozaradan, S., Zerouali, Y., Peretz, I., & Mouraux, A. (2015). Capturing with EEG the neural entrainment and coupling underlying sensorimotor synchronization to the beat. *Cerebral Cortex*, *25*(3), 736-747.

Ogawa, S., Lee, T. M., Kay, A. R., & Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *proceedings of the National Academy of Sciences*, *87*(24), 9868-9872.

Ogawa, S., Lee, T. M., Stepnoski, R., Chen, W., Zhu, X. H., & Ugurbil, K. (2000). An approach to probe some neural systems interaction by functional MRI at neural time scale down to milliseconds. *Proceedings of the National Academy of Sciences*, *97*(20), 11026-11031.

McFarland, D. J., McCane, L. M., David, S. V., & Wolpaw, J. R. (1997). Spatial filter selection for EEG-based communication. *Electroencephalography and clinical Neurophysiology*, *103*(3), 386-394.

Okawa, H., Suefusa, K., & Tanaka, T. (2017). Neural entrainment to auditory imagery of rhythms. *Frontiers in human neuroscience*, *11*, 493.

Oostenveld, R., Fries, P., Maris, E., & Schoffelen, J. M. (2011). FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Computational intelligence and neuroscience*, *2011*.

Otero, M., Prado-Gutiérrez, P., Weinstein, A., Escobar, M. J., & El-Deredy, W. (2020). Persistence of eeg alpha entrainment depends on stimulus phase at offset. *Frontiers in human neuroscience*, *14*, 139.

Osipova, D., Hermes, D., & Jensen, O. (2008). Gamma power is phase-locked to posterior alpha activity. *PloS one*, *3*(12), e3990.

Owen, A. M., McMillan, K. M., Laird, A. R., & Bullmore, E. (2005). N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies. *Human brain mapping*, *25*(1), 46-59.

Park, H., & Kayser, C. (2019). Shared neural underpinnings of multisensory integration and trial-by-trial perceptual recalibration in humans. *Elife*, *8*, e47001.

Pasley, B. N., Inglis, B. A., & Freeman, R. D. (2007). Analysis of oxygen metabolism implies a neural origin for the negative BOLD response in human visual cortex. *Neuroimage*, *36*(2), 269-276.

Pauling, L., & Coryell, C. D. (1936). The magnetic properties and structure of hemoglobin, oxyhemoglobin and carbonmonoxyhemoglobin. *Proceedings of the National Academy of Sciences*, *22*(4), 210-216.

Paulus, W. (2014). Transcranial brain stimulation: potential and limitations. *Neuroforum*, *20*(2), 29-36.

Pfurtscheller, G., Stancak Jr, A., & Neuper, C. (1996). Event-related synchronization (ERS) in the alpha band—an electrophysiological correlate of cortical idling: a review. *International journal of psychophysiology*, *24*(1-2), 39-46.

Poerio, G. L., Sormaz, M., Wang, H. T., Margulies, D., Jefferies, E., & Smallwood, J. (2017). The role of the default mode network in component processes underlying the wandering mind. *Social cognitive and affective neuroscience*, *12*(7), 1047-1062.

Popov, T., Kastner, S., & Jensen, O. (2017). FEF-controlled alpha delay activity precedes stimulus-induced gamma-band activity in visual cortex. *Journal of Neuroscience*, *37*(15), 4117-4127.

Posner, M. I. (1980). Orienting of attention. *Quarterly journal of experimental psychology*, *32*(1), 3-25.

Proix, T., Spiegler, A., Schirner, M., Rothmeier, S., Ritter, P., & Jirsa, V. K. (2016). How do parcellation size and short-range connectivity affect dynamics in large-scale brain network models?. *NeuroImage*, *142*, 135-149.

Przezdzik, I., Bagshaw, A.P., Mayhew, S.D., 2013. Some brains are more strongly functionally connected than others: a resting-state fMRI study of inter and intra network coherence. Proc ISMRM 2262.

Raffaelli, Q., Mills, C., & Christoff, K. (2018). The knowns and unknowns of boredom: a review of the literature. *Experimental brain research*, *236*(9), 2451-2462.

Raichle, M. E. (2010). Two views of brain function. *Trends in cognitive sciences*, *14*(4), 180-190.

Raichle, M. E. (2011). The restless brain. *Brain connectivity*, *1*(1), 3-12.

Raichle, M. E. (2015). The brain's default mode network. *Annual review of neuroscience*, *38*, 433-447.

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences*, *98*(2), 676-682.

Rapp, A. M., Mutschler, D. E., & Erb, M. (2012). Where in the brain is nonliteral language? A coordinate-based meta-analysis of functional magnetic resonance imaging studies. *Neuroimage*, *63*(1), 600-610.

Rees, G., Friston, K., & Koch, C. (2000). A direct quantitative relationship between the functional properties of human and macaque V5. *Nature neuroscience*, *3*(7), 716-723.

Rekkas, P. V., & Constable, R. T. (2005). Evidence that autobiographic memory retrieval does not become independent of the hippocampus: an fMRI study contrasting very recent with remote events. *Journal of Cognitive Neuroscience*, *17*(12), 1950-1961.

Rihs, T. A., Michel, C. M., & Thut, G. (2007). Mechanisms of selective inhibition in visual spatial attention are indexed by α-band EEG synchronization. *European Journal of Neuroscience*, *25*(2), 603-610.

Ritter, P., & Villringer, A. (2006). simultaneous EEG–fMRI. *Neuroscience & Biobehavioral Reviews*, *30*(6), 823-838.

Robitaille, N., Marois, R., Todd, J., Grimault, S., Cheyne, D., & Jolicœur, P. (2010). Distinguishing between lateralized and nonlateralized brain activity associated with visual short-term memory: fMRI, MEG, and EEG evidence from the same observers. *NeuroImage*, *53*(4), 1334-1345.

Rohenkohl, G., & Nobre, A. C. (2011). Alpha oscillations related to anticipatory attention follow temporal expectations. *Journal of Neuroscience*, *31*(40), 14076-14084.

Romei, V., Brodbeck, V., Michel, C., Amedi, A., Pascual-Leone, A., & Thut, G. (2008). Spontaneous fluctuations in posterior α-band EEG activity reflect variability in excitability of human visual areas. *Cerebral cortex*, *18*(9), 2010-2018.

Romei, V., Driver, J., Schyns, P. G., & Thut, G. (2011). Rhythmic TMS over parietal cortex links distinct brain frequencies to global versus local visual processing. *Current biology*, *21*(4), 334-337.

Romei, V., Rihs, T., Brodbeck, V., & Thut, G. (2008). Resting electroencephalogram alpha-power over posterior sites indexes baseline visual cortex excitability. *Neuroreport*, *19*(2), 203-208.

Rottschy, C., Langner, R., Dogan, I., Reetz, K., Laird, A. R., Schulz, J. B., ... & Eickhoff, S. B. (2012). Modelling neural correlates of working memory: a coordinate-based meta-analysis. *Neuroimage*, *60*(1), 830-846.

Rossi, E. L., & Rossi, K. L. (2006). The neuroscience of observing consciousness & mirror neurons in therapeutic hypnosis. *American Journal of Clinical Hypnosis*, *48*(4), 263-278.

Rowland, L. M., Edden, R. A., Kontson, K., Zhu, H., Barker, P. B., & Hong, L. E. (2013). GABA predicts inhibition of frequency-specific oscillations in schizophrenia. *The Journal of neuropsychiatry and clinical neurosciences*, *25*(1), 83-87.

Sack, A. T., & Linden, D. E. (2003). Combining transcranial magnetic stimulation and functional imaging in cognitive brain research: possibilities and limitations. *Brain Research Reviews*, *43*(1), 41-56.

Samaha, J., Bauer, P., Cimaroli, S., & Postle, B. R. (2015). Top-down control of the phase of alpha-band oscillations as a mechanism for temporal prediction. *Proceedings of the National Academy of Sciences*, *112*(27), 8439-8444.

Samaha, J., Sprague, T. C., & Postle, B. R. (2016). Decoding and reconstructing the focus of spatial attention from the topography of alpha-band oscillations. *Journal of cognitive neuroscience*, *28*(8), 1090-1097.

Sauseng, P., Klimesch, W., Stadler, W., Schabus, M., Doppelmayr, M., Hanslmayr, S., ... & Birbaumer, N. (2005). A shift of visual spatial attention is selectively associated with human EEG alpha activity. *European Journal of Neuroscience*, *22*(11), 2917-2926.

Sauseng, P., Klimesch, W., Doppelmayr, M., Pecherstorfer, T., Freunberger, R., & Hanslmayr, S. (2005). EEG alpha synchronization and functional coupling during top-down processing in a working memory task. *Human brain mapping*, *26*(2), 148-155.

Sauseng, P., Klimesch, W., Schabus, M., & Doppelmayr, M. (2005). Fronto-parietal EEG coherence in theta and upper alpha reflect central executive functions of working memory. *International journal of Psychophysiology*, *57*(2), 97-103.

Sauseng, P., Klimesch, W., Heise, K. F., Gruber, W. R., Holz, E., Karim, A. A., ... & Hummel, F. C. (2009). Brain oscillatory substrates of visual short-term memory capacity. *Current biology*, *19*(21), 1846-1852.

Schäfer, K., Blankenburg, F., Kupers, R., Grüner, J. M., Law, I., Lauritzen, M., & Larsson, H. B. (2012). Negative BOLD signal changes in ipsilateral primary somatosensory cortex are associated with perfusion decreases and behavioral evidence for functional inhibition. *Neuroimage*, *59*(4), 3119-3127.

Scheeringa, R., Fries, P., Petersson, K. M., Oostenveld, R., Grothe, I., Norris, D. G., ... & Bastiaansen, M. C. (2011). Neuronal dynamics underlying high-and low-frequency EEG oscillations contribute independently to the human BOLD signal. *Neuron*, *69*(3), 572-583.

Schuhmann, T., Kemmerer, S. K., Duecker, F., De Graaf, T. A., Ten Oever, S., De Weerd, P., & Sack, A. T. (2019). Left parietal tACS at alpha frequency induces a shift of visuospatial attention. *PloS one*, *14*(11), e0217729.

Schurz, M., Radua, J., Aichhorn, M., Richlan, F., & Perner, J. (2014). Fractionating theory of mind: a meta-analysis of functional brain imaging studies. *Neuroscience & Biobehavioral Reviews*, *42*, 9-34.

Seo, J. K., Kim, D. H., Lee, J., Kwon, O. I., Sajib, S. Z., & Woo, E. J. (2012). Electrical tissue property imaging using MRI at dc and Larmor frequency. *Inverse Problems*, *28*(8), 084002.

Seubert, J., Freiherr, J., Djordjevic, J., & Lundström, J. N. (2013). Statistical localization of human olfactory cortex. *Neuroimage*, *66*, 333-342.

Shipman, S. L., & Astur, R. S. (2008). Factors affecting the hippocampal BOLD response during spatial memory. *Behavioural brain research*, *187*(2), 433-441.

Shulman, G. L., Corbetta, M., Buckner, R. L., Fiez, J. A., Miezin, F. M., Raichle, M. E., & Petersen, S. E. (1997). Common blood flow changes across visual tasks: I. Increases in subcortical structures and cerebellum but not in nonvisual cortex. *Journal of cognitive neuroscience*, *9*(5), 624-647.

Shmuel, A., Yacoub, E., Pfeuffer, J., Van de Moortele, P. F., Adriany, G., Hu, X., & Ugurbil, K. (2002). Sustained negative BOLD, blood flow and oxygen consumption response and its coupling to the positive response in the human brain. *Neuron*, *36*(6), 1195-1210.

Shmuel, A., Augath, M., Oeltermann, A., & Logothetis, N. K. (2006). Negative functional MRI response correlates with decreases in neuronal activity in monkey visual area V1. *Nature neuroscience*, *9*(4), 569-577.

Simmonds, D. J., Pekar, J. J., & Mostofsky, S. H. (2008). Meta-analysis of Go/No-go tasks demonstrating that fMRI activation associated with response inhibition is task-dependent. *Neuropsychologia*, *46*(1), 224-232.

Skrbina, D. F. (2017). *Panpsychism in the West*. MIT Press.

Sommer, I. E., Aleman, A., Bouma, A., & Kahn, R. S. (2004). Do women really have more bilateral language representation than men? A meta-analysis of functional imaging studies. *Brain*, *127*(8), 1845-1852.

Slagter, H. A., Prinssen, S., Reteig, L. C., & Mazaheri, A. (2016). Facilitation and inhibition in attention: functional dissociation of pre-stimulus alpha activity, P1, and N1 components. *Neuroimage*, *125*, 25-35.

Smith, A. T., Singh, K. D., & Greenlee, M. W. (2000). Attentional suppression of activity in the human visual cortex. *Neuroreport*, *11*(2), 271-278.

Smith, A. T., Williams, A. L., & Singh, K. D. (2004). Negative BOLD in the visual cortex: evidence against blood stealing. *Human brain mapping*, *21*(4), 213-220.

Spreng, R. N., Mar, R. A., & Kim, A. S. (2009). The common neural basis of autobiographical memory, prospection, navigation, theory of mind, and the default mode: a quantitative meta-analysis. *Journal of cognitive neuroscience*, *21*(3), 489-510.

Spreng, R. N., Sepulcre, J., Turner, G. R., Stevens, W. D., & Schacter, D. L. (2013). Intrinsic architecture underlying the relations among the default, dorsal attention, and frontoparietal control networks of the human brain. *Journal of cognitive neuroscience*, *25*(1), 74-86.

Stefanovic, B., Warnking, J. M., & Pike, G. B. (2004). Hemodynamic and metabolic responses to neuronal inhibition. *Neuroimage*, *22*(2), 771-778.

Sten, S., Lundengård, K., Witt, S. T., Cedersund, G., Elinder, F., & Engström, M. (2017). Neural inhibition can explain negative BOLD responses: a mechanistic modelling and fMRI study. *Neuroimage*, *158*, 219-231.

Stephan, K. E., Harrison, L. M., Penny, W. D., & Friston, K. J. (2004). Biophysical models of fMRI responses. *Current opinion in neurobiology*, *14*(5), 629-635.

Stevens, J. S., & Hamann, S. (2012). Sex differences in brain activation to emotional stimuli: a meta-analysis of neuroimaging studies. *Neuropsychologia*, *50*(7), 1578-1593.

Steriade, M. (2003). The corticothalamic system in sleep. *Frontiers in bioscience: a journal and virtual library*, *8*, d878-99.

Storm, J. F., Boly, M., Casali, A. G., Massimini, M., Olcese, U., Pennartz, C. M., & Wilke, M. (2017). Consciousness regained: disentangling mechanisms, brain systems, and behavioral responses. *Journal of Neuroscience*, *37*(45), 10882-10893.Svoboda, E., McKinnon, M. C., & Levine, B. (2006). The functional neuroanatomy of autobiographical memory: a meta-analysis. *Neuropsychologia*, *44*(12), 2189-2208.

Tallon-Baudry, C., & Bertrand, O. (1999). Oscillatory gamma activity in humans and its role in object representation. *Trends in cognitive sciences*, *3*(4), 151-162.

Teplan, M. (2002). Fundamentals of EEG measurement. *Measurement science review*, *2*(2), 1-11.

Thomas, B. P., Liu, P., Aslan, S., King, K. S., van Osch, M. J., & Lu, H. (2013). Physiologic underpinnings of negative BOLD cerebrovascular reactivity in brain ventricles. *Neuroimage*, *83*, 505-512.

Thulborn, K. R., Waterton, J. C., Matthews, P. M., & Radda, G. K. (1982). Oxygenation dependence of the transverse relaxation time of water protons in whole blood at high field. *Biochimica et Biophysica Acta (BBA)-General Subjects*, *714*(2), 265-270.

Thut, G., Nietzel, A., Brandt, S. A., & Pascual-Leone, A. (2006). α-Band electroencephalographic activity over occipital cortex indexes visuospatial attention bias and predicts visual target detection. *Journal of Neuroscience*, *26*(37), 9494-9502.

Thut, G., & Pascual-Leone, A. (2010). A review of combined TMS-EEG studies to characterize lasting effects of repetitive TMS and assess their usefulness in cognitive and clinical neuroscience. *Brain topography*, *22*(4), 219.

Thorsen, A. L., Hagland, P., Radua, J., Mataix-Cols, D., Kvale, G., Hansen, B., & van den Heuvel, O. A. (2018). Emotional processing in obsessive-compulsive disorder: A systematic review and meta-analysis of 25 functional neuroimaging studies. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *3*(6), 563-571.

Tootell, R. B., Hadjikhani, N., Hall, E. K., Marrett, S., Vanduffel, W., Vaughan, J. T., & Dale, A. M. (1998). The retinotopy of visual spatial attention. *Neuron*, *21*(6), 1409-1422.

Trachel, R. E., Clerc, M., & Brochier, T. G. (2015). Decoding covert shifts of attention induced by ambiguous visuospatial cues. *Frontiers in human neuroscience*, *9*, 358.

Tsubokawa, T., Katayama, Y., Kondo, T., Ueno, Y., Hayashi, N., & Moriyasu, N. (1980). Changes in local cerebral blood flow and neuronal activity during sensory stimulation in normal and sympathectomized cats. *Brain research*, *190*(1), 51-65.

Tuladhar, A. M., Huurne, N. T., Schoffelen, J. M., Maris, E., Oostenveld, R., & Jensen, O. (2007). Parieto-occipital sources account for the increase in alpha activity with working memory load. *Human brain mapping*, *28*(8), 785-792.

Van Diepen, R. M., Cohen, M. X., Denys, D., & Mazaheri, A. (2015). Attention and temporal expectations modulate power, not phase, of ongoing alpha oscillations. *Journal of cognitive neuroscience*, *27*(8), 1573-1586.

Van Dijk, H., Schoffelen, J. M., Oostenveld, R., & Jensen, O. (2008). Prestimulus oscillatory activity in the alpha band predicts visual discrimination ability. *Journal of Neuroscience*, *28*(8), 1816-1823.

Van Hoey, G., Van de Walle, R., Vanrumste, B., D'Havse, M., Lemahieu, I., & Boon, P. (1999). Beamforming techniques applied in EEG source analysis. *Proc. ProRISC99*, *10*, 545-549.

Van Overwalle, F. (2009). Social cognition and the brain: a meta-analysis. *Human brain mapping*, *30*(3), 829-858.

Van Overwalle, F., & Baetens, K. (2009). Understanding others' actions and goals by mirror and mentalizing systems: a meta-analysis. *Neuroimage*, *48*(3), 564-584.

Van Overwalle, F., Baetens, K., Mariën, P., & Vandekerckhove, M. (2014). Social cognition and the cerebellum: a meta-analysis of over 350 fMRI studies. *Neuroimage*, *86*, 554-572.

Van Veen, B. D., Van Drongelen, W., Yuchtman, M., & Suzuki, A. (1997). Localization of brain electrical activity via linearly constrained minimum variance spatial filtering. *IEEE Transactions on biomedical engineering*, *44*(9), 867-880.

Veldhuizen, M. G., Albrecht, J., Zelano, C., Boesveldt, S., Breslin, P., & Lundström, J. N. (2011). Identification of human gustatory cortex by activation likelihood estimation. *Human brain mapping*, *32*(12), 2256-2266.

Veldhuizen, M. G., & Small, D. M. (2011). Modality-specific neural effects of selective attention to taste and odor. *Chemical senses*, *36*(8), 747-760.

Vernet, M., Quentin, R., Japee, S., & Ungerleider, L. G. (2020). From visual awareness to consciousness without sensory input: The role of spontaneous brain activity. *Cognitive Neuropsychology*, 1-4.

Viard, A., Doeller, C. F., Hartley, T., Bird, C. M., & Burgess, N. (2011). Anterior hippocampus and goal-directed spatial decision making. *Journal of Neuroscience*, *31*(12), 4613-4621.

Vissers, M. E., van Driel, J., & Slagter, H. A. (2016). Proactive, but not reactive, distractor filtering relies on local modulation of alpha oscillatory activity. *Journal of Cognitive Neuroscience*, *28*(12), 1964-1979.

von Helmholtz, H. L. F. (2004). Some laws concerning the distribution of electric currents in volume conductors with applications to experiments on animal electricity. *Proceedings of the IEEE*, *92*(5), 868-870.

Vrba, J. (2002). Magnetoencephalography: the art of finding a needle in a haystack. *Physica C: Superconductivity*, *368*(1-4), 1-9.

Vorwerk, J., Cho, J. H., Rampp, S., Hamer, H., Knösche, T. R., & Wolters, C. H. (2014). A guideline for head volume conductor modeling in EEG and MEG. *NeuroImage*, *100*, 590-607.

Wang, B., Ke, W., Guang, J., Chen, G., Yin, L., Deng, S., ... & Shu, Y. (2016). Firing frequency maxima of fast-spiking neurons in human, monkey, and mouse neocortex. *Frontiers in cellular neuroscience*, *10*, 239.

Weisz, N., Müller, N., Jatzev, S., & Bertrand, O. (2014). Oscillatory alpha modulations in right auditory regions reflect the validity of acoustic cues in an auditory spatial attention task. *Cerebral cortex*, *24*(10), 2579-2590.

Wildegger, T., van Ede, F., Woolrich, M., Gillebert, C. R., & Nobre, A. C. (2017). Preparatory α-band oscillations reflect spatial gating independently of predictions regarding target identity. *Journal of neurophysiology*, *117*(3), 1385-1394.

Wilke, M. (2017). Consciousness regained: disentangling mechanisms, brain systems, and behavioral responses. *Journal of Neuroscience*, *37*(45), 10882-10893.

Wilsch, A., Mercier, M., Obleser, J., Schroeder, C. E., & Haegens, S. (2020). Spatial attention and temporal expectation exert differential effects on visual and auditory discrimination. *Journal of Cognitive Neuroscience*, 1-15.

Wilson, R. S., Mayhew, S. D., Rollings, D. T., Goldstone, A., Przezdzik, I., Arvanitis, T. N., & Bagshaw, A. P. (2015). Influence of epoch length on measurement of dynamic functional connectivity in wakefulness and behavioural validation in sleep. *Neuroimage*, *112*, 169-179.

Worden, M. S., Foxe, J. J., Wang, N., & Simpson, G. V. (2000). Anticipatory biasing of visuospatial attention indexed by retinotopically specific α-bank electroencephalography increases over occipital cortex. *Journal of Neuroscience*, *20*(6), RC63-RC63.

Worden, M. S., Martinez, A., & Posner, M. I. (2006). Spatial Attention, Neural Basis of. *Encyclopedia of Cognitive Science*.

Yanagisawa, T., Yamashita, O., Hirata, M., Kishima, H., Saitoh, Y., Goto, T., ... & Kamitani, Y. (2012). Regulation of motor representation by phase–amplitude coupling in the sensorimotor cortex. *Journal of Neuroscience*, *32*(44), 15467-15475.

Zaehle, T., Rach, S., & Herrmann, C. S. (2010). Transcranial alternating current stimulation enhances individual alpha activity in human EEG. *PloS one*, *5*(11), e13766.

Appendix: 1 - Public Engagement Chapter

In 2018, whilst studying my PhD and training as both a psychologist and neuroscientist, I created the show WaterCooler Neuroscience which became the WaterCooler Neuroscience Podcast Network and now has become WaterCooler FM. This appendix covers my reasons for doing so, how it affected my PhD and development as a scientist and my plans for the public dissemination of information in this thesis.

Throughout my postgraduate studies, I have regularly spent time giving talks and running activities to engage the public in science communication. While I also did this following my undergraduate degree in Psychology the importance of it was more apparent after studying Cognitive Neuroscience. In my experience, the two fields both have challenges when presenting them to the public however despite both being focused on the brain these challenges are quite different.

When communicating the science of Psychology, the challenge is that while the conscious experience is the dominant factor of everyone's lives, by definition arguably, this does not automatically mean experiencing consciousness results in an understanding equivocal to scientific study. Firstly, this does not only require explaining several non-intuitive elements of cognition but also talking about how introspection is not an adequate tool for a proper exploration of the workings of the mind or brain. The need for more sophisticated tools in studying the mind such as experimental design and statistical analyses results in an accusation of scientific gatekeeping which forces the layperson to not have their voice heard. On top of this Psychology's limitation of viewing the brain as a black box and needing to construct theories that are not necessarily found in the biological architecture and functioning of the brain can cause further problems. Scientifically the solution to this limitation of Psychology is Neuroscience but this brings new difficulties in communication.

In Neuroscience, the principal concerns of science communication appear, at times, in the obtuse difficulty of Neuroscience methods and the long period of education required for a person to acquire proficiency in these methods. The time needed to understand the physics behind the instruments used, the advanced mathematical and statistical models applied to interpret the measurements made by those instruments, the decades of biological evidence scientists have accrued about the brain and learning to understand the main conflicting models of the brain, mean that to a non-scientist the area can be, in a word, unapproachable. While I have seen arguments presented that Neuroscience, due to its high educational requirements, is therefore not for the public to understand this in my experience leads to disenfranchisement and disillusionment from the public. The presentation of soundbites for consumption by the public has been the primary solution but with limited focus on true engagement results in a conflict with fundamental human curiosity. To present a finding to the public and then have an example citizen feel the desire to want to manipulate and alter that finding in a way to better understand how the brain works is natural. It is one of the key cognitive patterns seen in scientists themselves but the snippets of information given to the public mean they lack enough information to properly process the findings they have been given, which naturally leads to flawed assumptions, equally flawed responses and the problem that people are told they have no valid input to give. This, while not mean-spirited, is exclusionary and ultimately exclusionary tactics do lead to the aforementioned disenfranchisement and eventually anti-scientific movements.

The following arguments I present in this chapter show, in my opinion, why the rise of alternative facts and post-truth has been so prolific. There is a strong role for the rapid spread of information that is now possible, but the uptake of anti-intellectualism ultimately shows that movement has appeal to many. The difficulties of the non-intuitiveness of Psychology and the barrier to entry caused by the heavy presence of natural sciences found in

Neuroscience offer complementary approaches in trying to engage the public. The difficulty in tackling these problems is the lack of unification in the sciences (that statement is only made as a commentary, not a criticism). Just as there is no unified body of Neuroscience that identifies keep areas and prescribes what a set researcher is to do to ensure a cohesive research approach to understanding the brain in a given decade or era the same is true for scientific communication. There are many guides, suggestions, and theories but they are all optional, as such the many choices available naturally leads to diversion, heterogeneity, and a lack of cohesion. This is unavoidable to provide scientists the desired freedom to explore their 'field of interest' instead of the 'field/s of the greatest importance' and the pros and cons to both methods are clear. I do not advocate for an all-controlling body that sets research agendas on a person by person basis but it is an interesting thought experiment nonetheless especially when it highlights issues with subject-wide approaches to issues such as opacity in the direction of scientific research and communication.

This is where the Water Cooler Neuroscience podcast that I created came in. During my employment as a public engagement speaker, I was very successful in giving talks, not on my work, but on the fundamentals that were required to understand my work, and these gained repeat employment over the years. However, there was a trend upon each subsequent contract for requests to reduce the time of engagement with a group and focusing less on the fundamental science but instead solely communicating interesting findings; this being the exact opposite of the trends seen in the teaching work I was doing at the same time. I came to see the tension in how the public and the students were being presented Psychology and if the approach for students was meant to educate them in the sciences the method given to the public, by nature of it being the opposite, would ultimately serve to not educate.

This realisation led me to look at how the public was presented with the sciences in general. My time spent in conferences and research meetings both in my home institution and at other

universities showed me a quick and immediate issue. When scientists speak amongst themselves the focus, sometimes the only focus is on the methodology or more pithily the HOW. A keynote lecture or workshop, once freed to audience questions, quickly descends into a maelstrom of varied methodological questions because regardless of how impressive the findings are if you failed to properly construct and create the experiment the findings are irrelevant. Once the room was sated the findings were accepted without ceremony but in the scientific community that is rare. In contrast, as has been mentioned above, the public isn't presented with the methodologies on any intelligible level. It would not be seen as satisfactory in undergraduate or postgraduate teaching to explain the methodology of a study in only a couple of minutes but focus on results for the remainder of the lecture and yet that is the approach for a considerable portion of modern-day science communication.

With this insight in mind, I created a podcast that allowed me to present only experts and more importantly quiz them on their methodology as much as required for the show. It would be foolish to say that the shows I have created are a substitute for a rigorous academic education but a key focus on HOW over WHAT still plays a central role in the ethos of the content. The next central part of the show was that each episode would focus on the backgrounds of the guests, explain their training and research so while the show highlights that laypeople did not have the same ability to discuss the brain it was because of career choices and decades of work instead of focusing solely on intellect and implied worth. The show works to discuss the methodology of the brain sciences as best as can be done through a podcast without the help of visual aids or being able to talk to a teaching assistant. This required the episodes to be as long as lectures on average, something that I was no longer able to do through the science communication channels I was being employed by at the time. The final part of the show that is important is that each show starts with a myth, a discussion

of the incorrect perception of the brain the public has but with a quick focus on providing the truth and showing the reasoning behind the guest's argument for what the truth is.

To date, there are three shows which have both released series and miniseries.

Water Cooler Neuroscience – this is the flagship show of the podcast and shares its name with the podcast in general. The aim of this show has already been described with its focus on methodology, clarifying the background of researchers and their research, and regular admissions of the limitations of the field, technologies, and the guests themselves. These are all things we ask students and laypeople to admit when participating in public engagement tasks so for the expert guests to do it too is only natural.

The show has had two series released with the first made with heavy support from the Centre for Human Brain Health and the University of Birmingham in general. That series was composed of three mini-series

1. Episodes 1-4 were on non-adult human thinking and coming to terms with presentations of cognition that were not usually available in day-to-day life. A deeper look at childhood and the oddities of infant cognition was first but this quickly descended into primates, Corvians, and then many other animals which show cognitive abilities.
2. Episodes 5-6 were a breakdown of the two standard neuroimaging methods, electroencephalography, and functional magnetic resonance imaging. These episodes were challenging to make and had to condense what had been multiple lectures of my masters into two forty-minute episodes. These episodes, however, have been successful and repeatedly mentioned throughout subsequent episodes.
3. Episodes 7-10 focused on neuroimaging and how face-to-face reporting on topics like learning and sleep was not satisfactory for continued academic studies. The episodes

> looked into a range of topics and highlighted the limits of our understanding from classical psychology paradigms which were now being answered by neuroimaging studies.

Season two moved onto more challenging topics. While the first series alluded to the need for complex statistical models in understanding neuroimaging and psychological data, it was only in episodes 5-6 that this topic was given any real attention. Season two then focused on what is known in the UK as cognitive or systems neuroscience and computational neuroscience or machine learning supported neuroscience. A range of guests from across the United Kingdom, United States of America, and Europe were invited and interviewed. This cross-section of researchers from different cultures and countries brought up discrepancies in language and differences in scientific philosophies that are rarely brought out in non-specialist outlets.

Season three of the show was sponsored by the Biochemical Society and discussed the cytoarchitecture, genetic influences, and neurobiology of the brain. While a topic that I only have a fleeting academic training in it is again centrally important to be presented to the public. Chemistry as a topic is the most underrepresented as a topic of science communication and yet the role of chemistry in daily lives is so fundamental that it is futile to do it justice in this paragraph or even chapter. The biochemistry of the brain is the very foundation of our understanding of the brain from the perspective of the natural sciences and therefore it duly deserves a place in this extended project. The topics covered involve the fundamentals of cell information transmission, genetic expressions which alter cell function, cell energy use, and its more applied uses in clinical applications from medical to mental diseases. Season 4 then moved onto artificial intelligence both for statistical methods and the more general layperson understood concept of artificial intelligence. This season brought forward the discussion on how Psychology and Neuroscience were using AI to improve

research and analytical methods but also venturing into having to understand non-human thinking/Psychology when trying to understand the outputs generated by AI programs.

With a listenership in the hundreds of thousands of downloads per quarter, I am pleased with the success of the show and the response that people have given. By no means has the show brought about a wave of education in the population but it has succeeded in offering brain science methodology as a topic that can be approached and ignited interest and respect for the sciences without rejection.

The other two shows are Brains Talking about Brains and Think Fast. Think Fast is a weekly show that served a sub-audience that was found during the analysis of the data on listenership traffic. This show presents the audience with inspiration to learn more about the show by providing a 15 minute or longer interview with an academic who is active in current research and discussing either their most recent work or their ongoing research. While the show may seem to counter the goals of WaterCooler Neuroscience with its considerably shorter times, 1. It is only a supplementary or additional show and 2. It is a show that serves to inform about the methodologies being used and how researchers would communicate over a short period of 15 to 30 minutes such as during a lunch break at a conference. The other show is Brains Talking about Brains and this is a duet show done with myself and a clinical psychologist and neuroscientist, Jordana Adler, who has worked in neurofeedback clinics for a number of years. This show instead presents the difference in education and therefore world viewpoint that trained scientists can have. The show centers around key papers or findings and discusses what information we find interesting i.e., a statistical trend, an attempt at a new imaging method, or a discussion around the synthesis of new ideas and when flashy headlines fail to impress us i.e. claims of mind-reading, understanding dreams as portents to deeper psychological understanding or presentations of combining new imaging techniques where it is just routine. This show intends to support the other two shows by presenting an

anthropological look into how trained brain researchers/professionals understand people and their brains to explain ‘culture shocks’ which can occur for listeners to the other shows.

Regarding the relevance of the shows to this thesis, since the above provides its relevance to my Ph.D. and growth as a scientist. I believe that since a thesis is a scientific document and in the UK usually involves the use of taxpayer money at least at some point during the course of the program that public engagement is key. The public should have a way to understand a thesis without the thesis losing its deeply technical and scientific nature. To accomplish this an episode per experimental chapter will be created and published upon this thesis being accepted as holding scientific legitimacy. These episodes will be the full-length WaterCooler Neuroscience episodes and provide both a scientific breakdown of the concepts found in the chapters but also the same autobiographical tone that WaterCooler Neuroscience episodes are known to have.

The creation of these shows is my best attempt at working to provide both the scientific and lay community with a full presentation of the work discussed in this thesis and will be published online free of charge.

Anyone wishing to listen can find the episodes for free at www.watercoolerneuroscience.co.uk.