NEUROPHYSIOLOGICAL MECHANISMS OF AUDIO-VISUAL INTERSENSORY ATTENTION: EVIDENCE FROM HIGH-DENSITY SURFACE EEG AND HUMAN INTRACRANIAL RECORDINGS

By

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Abstract

NEUROPHYSIOLOGICAL MECHANISMS OF AUDIO-VISUAL INTERSENSORY ATTENTION: EVIDENCE FROM HIGH-DENSITY SURFACE EEG AND HUMAN INTRACRANIAL RECORDINGS

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The spatio-temporal dynamics of audio-visual intersensory attention were investigated in a series of neurophysiological studies in cognitively healthy individuals. Four studies recorded electrophysiological (EEG) activity from high-density surface electrodes to investigate the broadband and band-specific mechanisms of attention in low and high-order cortices. A separate study recorded electro-cortico (ECoG) activity in two cognitively-healthy individuals to assess entrainment mechanisms at the earliest levels of auditory cortex during an audio-visual attention task. The results further established the role of the alpha (8 – 14 Hz) frequency band as an active gating mechanism in early sensory cortex during intersensory attention. Further, the data revealed that oscillatory power in this frequency band can serve as a neurophysiological marker for behavioral outcome during high-demanding intersensory attentional deployments. In a rhythmic and predictable task, alpha-band power was modulated by the periodicity of a delta-band (1-3

Hz) frequency oscillation, thus further suggesting that higher frequency oscillations (> 8 Hz) influence sensory processing through power fluctuations, while slow oscillations (< 7 Hz) influence activity through phase-dependent mechanisms. In addition, the data also revealed that neuronal activity within the alpha-band is highly sensitive to the natural pharmacological agent L-Theanine. Finally, the data suggests that by allowing participants to voluntarily generate an attentional deployment, top-down attentional signals get reconfigured, which might give rise to a more endogenous (or less automatic) attentional set. Taken together, the present data firmly supports the ‘early-model’ of attention in that top-down attentional signals were found to have an effect on neural activity in early sensory areas and at relatively ‘early’ stages of stimulus processing.

Dedication

This dissertation is dedicated to my loving and supportive family. I am eternally grateful for your unconditional support along every step in this long and joyful journey.

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"If we live for some time in the vicinity of a waterfall, we cease to notice the noise, but if someone draws our attention to it, we remember it, and are conscious of having had at the time some feeling of it."… "We are aware of the sound of the sea breaking on the shore but not of the sound made by a single wave. But the sound of one wave must be affecting us, since otherwise the sound of many such waves would not be audible; a hundred thousand nothings cannot make something" (Leibntiz 1796).

From the observations of Herman Helmholtz (1851) to the experimental findings by the ***Broadbent*** (Broadbent 1958), ***Desimone*** (Desimone & Duncan 1995) and ***Hillyard*** groups (Martinez et al 1999), the subject of attention has evolved into a topic that is studied in a wide range of academic fields and investigated at many levels of the human peripheral and central nervous system. In particular, during the past two decades, the implementation of high-density electrophysiological (EEG) and neuroimaging technologies has generated an abundance of studies investigating the brain mechanisms underlying selective attention (e.g. the ability to ignore distraction and focus on the relevant features of the environment). For the most part, selective or so-called voluntary attention studies are generally conducted within a single sensory modality (mostly within vision), and have led to the discovery of a number of cortical and subcortical processes believed to operate in an orchestrated fashion to mediate selection of relevant inputs. For example, based on findings from neuroimaging and EEG research, a handful of sources within the frontal and parietal cortex are considered central in the execution of attentional deployments in space (see Corbetta et al 2000; Mesulam 2000; Hopfinger et al 2000; Praamstra et al 2005; Grent-'t-Jong and Woldorff 2007; Doesburg et al 2008a). Further, a number of EEG studies have identified a collection of spatially specific, or perhaps retinotopically-mapped, EEG processes believed to underlie the establishment and maintenance of endogenous spatial attention (see Eimer et al 2002; Eimer et al 2003; Worden et al 2000; Kelly et al 2006; Thut et al 2006). However, while much is known about the mechanisms that underlie voluntary attention within single modalities, very little is known about the mechanisms that facilitate selective attentional deployments across the senses. Indeed, this is an important area of research since our environment is extremely multisensory and excessively saturated with distracting stimuli from different sensory modalities. The aim of this thesis project is to further our understanding of the brain mechanisms instantiated during intersensory selective attention to the auditory and visual modalities.

In the following sections, a short description of the most influential selective attention work during the past two centuries is given. A brief description of how earlier models of attention have evolved into more current models of information processing is provided. In addition, the electrophysiological (EEG) markers believed to underscore the processes of establishing and sustaining attention, as well as the effects that voluntary attention exert on stimulus processing are outlined. Finally, I endeavor to describe the oscillatory mechanisms believed to play a key role in selective attention functions, and detail the objectives of the current dissertation work.

1.1 Attention: A brief history

The work by Helmholtz paved the way for the empirical testing of many theories in cognitive psychology. In 1851 he invented the first instrument used to examine the inside of the human eye (the ophthalmoscope), and in 1867 he published what is considered by many as one of his greatest accomplishments, “The Handbook of Physiological Optics.” Both of these great achievements provided great insight for the empirical testing of many theories in spatial vision, color vision, and motion perception. His efforts in sensory physiology were the basis for the revolutionizing book “Principles of Physiological Psychology” written by one of his apprentices Wilhem Wundt. This book along with many of his groundbreaking essays merited Wundt the shared title of “one of the founding fathers of psychology”. In addition, Wundt is credited with establishing the first laboratory dedicated to psychological research in 1879 (Johnson & Proctor 2004, p5). Wundt contended that many psychological processes could be understood only in terms of their goals and consequences, and that apperception[1] and attention are processes of active synthesis. Further, Wundt was a firm believer of the concept of psychological volition, which he conceptualized as the process of conscious decision and choice.

During the same timeframe as Wundt, another brilliant mind was at work on the other side of the Atlantic Ocean. Also renowned as “one of the founding fathers of psychology”, William James’s views on attention are probably the most well known of the early psychologists:

'It is the taking possession by the mind, in clear and vivid form, of one of what seem several simultaneously possible objects or trains of thought. Focalization and concentration of consciousness are of its essence. It implies withdrawal from some things in order to deal effectively with others…” (see Posner 2004, p3, and Johnson & Proctor 2004, p11)

Similar to Wundt, the book by James “The Principles of Psychology” is widely considered to be one of the most important texts in the history of modern psychology. As a psychologist, James was extraordinarily interested in the field of psychopathology, as

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[1] A psychological construct created by Wundt, which implies the entry of external information into the inner focus of consciousness.

well as in the understanding of exceptional mental states (Wozniak 1999). Many critics say however, that out of all James's contributions there are three for which he has been especially famous in the area of psychology (Wozniak 1999): the (1) analysis of stream of thoughts, (2) characterization of the self, and (3) theory of emotion. One of Dr. James's theories on emotion for example, was the first to recognize the relationship between action and the physiological concomitants of emotion. In addition, he was the first to claim that memory or imaginative processes could easily trigger an emotional behavior. As he phrased it, “One may get angrier in thinking over one's insult than at the moment of receiving it” (see Wozniak 1999).

Parallel to the work of Wundt and James, the work by Donders and De Jagger in 1869 introduced to the world of psychology another important concept known as the speed of mental processes or ‘mental chronometry’. This concept is considered to be one of the central tenets of cognitive psychology, and for a long period of time served as the most commonly used tool for making inferences about learning, memory, and attentional neural processes. This idea stemmed from a series of experiments conducted by Donders and De Jagger (1869), which focused on the measurement of the time required to identify a stimulus and to select a motor response. For instance, in one of the experiments, participants were required to respond to a red light with the right hand and to a white light with the left hand. Their findings revealed that the mean reaction time (RT) was 356 ms, which was 172 ms longer than a simple reaction to the same stimuli (i.e. executing a single response to any stimulus presented – see Johnson & Proctor 2004, p 6). Donders and his colleague argued that by adding a process to a task and then taking the difference in RT between the two tasks, one could estimate the time for a particular neural process to be executed. They labeled this analysis technique as the ‘subtractive method’. They also distinguished between three types of reactions: (1) a simple reaction, (2) a choice reaction, and (3) a go or no-go reaction. To date, these reaction-type processes continue to be implemented in tasks assessing attentional control and decision-making processes. Moreover, because of their advantage of allowing a proper assessment of attention effects, without the contamination of motor and/or premotor artifacts, a great deal of current EEG and neuroimaging attention studies make use of these so-called go/no-go reaction type tasks.

It is said that in the period between the early 1900s and the 1930s the topic of attention received very little interest. Many critics believe that this lack of interest was largely due to researchers’ sudden fascination with the field of clinical psychology, and especially with the schools of psychoanalysis and behaviorism (see Johnson & Proctor 2004, p14). However, in the beginnings of the 1930s there was a renewed interest in the study of attentional volition, which is mostly attributed to the work of Telford (1931) and Stroop (1935).

Telford (1931) mentioned that numerous physiological studies showed that a cell exhibited a ‘refractory period’ in the time following excitatory stimulation (i.e. the hyperpolarization phase, see Hodgkin 1976 for a comprehensive review). He argued that if such behavior occurred at the single cell level then it is also likely to be observed at the ‘global’ cognitive level. In his study, Telford (1931) instructed subjects to make a simple reaction to the occurrence of a tone. He showed that when the interval between two auditory tones was relatively short, participants RT significantly increased with respect to auditory stimuli that were presented much further apart. He termed this behavior the “psychological refractory period effect”, and argued that the underlying mechanisms for this effect could be observed at the single neuron level.

The study by Stroop (1935) is certainly one of the most widely cited studies in the field of psychology. Stroop demonstrated that the attentional system is not fully able to suppress distracting or unwanted inputs in the environment, because certain stimuli can significantly interfere with the effective performance of a given task. Specifically, Stroop (1935) instructed subjects to name the color of a word stimulus printed on a list containing a total of 100 stimuli. Subjects read a total of two lists. In one of the lists, the word stimuli had incongruencies with respect to the color in which the stimulus was printed and what the stimulus actually read. For example, the word green was printed in the color red. In contrast, the remaining list contained word stimuli that were congruent, in that the word matched the color (e.g. the word blue printed in color blue). The results showed that subjects took an average of 110 seconds to name all the stimuli in list that contained the so-called ‘incongruent’ stimuli, while it only took 63 seconds to name the same amount of stimuli in the ‘congruent’ list. To verify whether this effect was selective to words and not color, in a separate session Stroop (1935) switched the instructions such that subjects had to name the word and not the color. The findings in this session however, revealed no difference between the ‘congruent’ and ‘incongruent’ lists, thus showing that the interference effect was unidirectional.

From the period of the 1950s onward, attention has been mostly investigated from the perspective of ‘information processing’. This period has been mostly influenced by the groundbreaking work of the cognitive scientists. Some of these include:

(1) Cherry (1953), who was first to report the “cocktail party phenomenon.”

(2) Broadbent, who developed the famous ‘filter theory of attention’[2] (see Broadbent 1958).

(3) Triesman, who developed the influential theory of “feature integration” (see Triesman and Gelade 1980), as well as the theory of ‘filter-attenuation’ (see Treisman 1960).

(4) Posner, who developed the famous “Posner cueing paradigm’ - regarded as one of the most influential paradigms in the attention field - (see Posner 1980).

(5) Hillyard who through the use of electrophysiology (EEG) and neuroimaging techniques showed that selective attention can influence activity at relatively ‘early’ stages of sensory processing (see Heinze et al 1990).

(6) Desimone & Duncan who through many single-unit EEG studies in non-human primates developed the “biased competition model of attention” (see Desimone and Duncan 1995).

(7) LaBerge, who developed the “Triangular Circuit Theory of Attention” (see LaBerge 1997).

The work conducted by Cherry (1953) was central to the development of many current theories of attentional processing. Cherry was primarily concerned with humans’ ability to select and extract information from an individual’s voice among other distracting voices and noises (i.e. the ‘cocktail party phenomenon’). He used the dichotic listening paradigm in which he presented different messages to each ear, and subjects were instructed to repeat aloud, or internally track, one of the two messages while ignoring the other. As expected, subjects had very little trouble accomplishing the task. However, when asked about the unattended channel, subjects were only able to describe

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[2] Broadbent’s filter was initially inspired by William James’s ‘multi-storage paradigm’ theory (1890) and Atkinson & Shiffrin's 'multi-store' memory model (1968)

certain aspects of the conversations, such as certain speakers' physical characteristics. They even failed to reliable report whether the language in the unattended channel was English or German.

Following a short period of time, Broadbent conducted several experiments that produced converging results to those of Cherry (1953). The study by Cherry (1953) along with his own findings led him to the development of his prominent 'filter' theory of attention. Broadbent argued that the brain has a limited capacity with regards to how much information it can process at a given moment. He also claimed that selective attention is necessary in order to filter out the overwhelming quantity of information constantly impinging on our senses. In 1958 Broadbent conducted a study where two sets of auditory stimuli, composed of three digits each, were concurrently presented to each ear. Subjects were instructed to recall as many digits as possible from both ears. The results showed that subjects tended to recall all of the digits presented to one ear before trying to recall the digits presented to the other ear. He proposed that information is held in a preattentive temporary store, and only sensory events that have some physical feature in common (e.g. spatial location) are selected to pass into the limited capacity processing system. In his 'filter theory' of attention, he proposes that the meaning of unattended signals is not identified, and that a 'relatively' lengthy amount of time is required to shift the filter from one channel of events to another.

However, as numerous studies have pointed out, contrary to Broadbent's theory, unattended signals are not fully suppressed and many times they are even represented in 'higher order' executive functioning areas (see Stroop 1935; Treisman 1960; Deutsch & Deutsch 1963; Ritter et al 1992; Sinai & Pratt 2003; Tse et al 2005; Ritter et al 2006;

Calvo & Nummenmaa 2007). Dr. Anne Treisman (1960) first asserted this claim, and developed the so-called ‘filter-attenuation’ theory of attention. She claimed that ‘early’ selection still precedes stimulus identification, but the ‘attentional filter’ only highly attenuates the information in the unattended channels rather than operating as a complete gating system. This attenuated signal however, may be sufficient to allow identification of the unattended stimulus in so-called ‘awareness’ areas.

Another highly influential theory in the field of cognitive science, developed by Treisman & Gelade (1980), is the ‘feature integration theory’ of attention. According to this model, attention binds different features of an object (e.g., color and shape) into consciously experienced wholes. This theory assumes that basic stimulus features are encoded into parallel maps across the visual field at a preattentive stage; this is the first stage of processing and allows for the search of a distinguished target that may be embedded in an array of distracters. The second stage involves focusing attention on a specific location and combining features that occupy the location into objects. They argue that a search for a specific target, distinguished from distracters, by a conjunction of features requires attention for integration of the features. As such, performance in conjunctive search tasks decreases as the number of distracters increases because the attentional spotlight must be moved sequentially across the search field until a target is detected (see Johnson & Proctor 2004; see Treisman & Gelade 1980; Treisman 1991; Treisman 1998; for a detailed explanation). Inherent in the differences between these early theories (i.e. filter vs. feature integration) is the level of processing at which attentional selection is made: the former arguing for very early, whereas the latter argues for a relatively late.

In fact, this is the issue that dominated attention research in the 1980s and 1990s. Namely, characterizing the level at which attended and/or unattended sensory information is ‘gated’ by top-down attentional signals.

This issue, which stemmed from the conflict of the ‘early vs. late’ selection model, was first battled between Deutsch & Deutsch (1963) and Broadbent (1958) & Treisman (1960), but has been largely resolved in favor of the ‘early selection model’ by the findings from the ***Hillyard lab*** (Heinze et al 1990; Clark & Hillyard 1996; Hillyard & Anllo-Vento 1998; Martinez et al 1999). The ‘early selection model’ holds that attention serves to select which stimuli will be further semantically processed and stored in long term memory. On the other hand, the ‘late selection model’ maintains that selective attention begins to operate only after all stimuli are semantically processed.

In 1995 Desimone & Duncan presented their highly influential ‘Biased competition model of attention’. According to this model, which is largely based on single-unit data from non-human primate studies and behavioral studies in healthy humans, all stimuli distributed in space compete for processing capacity in visual search. This neural competition is mediated by an “attentional template”, which works by favoring the sensory inputs that have overlapping features with the behaviorally relevant object. For example, if in a crowed environment the discrimination between the relevant and irrelevant targets is trivial, there will be a fast discrimination because the non-targets are poor matches to the attentional template and receive a weak competition bias. In contrast, if the non-targets are similar to the targets, then the competitive advantage of the target is reduced because each non-target shares the bias provided by the attentional template (see Desimone and Duncan 1995). The authors suggest that this model operates at the level of receptive fields (RF), and it is achieved by 'tuning the response of the RF to that of the attended object, thus leaving the unattended information outside the focus of the neuron's RF.

Clearly, there has been considerable interest in the topic of attention over the past two centuries. In this necessarily limited and selective historical survey we see how the subject of attention has moved from a 'mind & body' philosophical perspective to a neural mechanistic model of information processing. This shift in perspective has occurred because of two major factors: (1) The innovation of new EEG and neuroimaging technologies, and (2) the incorporation of other disciplines (e.g. engineering, mathematics, computer science, biology, etc) in the study of cognitive psychology[3]. In this thesis we focus on volitional aspects of attentional control especially in the area of audio-visual intersensory attention. Further, we provide evidence that suggests that both endogenous and exogenous attention, as they have been studied so far, are not necessarily a mutually exclusive phenomenon, and that they may operate using common neural networks.

1.2 Endogenous and exogenous aspects of attention:

When placed in an anticipatory state, humans are able to selectively bias their attention towards whatever information is relevant to current behavior. This ability plays a crucial role since the overflow of sensory information can inundate our sensory system and encumber the completion of the task at hand. This form of biasing is controlled by

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[3] For example, in recent years, researchers in the brain-computer-interface (BCI) field have become greatly interested in studying the electrical brain signals that index the mechanisms of attention control. Their primary goal is to understand the spatial and temporal dynamics of these signals in order to apply them in individuals suffering with severe motor and communication disabilities such as amyotropic lateral sclerosis, and/or the so-called locked-in syndrome (see Donchin et al 2000; Lalor et al 2005; Kelly et al 2005; Allison et al 2008).

so-called ‘top-down attentional signals’ and it is achieved by a voluntary or endogenous action of attentional control. Other forms of attentional biasing occur when a strong and unexpected external event (i.e. a handclap or a strong flash of light) captures the individual’s attention without the need of any deliberate orienting. This attentional process is commonly referred to as exogenous attention, and it operates through a rapid mechanism that reaches effects approximately ~100 – 300 ms after stimulus onset (Pashler 2001). The greatest behavioral benefit in exogenous attention tasks is observed when the interval between the first (i.e. the priming stimulus) and second stimulus is ~100 ms (see Posner 1980; Jonides 1981; Yantis & Jonides 1984; Cheal & Lyon 1991). This behavioral benefit reverses when the interval between the two stimuli is longer than 300 ms; an effect referred to as the inhibition of return (IOR) (Posner & Cohen 1984). Exogenous attention is regarded as a ‘bottom-up’ driven process controlled by the presentation of an external and unexpected stimulus that shares somewhat similar reaction time (RT) cost-benefit patterns with endogenous attention (see Posner 1980). In fact, several studies indicate that both endogenous and exogenous attentional mechanisms may operate within the same neural circuitry, or at least have many overlapping cortical and sub-cortical nodes (see Peelen et al 2004; Kincade et al 2005; Natale et al 2006).

Typically, in order to study both endogenous and exogenous states of attention, studies make use of so-called cueing paradigms. There are fundamental differences however, in the way that these cueing paradigms induce an exogenous or endogenous attentional deployment. For example, in exogenous attention, a salient sensory stimulus is presented at a particular location, typically in the periphery, which primes the subject for an upcoming stimulus at that same location. The sudden presentation of the priming stimulus produces an automatic covert attentional shift to that location. In contrast, in endogenous attention, a centrally presented ‘symbolic’ cue (e.g. an arrow in visuo-spatial attention studies) is typically employed, which informs the individual of the upcoming task to perform. In this situation, individuals need to ‘decode’ the instructional information provided the ‘symbolic’ cue, and subsequently orient attention to the instructed location, sensory modality, feature, object etc. It is argued that this form of attentional cueing represents a ‘relatively’ nice experimental version of what is regarded as a natural way to apportion attention in our environment.

In the remaining sections we detail how a typical cueing-paradigm is implemented in an endogenous attention task. In addition, we thoroughly describe the common behavioral, electrophysiological and neuroimaging results observed in the literature to date. Major emphasis is given to visuo-spatial attention studies, as an abundant amount of information exist in the literature. Further, we highlight the common neurophysiological and behavioral findings between visuo-spatial and audio-visual intersensory attention tasks.

1.3 The cueing paradigm:

In the year 1980 Dr. Michael Posner introduced to the world of cognitive science one of the most influential paradigms in its field. First applied to the visual-spatial domain, the cueing paradigm, which is typically referred to as the “Posner paradigm”, still remains one of the most widely used experimental paradigms for the study of attentional orienting in many domains such as: space, features, objects, temporal expectations, and sensory modalities, just to name a few. In its most basic form, the rules of this design typically involve subjects to fixate on a central mark, while a centrally presented symbolic cue (instructive stimulus, S1) covertly directs attention to a particular location (spatial attention), sensory modality (intersensory attention), color (feature attention), temporal event (temporal attention), or object (object-based attention). After a short period of time, typically referred to as the cue-target-interval (CTI), a target stimulus (imperative stimulus, S2) is presented and subjects typically perform a go/no-go task depending on whether the stimulus presented is the designated target deviant. Figure 1a and 1b in the appendix show a visual description of a trial in a typical visuo-spatial attention and intersensory study, respectively.

There are several benefits in implementing this type of experimental design. Firstly, it allows researchers to investigate, on a trial-by-trial basis, the attentional control mechanisms uncontaminated by the processing of the target stimulus. These neural mechanisms include cognitive events such as: engagement and disengagement neural attentional processes, and preparatory biasing mechanisms, just to name of few. Secondly, it allows researchers to investigate the attentional effects exerted on stimulus processing during a 'relatively' naturalistic scenario. The former is commonly investigated by analyzing the brain activity between the onset of the instructional S1-cue and the presentation of the target stimulus (i.e. CTI), while the latter is achieved by analyzing the activity after the presentation of the target stimulus.

1.4 Attention effects on target processing:

It is well established that individuals are not able to focus attention to the entire environment in just one visual or auditory snapshot. Instead, humans interact through the world by focusing attention to a particular set of objects, and selecting the most relevant information at the expense of other types of distracting and/or irrelevant stimuli. In fact, if we were able to attend to everything in the environment then we would constantly be distracted and unable to carry out any meaningful action at all. Clearly, having this capacity to attend to certain objects and not others is a useful tool that allows for effective navigation through our convoluted environment. This cognitive ability is known as selective attention, and has been extensively studied in laboratory (for a review see Umilta & Moscovitch 1994; Johnson & Proctor 2004; Posner 2004) and outdoor situations (Simons & Levin 1998; Simons & Rensink 2005 for a comprehensive review).

In a typical behavioral study, evidence for a selective attention effect is asserted when participants exhibit an improvement in the detection of a target that is inside the locus of the attentional spotlight, in comparison to when the target is outside the locus of the attentional spotlight. This accuracy improvement is commonly accompanied by a decrease in RT (see Posner et al 1980; Klein & Shore 2000; Melara et al 2002). The rationale is that the information provided by the S1-cue triggers a voluntarily or endogenous action of attentional control. In turn, this endogenous mechanism places the brain in an attentional biased state that preferentially processes relevant information at the expense of distracting inputs. This view is supported by several behavioral studies that have revealed so-called ‘attentional cost/benefit’ effects by showing that subjects exhibit slower RT in trials where the target is invalidly cued in comparison to when the target stimulus is valid, or when it is preceded by a ‘neutral’ cue[4] (see Posner et al 1980; Castiello & Umiltà 1992; Robin & Rizzo 1992). In support of this claim is data from

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[4] Validly cued trials: Trials where the target stimulus is in accordance with the instructional information of the S1 cue.
Invalidly cued trials: Trials where the target stimulus is in not accordance with the instructional information of the S1 cue.
Neutrally cued trials: Trials where the cue has no instructional validity. Subjects do not ‘build’ any expectation. It is believed that in such trials subjects divide their attention equally to all possible outcomes of the target stimulus.

neurophysiological and neuroimaging studies that have shown that apportioning attention to where the S1-cue previously instructed, results in greater neural response in the sensory-relevant and 'higher-order' cortical and subcortical areas.

There is still however, a great deal of debate regarding at which sensory processing stage does attention begin to exert its influence. While it is clear from ERP studies conducted by the ***Hillyard*** (see Heinze et al 1990; Clark & Hillyard 1996; Hillyard & Anllo-Vento 1998; Martinez et al 1999), ***Woldorff*** (see Woldorff et al 2002; Talsma & Woldorff 2005), ***Knight*** (Karns & Knight 2008), and ***Foxe*** lab (see Foxe et al 2005b; Kelly et al 2008) that attention operates at relatively 'early' cortical stages (i.e. ~80 to 100 ms past stimulus onset), there are still mixed and contradictory results in ascertaining the initial site of attentional selection in neocortex.

In the visual modality for example, studies by the Hillyard group indicate that top-down attentional signals begin to exert effects only after the sensory inputs have passed primary visual cortex (V1 – see Clark & Hillyard 1996; Martinez et al 1999). In one of the most recent influential studies in the field of cognitive science[5], Martinez and colleagues (1999) conducted a combined EEG and fMRI spatial attention study where participants discriminated deviant targets embedded in distracter arrays. The EEG data indicated that the initial neural activity, which occurred at 50 – 55 ms after stimulus onset and was source localized to striate cortex, was not modulated by spatial attention. Oddly however, the neuroimaging data did revealed attention effects at the level of primary visual cortex. Through the use of source modeling techniques, the authors found that a subsequent bulk of neural EEG activity in striate cortex was modulated by attention. This

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[5] A simple search in Google scholar revealed 341 citations to date, yielding approximately 38 citations per year.

led to the conclusion that top-down signals can exert effects over V1 but only through a reentrant feedback mechanism that emanated from higher-order visual areas. Moreover, Martinez and colleagues (1999) found that the earliest facilitation of attended signals was observed in extrastriate visual areas at ~70-75 ms, which corresponds to the initial activation of the P1 ERP component.

Nonetheless, recent fMRI, EEG and MEG studies of attention provide indirect evidence that top-down signals can significantly influence the initial activity in striate cortex (see Kastner et al 1999; Yamagishi et al 2005; Smith et al 2006; Silver et al 2007; Lakatos et al 2008). One study in particular, recorded EEG activity directly from V1 and showed that attention reorganizes the oscillatory-phase distribution of a delta-band (1 – 3 Hz) rhythm, just before the presentation of sensory stimulus (see Lakatos et al 2008). It was claimed that this oscillatory-phase reorganization operates as sensory selection tool such that relevant stimuli appear at the ‘high excitability’ state of the oscillation, while irrelevant stimuli appear at the ‘low excitability’ state of the oscillation. Further, studies by Kastner et al (1999) and Silver et al (2007) demonstrated that in the absence of any sensory stimulation there is sustained increased hemodynamic activity in the period preceding the presentation of a visual stimulus in human V1. Taken together, these patterns of results motivate the following obvious question: “Why would attention not influence sensory activity at the initial moment of sensory contact, but exert effects in the period immediately preceding the presentation of a sensory stimulus?”

In a recent experiment, Kelly and colleagues (2008) argued that a plausible reason of why ERP studies have failed to report reliable attention effects, during the initial volley of activation in V1, might be due to the variable and inadequate measurement of the C1

ERP component itself. The C1 ERP component, as indicated by several ERP studies using topographical and source localization techniques, mainly reflects activity from striate cortex (see Gomez-Gonzalez et al 1994; Clark et al 1995; DiRusso et al 2002; Foxe et al 2002; Kelly et al 2008). Many studies however, have shown that the anatomical distribution of striate cortex varies immensely across individuals (see Polyak 1957; Jeffreys & Axford 1972; Clark et al. 1995; Foxe & Simpson 2002; Proverbio et al. 2007). V1 has been found to vary in shape, size, and areal extent relative to anatomical landmarks in histological studies (Rademacher et al. 1993). As such, Kelly and colleagues (2008) devised an experimental paradigm that maximized the likelihood of measuring a robust C1 ERP component on a subject-by-subject basis. In contrast to the findings by Martinez et al (1999), the authors showed that attention significantly influenced stimulus processing in V1[6] starting at 57 ms past stimulus onset (see Kelly et al 2008). Furthermore, the first statistically significant point that revealed a selective attention effect coincided with the first point that deviated from baseline activity, thus further reinforcing the view that attention affects sensory information at the very first stage of stimulus processing. Similar findings were also observed by Poghosyan & Ioannides (2008).

Indeed, a great deal of information is known about the neural mechanisms underlying the effects of attention on stimulus processing. Numerous studies have shown that attention can operate both at an ‘early’ and ‘late’ stage of sensory processing. In the spatial attention domain we have elucidated that attention can influence relatively ‘early’ sensory activity during the C1[7] and P1 ERP components (see Heinze et al 1990; Eimer

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[6] Confirmed by source localization techniques using the LAURA algorithm as implemented in CARTOOL.
[7] This should be treated with caution until future studies consistently replicate the findings.

1993; Clark & Hillyard 1996; Martinez et al 1999; Macaluso et al 2005; Yosor et al 2008; Kelly et al 2008; Poghosyan & Ioannides 2008), as well as so-called 'late' sensory activity defined as activity occurring during the N1, P2, N2 and P3 ERP components (see Heinze et al 1990; Eimer 1993; Yamaguchi et al 1995; Clark & Hillyard 1996; Martinez et al 1999; DiRusso et al 2002; Eimer et al 2002; Woldorff et al 2002; Macaluso et al 2005).

In studies of 'temporal orienting' however, attention modulations have only been observed during the 'late' phases of sensory processing. In these studies, mostly conducted by the ***Nobre*** lab, orienting attention in time has only been shown to influence activity during the timeframe of the visual N1 (Griffin et al 2002), N2 and P300 ERP components (Miniussi et al 1999; Griffin et al 2002; Doherty et al 2005). Similarly, in object-based attention studies, the earliest timeframe of attentional modulations has been observed during the visual N1 ERP component and beyond (see Martinez et al 2006; Martinez et al 2007a; Martinez et al 2007b; Busse et al 2005; Molholm et al 2007). In fact, the studies by Martinez and colleagues (2006, 2007a & 2007b) revealed highly interesting pattern of effects. The authors used combined EEG and fMRI techniques to assess whether spatial attention plays a role in the selection of objects embedded in a visual scene. The findings across all three studies revealed highly overlapping effects, in that they all showed that spatial attention initially modulated activity during the timeframe of the visual P1 component, while object-based attention affected stimulus processing during the time period of the N1 component. This pattern of effects strongly indicates that space-based attention operates at an earlier timescale than object-based attention.

The findings in the intersensory attention domain are closely related to those observed in spatial attention, in that they show that attention is able to influence activity at 'early' and 'late' stages of sensory processing. The findings by Karns & Knight (2008) showed that when attention is deployed to the auditory modality, auditory processing is modulated at the latency of the Na ERP component (~ 30ms) and during the auditory P1 ERP component (~90 ms). Further, when attention is deployed to the visual modality, visual inputs are modulated at the latency of the early phase of the C1 ERP component (~ 60 ms, Karns & Knight 2008), as well as during the P1 (80 – 100 ms) and N1 ERP component (see Talsma & Woldorff 2005; Foxe & Simpson 2005b; Karns & Knight 2008). Finally, when attention is deployed to the somatosensory modality, attention begins to influence activity during the N160 ERP component, which is thought to arise from secondary association somatosensory cortex (see Karns & Knight 2008). Further, through source modeling techniques in MEG data, Poghosyan & Ioannides (2008) revealed attentional modulations in putative primary auditory cortex (A1) at 30-50 ms after stimulus onset during non-spatial attentional deployments to the auditory and visual modalities.

The vast majority of studies investigating attentional effects on stimulus processing make use of standard analyses procedures such as contrasting neural activity from attended vs. unattended (or ignored) stimuli. The contention is that by comparing the sensory activity evoked by the same physical stimuli, but in different attending conditions, one can unequivocally conclude that whatever difference is observed must be due to an attentional account. Indeed, a great deal of understanding has been achieved by implementing these types of analyses techniques. However, perhaps a more useful way to understand attentional control mechanisms might be to examine the brain activity that occurs in anticipation to an attended sensory stimulus. As mentioned above, by implementing so-called S1-S2 cueing paradigms and inspecting brain activity in the CTI, researchers can assess the neural mechanisms that establish and maintain the biased attentional state such as: engagement and disengagement, attentional orienting, and sustained attentional processes, just to name a few.

1.5 Electrophysiological indices of anticipatory attentional deployments

When individuals voluntary bias their attention to whatever aspect of a visual or an auditory scene, a collection of transient and long-lasting neural processes are instantiated throughout the attentional system. It is believed that these sets of preparatory processes are put in place in order to establish and maintain a biased attentional state. Further, it is contended that these anticipatory mechanisms operate in a sequential and parallel manner across distributed networks spanning anterior & posterior cortical and sub-cortical areas. We contend that this collection of neural processes are encoded in the following stages: (1) the intention of an attentional selection, (2) the reengagement or disengagement from the previous attended location, modality, feature etc, (2a) an attentional shift to the new instructed locus, (3) and the maintenance and holding of attention to that locus[8]. This framework of attentional deployment is largely motivated by work of Rafal and Posner (1987) and Foxe and colleagues (1998), and a visual description of this model can be observed in Figure 2 in the appendix.

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[8] In a laboratory setting however, if one would characterize the set of operations that instantiate this attentional biased state, the following stages need to be satisfied: (1) the sensory processing of the instructional cue, which most probably comprises ‘low-level’ regions of the sensory modality in which the cue was presented, followed by (2) the extraction of the meaningful code from the cue symbol, (3) the decoding of the relevant information extracted from the cue, (4) the voluntary orienting to the instructed locus, and (5) maintenance of attention in the location where the stimulus is most likely appear (see Giesbrecht and Mangun 2005).

Indeed, a vast number of EEG and neuroimaging studies of selective attention have uncovered a number of neural processes believed to be the physiological indices of these neural processing stages. For instance, in an intersensory study conducted by Foxe and colleagues (2005), the authors showed that the cue-encoding process is represented in the period of ~120–220 ms past cue onset over lateral frontal cortices. Further, the authors suggest that the process of voluntary orienting is represented by activity over frontal and parietal cortices beginning ~240 ms after cue onset. Finally these authors, in addition to Talsma et al (2008), showed that sustaining attention to the instructed modality was also reflected over an extended network of frontal and parietal cortices in the period preceding the presentation of the S2-stimulus.

In spatial attention there are also numerous findings mirroring those of the audio-visual intersensory domain. Studies have reported a number of symmetrically organized ERP components, that occur in both a sequential and parallel order, and span both anterior and posterior cortical areas (see Harter et al 1989; Eimer 1993; Nobre et al 2000; Hopf & Mangun 2000; Eimer et al 2002; Green et al 2005; Praamstra et al 2005; Talsma et al 2005; Simpson et al 2006; Grent-'t-Jong & Woldorff 2007). Figure 3 in the appendix shows a meta-analysis of the commonly reported ERPs across seventeen studies in the spatial attention domain. These ERP components are: The ‘early directing attention negativity’ (EDAN), which starts approximately 200 ms after the onset of the cue and arises over left and right parieto-occipital cortices. The EDAN is commonly followed by a bilateral negative deflection over frontal cortices known as the ‘anterior directing attention negativity’ (ADAN), and the retinotopically distributed ERP component ‘late directing attention positivity’ (LDAP). In what follows we described the temporal and spatial profile of these three ERP components, and their relationship to attentional control processes and behavior.

1.5.1 Early Directing Attention Negativity (EDAN):

The EDAN is a negative-polarity deflecting ERP component found over the parietal and occipital scalp contralateral to the direction of the S1-cue. It starts as early as 160 ms and last until 440 ms past S1-cue onset (Harter et al 1989; Yamaguchi et al 1994; Nobre et al 2000; Van Velzen & Eimer 2003; Slagter et al 2005; Talsma et al 2005). It is described as the neural correlate of selecting and establishing spatial attention control. The spatial distribution of the EDAN is to a large degree stable over bilateral parietal/occipital scalp regions (Harter et al 1989; Slagter et al 2005). However, Yamaguchi and colleagues (1994) observed that while the early phase of the EDAN (~240 – 380 ms post-cue onset) emerges over posterior scalp regions there is a topography shift to fronto-central regions during the late phase (~ 380 – 440 ms). Moreover, some studies indicate that the EDAN exhibits an asymmetric effect over the left hemisphere, which is believed to arise from a right-hemisphere dominance of attentional control (Nobre et al. 2000; Hopf and Mangun 2000; Talsma et al. 2005).

The involvement of the EDAN as a neural correlate of attentional deployment has been disputed, mainly on the basis of a sensory processing artifact (see Nobre 2000; Van Velzen & Eimer 2003; Green et al 2005). It is contended that this ERP component resembles the so-called N2pc effect typically seen in visual search paradigms (see Van Velzen & Eimer 2003). Van Velzen & Eimer (2003) contended that although the S1-arrow-cues are symmetrical in shape they are not symmetrical with respect to the location of the relevant arrowhead[9]. Thus, it is suggested that this EDAN or N2pc-type component reflects the selection of relevant elements of the S1-cue for further processing, rather than brain activity underlying preparatory orienting of attention. In support of this claim, the study from Green et al (2005; 2006) found no evidence of an EDAN or N2pc-like component when using an auditory verbal or tone S1-cue stimulus. However, while there is a compelling case suggesting that the EDAN is not strictly linked to attentional control processes, a recent study showed a significant strong correlation between the EDAN and RT across subjects (see Jongen et al 2006), thus arguing that this component might play some role in the establishment of attentional control.

1.5.2 Anterior Directing Attention Negativity (ADAN):

Evidence from human lesions and neuroimaging studies suggest that frontal cortices play a critical role in attentional control processes, especially those associated with voluntary focusing and maintaining attention (De Renzi et al, 1982; Posner and Petersen, 1990; Corbetta et al, 1993; Giesbrecht and Mangun 2005). These frontal regions include the superior frontal sulcus (SFS), middle frontal gyrus (MFG), superior frontal gyrus (SFG), supplementary motor area (SMA), and pre-central sulcus (PreCS). The leading tenet states that these structures operate in concert with other regions in the parietal lobe to give rise to the preparatory biasing state of attention. Figure 4 in the appendix illustrates a meta-analysis of the commonly reported fMRI activations across twelve studies in the spatial attention domain.

Numerous ERP studies have found neurophysiological evidence of a frontal cortical process that selectively responds to the direction of the instructional cue (Hopf and

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[9] Arrowheads directing attention to the right were always presented on the right side of fixation, while arrowheads directing attention to the left were always presented on the left side of fixation.

Mangun 2000; Nobre et al 2000; Eimer et al 2002; Eimer & Van Velzen 2002; Griffin et al 2002; Green et al 2005; Praamstra et al 2005; Talsma et al 2005; Simpson et al 2006; Dale et al 2008). This component, known as the 'anterior directing attention negativity' (ADAN), emerges around 300 ms after S1-cue onset and has duration of approximately 200 – 300 ms. The anatomical generators of this component have been sourced to lateral premotor cortices (Praamstra et al 2005), and bilateral medial frontal cortices - Broadmann's area 6, within the supplementary motor area- (Grent-t-Jong & Woldorff 2007). The exact function of this component has yet to be pinpointed, but it is generally regarded as a frontal executive control mechanism involved in redirecting attention in space (Hopf and Mangun 2000). The ADAN has not only been observed in studies of visuo-spatial attention, but it is also instantiated in studies of auditory and somatosensory spatial attention (Eimer et al 2002; Van Velzen et al 2002; Van Velzen & Eimer 2003; Eimer et al 2003a; Eimer et al 2003b), thus suggesting that this ERP component might reflect a supramodal, or in our preferred terminology suprasensory[10], process of spatial attentional control. Further, the ADAN has also been observed in the blind population, while subjects made attentional deployments to left and right spatial locations in anticipation of auditory and somatosensory stimuli (see Van Velzen et al 2006).

1.5.3 Late Directing Attention Positivity (LDAP):

Several human and non-human primate fMRI and EEG studies have shown that 'early' sensory regions are placed in a biased state in anticipation of an upcoming stimulus (see Luck et al 1997; Kastner et al 1999; Worden et al 2000; Hopfinger et al 2001; Eimer et al 2004; Foxe et al 2005a; Kelly et al 2006; Grent-'t-Jong & Woldorff

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[10] Although the term supramodal process has been traditionally used to denote a "general" or "overarching" process occurring across different sensory modalities, we believe that it severely lacks specificity as a simple search in Pubmed yields highly confounding results.

2007). This phenomenon is believed to be manifested as a baseline shift in activity levels in the period just preceding the presentation of the imperative stimulus (see Luck et al 1997; Foxe et al 2005). In the spatial attention domain two EEG processes that fit this profile have been identified: (1) the late- directing attention positivity (LDAP) and (2) pre-target alpha biasing effect (discussed in the following section).

The LDAP component is a sustained positive-polarity deflection observed over posterior cortices with spatially specific properties, which occurs during the late phase of the attentional deployment period. It onsets as early as 400 ms after cue presentation and lasts until the presentation of the S2 (see Harter et al, 1989; Nobre et al, 2000; Hopf and Mangun, 2000, Van Velzen et al 2002; Eimer et al 2003; Green et al 2005; Praamstra 2005; Simpson et al 2006). The LDAP is described as a suprasensory process involved in the coding of the to-be-attended location in preparation for an upcoming target (Eimer et al 2002; Green et al 2005; Green et al 2006). The LDAP has a ventral topographical distribution centered over lateral occipital regions when subjects are preparing for a visual target, while a dorsal distribution centered over temporo-parietal sites when subjects are preparing for an auditory target (see Green et al 2006). Further, the LDAP is one of the most consistently reported EEG markers of attentional deployment in space. It has not only been reported in visual tasks but also in auditory and/or somatosensory spatial attention tasks, thus indicating that this component reflects a suprasensory process of sustained attentional control (see Eimer et al 2002; Van Velzen et al 2003; Eimer et al 2003; Green et al 2005; Green et al 2006). Many of its properties however, are still poorly understood and a great deal of discrepancy regarding its functional role exists. For example, some spatial attention studies have found the polarity of the LDAP to reverse (e.g. an LDAN) depending whether the upcoming relevant stimulus appears above or below the vertical meridian (see Worden et al 2000; Griffin et al 2002; Eimer et al 2003; Green et al 2005; Grent-'t-Jong & Woldorff 2007; Dale et al 2008). Interestingly, this pattern of activity is only exclusive to the visual modality in that it is not observed in audio-tactile crossmodal studies of attention. This strongly indicates, at least with respect to the visual modality, that the LDAP might be accessing 'early' retinotopically visual areas such as V1 or V4 just to name a few.

A similar ERP component has also been identified in tasks that do not require spatial attentional deployments, but rather require attention to be deployed to different sensory modalities. This slow-ongoing broadband potential, which we term the late-sustained parieto-occipital positivity (LSPOP), shares very similar temporal, magnitude and topographical characteristics as the LDAP component. For example, these two late-sustained ERP components onset approximately 400 – 500 ms after cue onset, last for a relatively similar amount of time (i.e. ~ until the presentation of the S2), have a similar differential-amplitude response with respect to the attending conditions[11], and are localized to lateral parieto-occipital cortical areas. In fact, given the overlapping temporal and amplitude features of the LDAP and LSPOP, we contend that these ERP components may reflect a slow ongoing oscillatory rhythm occurring in the delta range (1 - 3 Hz), whose ongoing oscillatory phase is reset by the onset of the instructional cue (see chapter 2).

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[11] In spatial attention, attending to a particular hemifield results in greater broadband activation over the contralateral hemifield over parieto-occipital cortices. In intersensory attention, attending to the visual modality results in greater broadband activation over the same cortices.

1.6 Oscillatory Mechanisms and Selective Attention

A reasonable claim is that attentional operations are instantiated by highly complex and diffuse modules that are likely to operate in concert during transient and long periods of time. Recently, there have been several assertions indicating that synchronized neural oscillations is the likely mechanism mediating the effective communication within local neural ensembles and large-scale neural networks (see Engel & Singer 2001; Engel et al 2001; Varela et al 2003; Ward 2003; Fries 2005; Schnitzler & Gross 2005; Ward et al 2006; Doesburg & Ward 2008).

Oscillatory brain activity was first reported by Hans Berger (1929) when he recorded EEG activity in humans during periods of relaxed wakefulness, absence of sensory stimulation and general mental activity. He observed a dominant oscillating rhythm, centered around 10 Hz, which led him to suggest that periodic fluctuations in the EEG are associated with mental processes such as, arousal, memory and consciousness (see Pizzagalli 2007). Recent EEG animal studies indicate that synchronized oscillatory processes function to bias input selection, temporally bind neurons into assemblies, and promote synaptic plasticity (see Buzsaki & Draguhn 2004; Pizzagalli 2007; Lakatos et al 2008). In addition, it is contended that there are two major factors influencing neural behavior: (1) the magnitude response of higher-frequency rhythms and (2) the ongoing phase dynamics of lower-scale oscillations (see Fries 2005; Lakatos et al 2005; Canolty et al 2007; Lakatos et al 2008). Furthermore, recent findings indicate that higher frequency rhythms might originate from highly local neural ensembles, while lower-scale rhythms span larger neural populations (Buzsaki & Draguhn 2004).

Recently, there has been a huge reinvigoration of research efforts to address the role of oscillatory activity during sensory and cognitive processes. The current belief is that distinct frequency-bands are functionally related to specific sensory and cognitive neural processes. For instance, delta-band (1 – 3 Hz) oscillations are strongly implicated in learning and memory encoding during sleep (Steriade 1997; Battaglia et al 2004). Theta-band (4 – 7 Hz) oscillations in the hippocampus and frontal cortices have been strongly implicated in working memory tasks, as well as memory encoding and retrieval processes during active and engaged states (see Raghavachari et al 2001; Rizzuto et al 2003; Dragoi & Buzsaki 2006; Rizzuto et al 2006). Oscillatory activity in the alpha-band (8 – 14 Hz) has been associated with enhancement and suppression mechanisms in visual cortex (see Worden et al 2000; Fu et al 2001; Fries et al 2001; Sauseng et al 2005; Kelly et al 2006; Thut et al 2006; Rihs et al 2007; Gomez-Ramirez et al submitted). Beta-band (15 – 29 Hz) oscillations have been associated with motor behavior (see Babiloni et al 2002; Alegre et al 2004), object ‘closure’ processes (see Sehatpour et al 2008), and emotion (Ray and Cole 1985; Marosi et al 2001). Finally, gamma-band (> 30 Hz) oscillations have been implicated in binding-type processes (see Gray et al 1992; Singer & Gray 1995; Jiang et al 2008), selective attention mechanisms (see Fries et al 2001; Masuda & Doiron 2007; Doesburg et al 2008a; Lakatos et al 2008), and multisensory integration (MI) processes (see Kaiser et al 2005; Lakatos et al 2007; Yuval-Greenberg & Deouell 2007; Doesburg et al 2008b). In what follows, we thoroughly describe the relationship between oscillatory activity in the delta, theta, alpha, beta and gamma frequency bands and selective attention processes.

1.6.1 Delta band oscillations (1 – 3 Hz):

Delta band EEG activity is highly present in non-active resting states such as non-rapid eye movement sleep, and accounts for more than 50% of the EEG recordings during this stage (Gross 1992). It is also the predominant oscillatory rhythm during infancy (< 2 years), and it has been shown to decrease throughout development (John et al 1980). In adults, delta power is substantially large in areas close to brain lesions (Gilmore & Brenner 1981), tumors (Fernandez-Bouzas et al 1999), during states of intoxication and in individuals diagnosed with dementia or schizophrenia (see Hales et al 2007 for a review). It is contended that there are two types of delta-band activity, one generated within cortical structures and the other originating in thalamic structures (see Niedermeyer & Lopes Da Silva 2004). Further, this oscillatory rhythm is associated with inhibitory –type mechanisms (see Pizzagalli 2007 for a review).

Within the context of sensory and cognitive processes, it is believed that one function of this lower-scale oscillatory rhythm is to serve as an active mechanism of stimulus selection (Lakatos et al 2008). In a recent audio-visual intersensory attention task, Lakatos and colleagues (2008) showed that during a rhythmic and predictable situation the ongoing phase of a delta rhythm ‘entrained’ to the pace of the task, and the amplitude response of higher rhythms (theta, alpha and gamma band) modulated in accordance to this entrained phase oscillation. The contention is that the oscillatory-phase of the delta rhythm modulated such that relevant sensory stimuli appeared at the ‘high-excitable’ state of the oscillation, while irrelevant or distracting stimuli appeared at the ‘low-excitable’ state of the oscillation. In addition, delta-band power has been shown to modulate activity in somatosensory cortices with respect to attentional direction (Hauck et al 2007). This suggests that this slow oscillating rhythm operates at a suprasensory level during attentional control processes.

1.6.2 Theta band oscillations (1 – 3 Hz):

Theta band oscillations are generally considered to span EEG activity between 4 – 7 Hz, it is prominently observed during sleep and memory-related processes in limbic areas such as, hippocampus, entorhinal and cingulate cortex. It was first discovered in the rabbit hippocampus during arousal elicited by sensory or brainstem reticular formation stimulation (Green & Arduini 1954). Theta-band oscillations mainly arise in the entorhinal cortex, and this is mainly supported by data showing that removal of the entorhinal input abolishes the large theta dipole activity observed in the hippocampal fissure (Ylinen et al 1995). However, other studies have shown that theta-band oscillations can also originate in cingulate cortex independently of the hippocampal system (see Borst et al 1987). Further, this lower-scale rhythm is hypothesized to facilitate long-term potentiation (LTP) because stimulating the hippocampus every 200 ms (e.g. 5 Hz) results in the suppression of inhibitory post-synaptic potentials (IPSP) and prolongation of depolarization (Larson & Lynch 1988). Moreover, it has been speculated to function as a gating mechanism for the flow of information processing in limbic areas (see Vinogradova 1995).

The most reported finding however, is the involvement of theta-band oscillations with memory related processes and spatial navigation (see Jensen & Lisman 1996; Kahana et al 2001; Raghavachari et al 2001; Rizzuto et al 2003; Yamaguchi et al 2004; Dragoi & Buzsaki 2006; Rizzuto et al 2006). In addition, during selective attention tasks, theta oscillations have been shown to precede rapid motor responses (Delorme et al 2007), to be enhanced during a highly difficult visual search recognition task (Gomarus et al 2006), to be involved in spatial attention control processes across distant cortical sources (Green et al 2008), and to be highly affected in adults suffering from attention deficit hyperactive disorder (ADHD see Snyder & Hall 2006; Clarke et al 2008).

1.6.2 Alpha band oscillations (8 – 14 Hz):

The alpha rhythm occurs in the frequency range of 8 – 14 Hz, and is mostly distributed over parieto-occipital cortices. The neural generators of this alpha rhythm have been localized to the cortical layers IV and V in visual cortex, and they appear to be generated in small cortical areas from which the activity spreads in different directions by way of cortico-cortical connections, and possible cortico-thalamic loops (see Lopes da Silva 1991 for a review). Further, studies using in-vitro preparations have shown that neocortical neurons have intrinsic oscillating states occurring in this frequency band (Steriade et al 1990; Lopes da Silva 1991; Silva et al 1991). The physiological/functional role of the posterior alpha rhythm remains somewhat unknown. However, it know to function as a pacemaking mechanism in entorhinal and some neocortical structures (Silva et al 1991; Flint & Connors 1996, Lukatch & MacIver 1997; Bollimunta et al 2008), it is associated with general states of arousal and vigilance (see Pfurtscheller 1992; Young et al 1992; Basar & Schurmann 1994; Klimesch et al 1998; Makeig et al 2002; Ramos-Loyo et al 2004; Dockree et al 2007), and to function as a cortical “idling” or active gating mechanism for sensory inputs (Pfurtscheller et al 1996; Foxe et al 1998; Worden et al 2000; Fu et al 2001; Yamagishi et al 2003; Kelly et al 2006; Thut et al 2006).

This so-called active gating mechanism has been observed in spatial, intersensory, and object-discrimination studies (see Vanni et al 1997; Foxe et al 1998; Worden et al

2000; Fu et al 2001; Yamagishi et al 2003; Kelly et al 2006; Thut et al 2006; Rihs et al 2007; Gomez-Ramirez et al 2007; Kelly et al 2008; Kelly et al 2008 submitted). For instance, Vanni and colleagues (1997) showed that alpha power significantly increased following the presentation of non-objects compared to meaningful objects during an object visual discrimination task. Moreover, in an intersensory attention task, Foxe and colleagues (1998) showed that alpha-band activity associated with deploying attention to the auditory modality is greater over right-parieto occipital cortices in comparison to deploying attention to the visual modality. Fu et al (2001) and Gomez-Ramirez et al (2007) also found evidence of this pre-target alpha-biasing effect, and it was proposed that this increase of power in the alpha-band reflects the disengagement of the visual attentional system in preparation for an anticipated auditory stimulus (see Fu et al 2001). In visuospatial attention studies, this pre-target alpha effect is embodied as an ipsilateral alpha power increase, relative to the direction of the symbolic cue, over parieto-occipital regions in the period preceding the imperative stimulus (Worden et al 2000; Yamagishi et al 2003; Kelly et al 2006; Thut et al 2006; Rihs et al 2007).

Recent studies have demonstrated a strong predictive link between alpha-band activity and behavioral performance. For instance, some visuospatial attention studies have shown that the magnitude of the pre-target alpha-biasing effect significantly decreased RT (Thut et al 2006; Kelly et al 2008 submitted) and increased detection sensitive measures such as d-prime (Kelly et al 2008 submitted). Further, using current-source-density (CSD) and multi-unit-activity (MUA) EEG measures in non-human primates, Bollimunta and colleagues (2008) showed that the amplitude of alpha activity in V2 and V4 was negatively correlated with behavioral performance, whereas the opposite was true in inferotemporal cortex (IT).

In addition to alpha playing a role in local neural ensembles, alpha-band mechanisms have been shown to facilitate communication between large-scale cortical regions (see Doesburg & Ward 2007; Doesburg et al 2008a; Doesburg et al 2008b). In particular, the studies by Doesburg and colleagues (2007; 2008a) found synchronized activity between anterior and posterior contralateral electrodes in the high alpha band (13.3 – 14.7 Hz) while subjects made left and right visuospatial attentional deployments.

1.6.3 Beta band oscillations (15 - 30 Hz):

Beta-band oscillations are typically defined as EEG activity ranging from 15 to 30 Hz. Surface EEG studies typically report beta-band activity with a symmetrical fronto-central distribution. Further, beta-band activity has been shown to increase with attention and vigilance tasks in animals (Bouyer et al 1992; Murthy & Fetz 1992; Murthy & Fetz 1996). Moreover, it is contended that long-axon and local-circuit cortical neurons generate beta rhythmicity at relatively depolarized values of the membrane potential (Llinás et al 1991, Nuñez et al 1992). In addition, in vivo studies indicate that certain neocortical neurons may pass from beta to gamma oscillation in very short periods of time, 500 – 1000 ms, with just a slight membrane depolarization (Steriade et al 1996). Beta-band oscillations have also been observed after voluntary movement and somatosensory stimulation (Neuper & Pfurtscheller 2001), in olfactory sensory processing (Neville & Haberly 2003), and visual object recognition processes (Sehatpour et al 2008).

1.6.4 Gamma band oscillations (> 30 Hz):

Gamma-band rhythms have been traditionally defined as activity above 30 Hz. Studies have shown that inhibitory neural networks play a crucial role in the generation of ~40 Hz EEG activity by preventing firing of excitatory neurons (i.e. pyramidal cells) every 25 ms or so (Whittington 1995; Jefferys et al 1996; Hasenstaub et al 2005; Bartos et al 2007). This inhibitory process is first initiated by the firing of the excitatory cells, which in turn excite these inhibitory neural networks. The current model proposes that after excitatory input, the inhibitory network generates synchronized activity at 40 Hz and imposes rhythmic inhibition onto the entire local network of pyramidal cells (see Fries et al 2007 for a review). Further, the excitatory cells are only able to fire during the fading time window of neuronal inhibition. This gamma-band mediated inhibitory mechanism is observed within entorhinal cortices, but evidence of these higher-scale oscillations have also been observed in thalamic and neocortical structures. For instance, neural ensembles within thalamocortical loops have been found to have intrinsic oscillating rhythms approximately at 40 Hz (see Pinault & Desch 1992; Steriade et al 1993). Furthermore, in neocortical areas, intrinsic cellular oscillators have been observed in neurons in layer 4, 5 and 6 (Llinas et al 1991; Nuñez et al 1992).

Oscillations in the gamma band are believed to mediate a number of cognitive operations within and across cortical and subcortical neural networks. For instance, it is believed to mediate rapid coupling and synchronize dispersed neural ensembles (see Singer 1993), coordinate activity between the CA1 and CA3 areas of the hippocampus during dependent memories retrieval (Montgomery & Buzsaki 2007), coordinate activity between intracortical areas in primary and association visual cortex (Gray & Singer 1989; Singer & Gray 1995; Gray 1999), facilitate integration of multiple sensory stimuli

(Lakatos et al 2007), enhance speech perception processes (Towle et al 2008; Kaiser et al 2005; Kaiser et al 2006), and facilitate object recognition processes (Yuval-Greenberg & Deouell 2007; Jiang et al 2008).

Gamma-band rhythms also play a central role in selective attention operations. For example, gamma-band synchronization mediates stimulus selection by amplifying the signals located within the locus of the attentional spotlight (Fries et al 2001; Fries et al 2002; Jensen and Colgin et al 2007). In fact, one study found that gamma-band oscillations predict speed of change detection during a visual attention task (Womelsdorf et al 2006). Further, these higher-scale oscillations have been shown to operate at a cross-sensory level by enhancing activity in visual (see Singer & Gray 1995; Fries et al 2001), auditory (see Tiitinen et al 1993; Debener et al 2003; Kaiser et al 2006), and somatosensory cortices (Palva et al 2005; Bauer 2006).

1.7 Selective Attention and natural pharmacological agents:

Natural pharmacological agents are consistently being used by humans to enhance cognitive and mood-related processes. Several studies have shown that attention-related processes are modulated by administration of noradrenergic and cholinergic neurotransmitters (Smith et al 1992; Coull et al 1995; Smith et al 1999; Coull 2005; Coull et al 2001). Recently, a vast number of studies have investigated the effects of the L-theanine agent on numerous cognitive functions such as, attentional switching, memory, visual processing and spatial attention deployment (see Gomez-Ramirez et al 2008; Haskell et al 2008; Kelly et al 2008b; Nobre et al 2008; Owen et al 2008; Rogers et al 2008). L-theanine is a naturally occurring non-proteinic amino acid that, along with caffeine and cathecins, is one of the three major constituents of tea (*Camellia sinensis).*

Further, ingestion of L-theanine has been shown to modulate oscillatory brain activity in the alpha-band during passive and highly active alerting states (see Juneja et al., 1999; Gomez-Ramirez et al 2007; Nobre et al 2008). As previously mentioned, this oscillatory brain rhythm has traditionally been associated with a relaxed state (Pfurtscheller 1992), and has also been linked to general states of mental alertness and/or arousal (e.g. Klimesch et al 1998). However, a few number of studies have shown that oscillations in the alpha-band are not just simply associated with general arousal states but that these oscillatory potentials are also key components in selective attentional processes (see Foxe et al 1998; Worden et al., 2000; Fu et al., 2001; Kelly et al., 2005; Thut et al, 2005; Rihs et al., 2005; Kelly et al 2006). In the last chapter of this thesis we assessed whether L-theanine modulates anticipatory alpha-band activity during selective attentional deployments to stimuli in different sensory modalities and to visual space.

1.8 Objectives:

The overarching goal of this thesis project is to further our understanding of the preparatory neural processes set in place during intersensory attentional deployments to the auditory and visual modalities. Our set of hypotheses is primarily based on the attentional model proposed by Rafal and Posner (1987) and Foxe et al (1998). The core concept in this model is that the instantiation of an attentional deployment is governed by a series of neural processes, which are not necessarily executed in a sequential manner, but involve the integration of local and large-scale neural networks comprised of frontal, parietal and sub-cortical structures (see Figure 2). These stages entail: (1) the intention of an attentional selection, (2) the reengagement or disengagement from the modality where attention was apportioned to, (2a) the shift of attention to the new modality, (3) and the sustention (i.e. biasing) of attention to the engaged-modality. It is contended that *Stage 1* is instantiated in a neural network comprised of anterior and posterior cortical areas (i.e. the so-called frontal attentional network observed in many neuroimaging studies) during the early period of the attentional deployment. It is proposed that oscillatory activity in the gamma-band (30 – 45 Hz) mediates communication across this frontal-parietal attentional network. *Stages 2 and 2a* on the other hand, are carried-out over local neural ensembles, and it is mediated by a phase-resetting mechanism of an ongoing slow-oscillatory activity in the delta-band (1-3 Hz). Finally, it is contended that sustaining attention to the relevant modality is instantiated by coordinated activity between anterior and posterior cortices, and this coordinated activity is mediated by oscillatory activity in the alpha-band (8 –14 Hz), where the sensory inputs are either enhanced or suppressed depending on their relevance to the current task.

Major emphasis is given to the analysis of oscillatory activity during the preparatory period of attentional deployments. Oscillatory processes, particularly in the form of oscillatory phase, play a critical role in the bridging of large-scale neural networks, as well as in the enhancement and suppression of incoming information from the crowded multisensory environment. Five EEG studies are proposed to elucidate the neural mechanisms that establish and maintain biased intersensory attentional sets. Using the high temporal resolution provided by surface electrodes and intracranial recordings from large grid electrodes in patients undergoing mapping for epilepsy, the present thesis is directed to characterize the temporal dynamics of these oscillatory neural processes, and show that these processes are instantiated both by coordinated activity within local neural ensembles and long-range cortical networks.

Experiment 1 (Chapter 2) was conducted in order to investigate oscillatory processes as a selection mechanism during intersensory attentional deployments. Oscillatory processes were restricted to the delta, alpha and gamma bands, since recent studies have shown that these oscillatory rhythms play a crucial role in mediating attentional processes within local and distributed neural networks. Three distinct hypotheses are formulated: (1) we expect to find a reversal in oscillatory phase in the delta band when subjects deploy attention to the auditory vs. visual modality. We suggest that this oscillatory phase reversal represents the frequency-domain analog of the late-sustained parieto-occipital positivity (LSPOP) ERP component observed in Foxe et al (2005a). Further, we contend that this delta-band activity functions as a selection mechanism by which relevant visual inputs appear at the 'high-excitability' state in visual cortical sites, while distracting inputs appear at the 'low-excitability' state. (2) We expect to find source coherence between posterior and anterior cortical regions in the alpha and gamma bands. Large-scale phase locking in the gamma band will be observed in the mid-stages (~400 ms after S1-cue onset) of the attentional deployment phase. In contrast, phase locking activity (PLA) in the alpha band will be observed during the late stages of the attentional preparatory phase (> ~900 ms after cue onset). (3) We aim to replicate the findings in the alpha band that shows increased power when attention is apportioned to the auditory modality (i.e. synchronization effect), as well as establish a predictive link between this anticipatory alpha process and behavior.

Experiment 2 (Chapter 3) was conducted in order to investigate the relationship between ongoing phase in lower frequencies (< 8 Hz) and amplitude responses in faster rhythms (8-14 Hz and 30 – 50 Hz) during intersensory attentional deployments. This form of cross-frequency coupling is expected to arise when subjects are engaged in a rhythmic predictable task. Slow oscillations will ‘entrain’ (or phase-lock) to the rhythmic pattern of the task and serve as a stimulus selection tool, while the faster oscillations will serve as a stimulus processing mechanism within ‘local’ neural ensembles in sensory regions. Mechanisms such as these can only be effectively investigated with electrodes positioned in the cortex itself and so we take advantage of our ability to record from intracranial electrode grids in patients with epilepsy.

Experiment 3 (Chapter 4) was conducted to assay the different neural representations of externally and internally-driven intersensory deployments of attention: In this experiment, we move beyond traditional S1-S2 designs, to evaluate whether traditional attention-directing cueing paradigms are an efficient means of inducing endogenous (voluntary) attentional deployments. We devised a target detection paradigm where subjects freely choose, on a trial-by-trial basis, to which modality they will deploy their attention. It is contended that by giving full control “back” to subjects, we can assess ‘purer’, or less automatic, endogenous attentional mechanisms. Further, it is hypothesized that signals generated when the subject is in complete control of the attentional deployment will more effectively engage biased attentional states such that more robust attentional modulations will be found during stimulus processing of the imperative stimulus (S2).

Experiment 4 (Chapter 5) was conducted to investigate the effects L-theanine on intersensory attentional deployments to the auditory and visual modalities. We assess whether L-theanine would cause modulation of anticipatory alpha-band activity during selective attentional deployments to stimuli in different sensory modalities. We reason that since L-theanine is now known to affect overall alpha-band activity during resting and active states, then it might also enhance (or indeed suppress) alpha-based attentional mechanisms during highly demanding intersensory attention task.

Experiment 5 (Chapter 6) was conducted to replicate the findings in experiment 4 during a visual-spatial attention task. The aims of the present experiment were twofold. First, we wished to investigate whether a similar enhancement in the cue-related, phasic alpha differential would be observed during a visuospatial attention task. Second, we wished to test for the finding of decreased tonic alpha on L-theanine as was observed in Gomez-Ramirez et al (2007).

CHAPTER 2

Oscillatory & Broadband Temporal Dynamics during Anticipatory Intersensory Attentional Deployments between the Auditory and Visual Modalities: A High-Density Electrical Mapping Study

1. ABSTRACT

By biasing the attentional state, humans can effectively process relevant information, while at the same time suppress potentially distracting inputs in the environment. This ability is believed to be mediated by a collection of band-specific and broadband mechanisms operating within sensory-specific and widely-distributed neural networks comprised of frontal, posterior and subcortical regions. Here, we investigate the role of oscillatory and broadband mechanisms during the biasing of attention to the auditory and visual modalities. On each trial, a cue indicated the to-be attended sensory modality, and participants were required to detect a target in that modality only. The results revealed that the cue reorganized the oscillatory-phase of a delta-band oscillation at the arrival of the imperative stimulus in each attention condition. The phase distributions across both conditions were significantly different. Further, gamma-band oscillations facilitated synchronization between anterior and posterior regions during the mid-stages of attentional deployments vision. The data also revealed a relative decrease in alpha activity over parieto-occipital when participants deployed attention to vision. This alpha-power decrease was a reliable predictor of subsequent behavioral performance, as measured by d-prime. Finally, the late-sustained-parieto-occipital-positivity ERP component also predicted d-prime and RT measures. The findings suggest that: (1) Oscillatory mechanisms mediate synchronization across widespread neural networks, and regulate the excitatory state of local neural ensembles in sensory-specific cortices. (2) Alpha-band mechanisms modulate processing in visual-related cortices that in turn

facilitate discrimination of visual stimuli in the presence of auditory distracters. (3) Anticipatory brain mechanisms serve as reliable predictor variables for behavioral performance.

2. INTRODUCTION

The natural world is nearly always a noisy place, with myriad sources of sensory input the norm rather than the exception. To effectively navigate this complex environment, humans must often focus attention on a specific object or a delimited set of objects, while at the same time try to ignore all other distracting information impinging on their senses. This ability to voluntarily deploy attention in a selective manner is commonly referred to as endogenous attention, and it is now established that it is subserved by a widely distributed network of cortical and sub-cortical regions spanning both anterior and posterior areas (see Posner and Petersen, 1990; Corbetta et al 2000; Hopfinger et al 2000; Pinsk et al 2004; Foxe et al 2005a; Doesburg et al 2008a; Green et al 2008). Such selective mechanisms can be instantiated in situations that require attention to different sensory modalities (see Spence & Driver 1997; Foxe et al. 1998, 2005a, 2005b; Gomez-Ramirez et al 2007; Trenner et al 2008; Lakatos et al 2008), to different spatial locations (see Posner 1980; Martinez et al 1999; Eimer et al 2002; Kelly et al 2008), to temporal expectations (see Griffin et al 2001; Babiloni et al 2004; Nobre & O'Reilly 2004) and to objects or features (see Shulman et al 2002; Liu et al 2003; Martinez et al 2006).

Recently, considerable effort has gone into detailing the brain mechanisms underlying attentional deployments to different sensory modalities, especially to the auditory and visual senses (see Fu et al 2001; Weissman et al 2004; Foxe et al 2005a; Gomez-Ramirez et al 2007; Trenner et al 2008; Lakatos et al 2008; Gomez-Ramirez et al 2008). The vast majority of these studies have used "Cueing" paradigms to isolate the anticipatory processes that establish and maintain biased attentional states in advance of an imperative stimulus. In intersensory cueing paradigms, a symbolic cue (labeled "S1") instructs the participant to direct attention to a particular sensory modality, and after a short period of time(1-2s), an imperative stimulus ("S2") is presented, upon which the participant must perform a difficult discrimination. Typically, subjects are instructed to detect a target in the relevant (cued) sensory channel and ignore all information in the other. By inspecting the brain activity between the presentation of the instructional cue and the arrival of the imperative stimulus (i.e. the cue-target interval, CTI), the preparatory processes, giving rise to these biased intersensory attentional states can be examined, uncontaminated by the presentation of the S2. Previous work has described several effects occurring during the CTI, in both the broadband ERP and in the frequency domain.

(1) A relatively early (~230 ms) broadband activation has been observed over frontal and parietal cortices, believed to reflect the initiation of the fronto-parietal endogenous attentional network (see Foxe et al 2005a). In addition, some studies have revealed a sustained broadband potential occurring in the late stages of the attentional deployment phase. This late sustained broadband potential is thought to reflect the maintenance of a sensory-specific biased attentional state in anticipation of the relevant imperative stimulus (Foxe et al 2005a).

(2) Several studies have shown significantly stronger parieto-occipital alpha-band (8 – 14 Hz) activity when attention is directed to the auditory modality compared to the visual modality (see Foxe et al 1998; Bastiaansen et al 1999; Bastiaansen et al 2001; Fu et al 2001; Gomez-Ramirez et al 2007; Trenner et al 2008). Fu and colleagues (2001) showed that this alpha power differential partly arises from a power increase, relative to baseline, when attention is deployed to the auditory modality. Further, this differential

activity occurs ~400 ms after the presentation of the cue and it is sustained throughout the anticipatory period and on through the arrival of the S2 stimulus. It is contended that this alpha effect reflects the suppression of distracting information in visual space (see Foxe et al., 1998).

An increasing number of studies have now shown that this alpha differential effect is not exclusive to attentional deployments between sensory modalities, but is also instantiated in tasks requiring visual attentional deployments in space (see Worden et al 2000; Yamagishi et al 2003; Kelly et al 2006; Thut et al 2006; Rihs et al 2007; Trenner et al 2008; Kelly et al 2008; Gomez-Ramirez et al 2008; Kelly et al (unpublished). In fact, during spatial attention deployments, several studies have established a direct relationship between behavioral performance and this pre-target alpha effect (see Thut et al 2006; Trenner et al 2008; Kelly et al (unpublished). Specifically, the differential magnitude across hemispheres of the anticipatory pre-target alpha rhythm predicted both the accuracy of detecting (Kelly et al (unpublished) and speed of reaction to a target stimulus (Thut et al 2006; Trenner et al 2008; Kelly et al (unpublished). The first major goal of the present study was to replicate the intersensory alpha suppression effect (Foxe et al., 1998; Fu et al., 2001; Trenner et al., 2008), and to extend this finding by assessing whether there was a predictive link between the anticipatory alpha-effect and behavioral facilitation during intersensory attentional deployments.

It is also becoming clear that other brain rhythms, outside the alpha band, play a role in establishing and maintaining biased attentional states (see Doesburg et al 2008a; Lakatos et al 2008; Green et al 2008). For example, Doesburg and colleagues (2008a) found that when attention was deployed in space (i.e. left vs. right spatial attention shifts) there was increased phase synchronization in the gamma-band (38 – 42 Hz) between posterior and anterior cortices over the contralateral scalp. Green and McDonald (2008) reported a sequence of frontal and parietal theta-band (4 – 7 Hz) activations during spatial attention deployment using electrical neuroimaging techniques in humans.

Lakatos and colleagues (2008) investigated the role of oscillatory-phase mechanisms during a rhythmic intersensory attention task. They recorded local field potential activity from primary visual cortex (V1) while monkeys performed a blocked and sustained attention task in either the auditory or visual modality. The experimental paradigm was devised such that a relevant or distracting sensory stimulus was presented approximately every 650 ms, in alternating sequence between sensory modalities (i.e. ~1.5 Hz stimulation rate). During this rhythmic and predictable task, it was found that neural oscillations in the delta band (1-3 Hz) were phase-locked to the attended stimulus stream, and it was hypothesized that this ‘entrainment’ represented a means of selecting the relevant sensory stimulus in the environment. That is, the attentional system entrains ongoing oscillations to the temporal structure of rhythmical tasks, such that the relevant stimuli appear at the ‘high-excitability’ state of the oscillation (i.e. an enhancement mechanism) while the distracting or irrelevant stimuli appear at the ‘low-excitability’ state of the oscillation (i.e. a suppression mechanism). This interpretation is in keeping with many studies showing that the phase of ongoing oscillations can index the excitability state of a local neural ensemble (see e.g. Bishop 1932; Kruglikov and Schiff 2003; Lakatos et al 2007; Rajkai et al 2008). These findings clearly have strong implications for the interpretation of broadband potential effects observed in tasks where stimulus timing is predictable and/or rhythmical. Although trial-by-trial cueing tasks of intersensory attention studies almost invariably use tasks of this class (see Foxe et al 2005a), the role played by oscillatory phase has not yet been investigated.

Late sustained Broadband Potentials: Cue-driven phase-reset of low frequency Oscillations?

Studies of selective attention using trial-by-trial cueing paradigms have uncovered a series of electrophysiological processes that are time-locked to the presentation of the instructional cue. Consistently observed among these processes during visuo-spatial attention tasks is a late sustained relative positivity, labeled the late-directing attention positivity (LDAP), which occurs ~500ms after cue onset and often lasts until the presentation of the imperative stimulus (see e.g. Harter et al 1989; Eimer et al 2002; Green et al 2006; Simpson et al., 2006; Kelly et al 2008). The LDAP is a relatively slow ERP component (~ 400 ms duration) observed over bilateral parieto-occipital cortices, which is thought to reflect the sustained modulation of excitability in location specific visual areas in anticipation of an imperative stimulus (see Kelly et al unpublished). The LDAP is also observed in tasks requiring spatial attention to the somatosensory and auditory modalities (see Eimer et al 2002; Green & McDonald 2006), which suggests that it reflects a supra-sensory neural process of sustaining attention in space. A similar ERP component has also been identified in tasks that do not require spatial attentional deployments, but rather mandate attention to different sensory modalities (see Foxe et al 2005a). This slow and long-lasting broadband potential, which we term the late-sustained parieto-occipital positivity (LSPOP) has comparable characteristics to shares very similar temporal, amplitude and topographical characteristics to those of the LDAP: they both onset approximately 400 – 500 ms after cue onset, last for a relatively similar amount of time (i.e. ~ until the presentation of the S2), have a similar differential-amplitude response with respect to the attending conditions[12], and are localized over lateral parieto-occipital scalp regions.

Given these characteristics, we hypothesize that these sustained broadband potentials may reflect a slow ongoing oscillatory rhythm occurring in the delta range (1 - 3 Hz), whose phase is reset by the onset of the instructional cue. If this is indeed the case, then we would predict that during a temporally predictable intersensory S1-S2 attention task, an ‘attend-visual’ cue will reset the phase of the delta rhythm such that the neural activity over visual-related areas will be in the ‘high-excitability’ state at the arrival of the relevant visual stimulus. Conversely, an ‘attend-auditory’ cue should cause a phase-reset in the delta rhythm such that the local neural ensemble over visual-related areas is in the ‘low-excitability’ state at the arrival of the distracting visual S2 stimulus. We view this phase-reset as a mechanism that reorganizes the ongoing oscillatory dynamics without adding any significant energy to the local neural network (i.e. a ‘pure’ phase-reset effect).

The fronto-parietal network of attentional control: Long-range source coherence in the gamma and alpha band.

Neuroimaging and electrophysiological studies have identified a handful of anatomical regions distributed over frontal and parietal cortices, that appear to play a crucial role in the deployment of attention in space (Kastner et al 1999; Corbetta et al 2000; Mesulam 2000; Hopfinger et al 2000; Foxe et al., 2003; Ro et al 2003; Foxe et al 2005a; Praamstra et al 2005; Grent-‘t-Jong and Woldorff 2007; Brunetti et al 2008; Stern et al 2007). This distributed network interacts with sensory and motor-related cortices,

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[12] In spatial attention, attending to a particular hemifield results in greater broadband activation over the contralateral hemifield over parieto-occipital cortices. In intersensory attention, attending to the visual modality results in greater broadband activation over the same cortices.

and comprises areas such as the medial and dorsolateral pre-frontal cortex (MPFC and DLPFC), cingulate cortex (CC), intraparietal sulcus (IPS), inferior parietal lobule (IPL), and superior parietal lobule (SPL). The DLPFC has been suggested to be the core source of top-down modulation during selective attention (see Mesulam 2000). Damage to this area leads to attention- and memory-related impairments in both human and in non-human primate populations (see Goldman-Rakic et al 1984; Petrides 1995; Goldman-Rakic 1996a; Goldman-Rakic 1996b). The DLPFC has reciprocal connections to visual, auditory and somatosensory association areas in the parietal and temporal lobes, which further supports its role as a general (i.e. supra-sensory) cortical site for attentional control. Further, the IPS, which contains the lateral intraparietal area (LIP), plays a significant role in covert orienting of attention and in the planning of saccades (see Colby & Goldberg 1999; Corbetta & Shulman 2002; Goldberg et al 2002; Yantis et al 2002; Woldorff et al 2004; Brown et al 2007; Luks & Simpson 2004; Luks et al 2008).

During the preparatory stage of an attentional deployment, both the DLPFC and IPS are activated in response to a symbolic cue (see Woldorff et al 2004; Brown et al 2007; Luks et al 2007; Luks et al 2008). The strength of this activation has been shown to vary with task difficulty (Luks 2007). Further, Woldorff and colleagues (2004) showed that lateral-frontal and parietal cortices show stronger activation during decoding of the symbolic cue in comparison to periods of baseline activity, which indicates that that these areas form part of the network that initiates an attentional deployment. Taken together, the data indicate that these areas might be functionally coupled during the setup and maintenance of a selective attentional state. However, it remains to be determined what mechanism(s) mediates communication between these distant cortical sources?

Furthermore, what is the temporal profile that characterizes this cortico-cortical coupling?

Recently, strong evidence has emerged to suggest that synchronized neural oscillations reflect a general mechanism by which neural populations across a given task-specific neural network are integrated (see Engel & Singer 2001; Engel et al 2001; Varela et al 2001; Ward 2003; Fries 2005; Canolty et al 2007; Doesburg et al 2008a). In particular, several animal studies have shown that theta band oscillations (3 – 7 Hz) coordinate activity across distant cortical regions such as the hippocampus and prefrontal cortices (see Jones & Wilson 2005a; Jones & Wilson 2005b; Siapas et al 2005; Young & McNaughton 2008). On the other hand, other studies suggest that transient coupling between low- and high- frequency rhythms might coordinate activity in distributed cortical areas (Canolty et al 2006). In particular, it has been found that the oscillatory phase of low-frequency oscillations (i.e. < 8 Hz) influence the magnitude of activity in higher-frequency bands (see Csicsvari et al 2003; Buzsaki 2004; Lakatos et al 2005; Canolty et al 2006; Lakatos et al 2007; Lakatos et al 2008). This relationship between low and high frequency oscillations is commonly referred to as phase-amplitude cross-frequency coupling, and it is believed that the slow oscillations serve as a bridging mechanism for long-range cortical networks, while the higher rhythms serve as an active mechanism involved in stimulus processing (see Buzsaki 2004; Fries 2005; Canolty et al 2006; Jensen & Colgin 2007 for comprehensive reviews).

Several recent studies on the other hand, have revealed that higher oscillatory rhythms (> 10 Hz) may also play a role in facilitating communication between distributed cortical sites (see Doesburg & Ward 2007; Doesburg et al 2008a; Doesburg et al 2008b;

Sehatpour et al 2008). In particular, the study by Sehatpour and colleagues (2008) found that beta-band (14 – 30 Hz) oscillations coordinated activity between the lateral occipital complex (LOC), prefrontal cortex, and the hippocampal formation during a visual object-processing task. In addition, Doesburg and colleagues (2008a) found synchronized activity between contralateral anterior and posterior electrodes in the gamma (38 – 42 Hz) band while subjects made visual attentional deployments in space, while Brancucci and colleagues (2008), using MEG technology, found increased phase coupling in the alpha band during a dichotic listening task in a "speech" cortical neural network comprising bilateral primary auditory cortex and Wernicke's areas. Finally, during the late stages of the attentional deployment phase, Doesburg & Ward (2007) found increased phase synchronization in the alpha band in a visual cortical network in the hemisphere contralateral to the attended location.

We aim to evaluate the role of oscillatory phase in the alpha and gamma bands during attentional deployments to the auditory and visual modalities. In accordance with previous studies, we expected to find significant source coherence, during the intermediate phase of the attentional deployment, between anterior and posterior cortical regions in the gamma-band. This cortico-cortical phase-locking represents a mechanism that initiates the so-called frontal-parietal network of attentional control. Furthermore, during the late stages of the anticipatory attentional period, we expected to find phase-locking between frontal and parietal areas in the alpha-band. It is contended that this form of source coherence reflects the engagement and disengagement of frontal and posterior cortices when attention is deployed to the visual and auditory modality, respectively.

The present study was conducted in order to further our understanding of preparatory mechanisms during intersensory attentional deployments to the auditory and visual modalities. As introduced above, our major focus is on oscillatory phase-dependent mechanisms, since recent studies have shown that these mechanisms play a crucial role in mediating attentional processes within local and distributed neural networks. Three distinct hypotheses are formulated: (1) we expect to find a reversal in oscillatory phase in the delta band when subjects deploy attention to the auditory vs. visual modality. We suggest that this oscillatory phase reversal represents the frequency-domain analog of the slow-sustained LSPOP component observed in Foxe et al (2005a). Further, we contend that this delta-band activity functions as a selection mechanism by which relevant visual inputs appear at the 'high-excitability' state in visual cortical sites, while distracting inputs appear at the 'low-excitability' state. (2) We expect to find source coherence between posterior and anterior cortical regions in the alpha and gamma bands. Large-scale phase locking in the gamma band will be observed in the intermediate-stages of the attentional deployment phase. In contrast, phase locking activity (PLA) in the alpha band will be observed during the late stages of the attentional preparatory phase. (3) We aim to replicate the finding of relatively increased alpha band power when attending to the auditory modality, as well as establish a predictive link between this anticipatory alpha process and behavior.

2. METHODS

Participants

Fourteen (seven females) neurologically normal, paid volunteers (mean age = 26.3, SD 7.3 years, age range 18 – 36 years) participated. All participants provided written informed consent, and the Institutional Review Board of the Nathan Kline Research Institute approved the procedures. All participants reported normal or corrected-to-normal vision and all were right-hand dominant as assessed by the Edinburgh handedness inventory (Oldfield, 1971). Two of the participants, 1 male and 1 female, were removed due to excessive eye-movements and noisy data. Subjects were required to refrain from drinking any caffeine-based products (such as soft drinks, soda, coffee or tea) for at least 24 hours before the day of testing. Subjects' neurological status was determined by conducting a shorten version of the Structured Clinical Interview for DSM-IV-TR (SCID).

Experimental Paradigm

The sequence of events in a typical trial is illustrated in Figure 1. A trial commenced with the onset of the cue-stimulus (S1) instructing participants as to which sensory modality they should attend. Stimulus onset asynchrony (SOA) between S1 and S2 was 1200 ms. The inter-trial interval (ITI: i.e. the period between each pair of Cue-target stimuli) was varied between 1400 – 2400 ms using a uniform distribution. A central fixation-cross (black, subtending 1^{o} of visual angle) remained on the screen throughout the experiment and participants were instructed to maintain fixation at all times. All visual stimuli were displayed on a gray background, while all auditory stimuli were presented through headphones. Participants completed a minimum of 15 blocks of trials, on each of 2 days of testing. Each block contained a total of 100 S1-S2 pairs, giving an average block run-time of 5 minutes. The specific details of the stimuli themselves follow.

S1 (Cues): The cue-stimulus (S1) was presented aurally and was either the syllable 'AUD' or 'VIS', spoken by a male speaker and presented bilaterally via Sennheiser HD600 headphones (duration 400 ms, 10 ms rise-fall, 80 dB SPL taken as a peak measure). The use of abbreviated words was motivated by the need to minimize differences in stimulus energy and durations between the two cues. The 'AUD' cue instructed participants to deploy their attention to the auditory modality, while 'VIS' instructed the participants to attend to the visual modality. These cue-stimuli appeared in random order throughout the experiment.

S2 (Targets): The S2 consisted of either an auditory-alone (pair of tones, 20%), visual-alone (pair of gabor patches, 20%), audio-visual compound (pair of tones and gabor patches, 40%), or a null stimulus ('no S2' stimulus, 20%). The auditory S2 stimulus consisted of a pair of binaural tones (e.g. 2000 Hz or 2100 Hz, 80 dB SPL, 100 ms duration each, 5 ms rise/fall) presented in a rapid sequence with a 5-ms interval in between (total duration 205 ms). The visual stimulus consisted of a pair of gabor patches (4.5° in diameter, centered 2.5° left and right of fixation, 100 ms duration, 10 cycles/degree). The audio-visual compound stimuli were a combination of the above-described auditory and visual stimuli. The null stimulus consisted of a period of fixation only. All visual stimuli were presented on an Iiyama VisionMaster Pro502 21" computer monitor.

On 85% of visual S2 trials, the pair of Gabor patches was identical and no overt response was required (i.e. these were non-target standards). On 85% of auditory S2 trials, the pair of tones was also identical and no response was required. On the other 15% of visual S2 trials, the orientations of the left and right Gabor patches were slightly different (see below) and subjects responded with a button push (i.e. these were target stimuli) when they had been cued to the visual modality. On 15% of auditory trials, the two tones were of slightly different pitch and detection of this difference also required a response when the auditory modality had been cued. The reader should note that the occurrence of a target in each modality was independent of the other modality, such that the probability of occurrence of a double target was approximately 1%. This design led to six possible S2 trial types: 1) Unisensory-auditory (A-A_{att}), 2) Unisensory-visual (V-V_{att}), 3) Multisensory-attend-auditory (AV-A_{att}), 4) Multisensory-attend-visual (AV-V_{att}), 5) Auditory null-stimulus (i.e. subjects were cued to attend to the auditory modality but no S2 occurred), and (6) Visual null-stimulus.

Our paradigm was designed such that the S1 had high predictive value, as a means to ensure effective intersensory deployments. That is, the cue was followed by an S2 containing stimulation in the cued sensory modality on fully 80% of all trials (the other 20% were the null trials). For example, a unisensory-auditory S2-stimulus was always preceded by an attend-auditory cue, while a unisensory-visual S2-stimulus was always preceded by an attend-visual cue. With regard to audio-visual compound stimuli, 50% of these S2s were preceded by an attend-auditory cue and subjects were instructed to focus attention only on the auditory portion of the stimulus. On the remaining half, the S2-

stimulus was preceded by an attend-visual cue and subjects were instructed to focus attention only on the visual portion.

Procedure

Participants sat in an electrically shielded and sound-attenuated booth, directly facing a computer monitor placed five feet (152.4 cm) away from them. Each subject underwent two separate days of testing, and they completed a minimum of 15 blocks on each day, with breaks as desired. On one of the testing days subjects were given a 250mg dose of a colorless and flavorless solution of L-theanine mixed with water. Anecdotally, participants were at chance in guessing whether they were taking the active compound or simply water. The findings related to treatment conditions are reported in Gomez-Ramirez et al (2007).

Before recording commenced on each day, the participants performed a psychophysical testing session wherein their performance on the auditory and visual discrimination tasks was individually titrated. We used this information to designate the difficulty level of the target stimuli to be used in the subsequent electrophysiological sessions such that each subject's performance accuracy was calibrated to be precisely 78% for both the auditory and visual discriminations. This behavioral titration was achieved using an Up-Down Transform Rule (UDTR, see Wetherill and Levitt 1965).

EEG Measurements

Continuous electroencephalographic (EEG) data, digitized at 512 Hz, were acquired through the ActiveTwo Biosemi electrode system from 168 scalp electrodes. Noisy channels were identified automatically by comparing the standard deviation of amplitude over 50-second data segments at each channel to that of the six closest surrounding channels. If the standard deviation of a channel was more than twice that of at least three of the six neighboring channels, the channel was interpolated using a weighted average of the 6 nearest neighbors. An artifact rejection criterion of ±100 microvolts was used thereafter to exclude trials containing blinks, large EMG artifacts and other noise-transients. Trials containing eye-movements, identified as deflections of >15 µV lasting > 20 ms appearing on both eye channels, were rejected offline.

Data Analysis

Source Current Density Transformation (SCD) In Frequencies > 7 Hz:

For the analyses of amplitude changes in the alpha-band and phase-coherence in the form of phase locking value (PLV), we transformed the recorded potentials into source-current-density (SCD) measures. One of the advantages of SCD measures is that it significantly minimizes volume conduction issues inherent in the recorded scalp-EEG. This procedure is critical for computations of cortical-cortical coherence because significant PLV might arise from volume conduction (see Foxe et al., 2002; Doesburg et al 2008a; Doesburg et al 2008b). In SCD analysis the second spatial derivative of the recorded potential is calculated, which is directly proportional to the current density. The SCD measurement emphasizes the local contributions to the surface map, thus providing better estimates of the approximate locations of the intracranial generators (see Perrin et al 1989; Foxe et al 2005a; Foxe et al 2005b; Doesburg et al 2008). The SCD algorithm was carried-out in the Fieldtrip MATLAB-based software version# 2008-04-05 (see http://www.ru.nl/fcdonders/fieldtrip/), which implements the spherical spline method for scalp potential and source current density measures as detailed by Perrin et al (1989).

Data re-referencing (Frequency < 8 Hz and Event-related-potential data):

After acquisition, the data used for the analysis of phase resetting in the delta band and broadband event-related-potential (ERP), were re-referenced to an electrode on the nose. For this particular analysis we used standard voltage potential measurements because SCD measures are known to distort the power-spectra of lower-scale oscillations (1 – 7 Hz, see Tenke & Kayser 2005).

Time Domain Analysis

Broadband ERP measurements:

Broadband ERP waveforms were derived for each of the two S1 types (attend-AUD and attend-VIS) using an epoch of –100 to 800 (or whatever it was when the extra stuff was shaved off), baselined relative to the interval –100 to 0ms. A two-tailed paired-sample t-test was used to statistically test for effects over the late stages of the attentional deployment phase. This analysis was conducted to replicate the findings in Foxe et al (2005a) and Gomez-Ramirez et al (submitted). We tested for effects over right parieto-occipital cortices between attending to the auditory vs. the visual modality. The time period of interest was 900 to 1100 ms after the onset of the S1 stimulus. The dependent measure was derived by calculating the average amplitude across four neighboring electrodes over right parieto-occipital scalp where the effects of interest have been previously described (Foxe et al., 2005a).

Time-Frequency Analysis:

We inspected oscillatory activity during the cue-to-target interval (CTI) only. Instantaneous power and phase activity was characterized on a single trial level using a Morlet wavelet decomposition method. This procedure provides an index of ‘induced’ activity as a function of time (see Lakatos et al 2007). For each accepted epoch, the wavelet decomposition was computed from 1 to 50 Hz. In order to avoid edge effects produced by the wavelet filter, accepted trials were epoched for the S1-cue stimuli over a relatively extended period from -1000ms pre-stimulus to 1500ms post-stimulus

Alpha-Band Effect:

A 2 x 2 x 2 repeated-measures analysis of variance (ANOVA) was used to statistically test for differential alpha-band activity across the two attending conditions. The ANOVA had factors of attention (attend auditory, attend visual), hemisphere (left, right), and time period (pre-cue, post cue onset). The average alpha-power between -300 to -100 ms pre-S1 stimulus onset constituted the pre-cue time period condition, while the average alpha-power between 900-1100 ms post-S1 stimulation constituted the post-cue time period condition. The dependent measure was derived by calculating the average SCD response across six neighboring electrodes over the right and left parieto-occipital scalp.

Delta-band Phase resetting and Mean Phase Differences Between Attending Conditions:

A phase resetting effect is identified when a particular event, either internal or external, causes a realignment of the oscillatory-phase such that the distribution becomes non-uniform. When it occurs in the presence of a power increase, a phase reset cannot be unequivocally inferred since phase-locked oscillatory mechanisms can arise from stimulus-evoked responses, as in the case of ERP responses (see Makeig et al 2004; Shah et al 2004). On the other hand, when a phase-reset occurs in the absence of a power increase this effect is referred to as a ‘pure’ phase-resetting mechanism, and it is believed to index ‘pure’ sensory or cognitive brain mechanics. ‘Pure’ phase resetting is assessed first by assuring that there is not power difference between pre-to-post stimulus events with a concomitant statistically significant non-uniform distribution.

In order to measure the phase distribution across trials, we normalized the complex wavelet-transform values (by dividing by magnitude) for each single trial. R was then calculated by taking the mean across all trials. We then tested for non-uniformity of these phase distributions using the Rayleigh's circular statistical test for the time points of –500 ms and 1200 ms relative to the onset of the S1-cue, and for frequencies in the delta band. A condition was deemed to elicit significant 'pure' phase resetting if the Rayleigh statistic revealed a p-value < 0.05 without a concomitant significant power increase in that frequency band. To test for phase differences between the two attending conditions, we compared the two distributions using a nonparametric test for the equality of circular means (see Fisher, 1993; Rizzuto et al 2003; Rizzuto et al 2006; Lakatos et al 2008; Rajkai et al 2008). To provide a standard metric for the extent of non-uniformity of phase, or the strength of phase resetting to the cue, we calculated the mean resultant length R by taking the mean across all trials of the unit-magnitude complex values at each timepoint of interest (-500 and 1200 ms relative to the onset of the cue). R ranges from 0 to 1; higher values indicate that the observations (phase at a given time point across trials) are clustered more closely around the mean. For each individual subject and attending condition we employed a bootstrapping technique ($n = 300$), and all statistical testing was performed on the same number of trials.

Phase coupling across anterior and posterior cortices:

We estimated phase-coupling between anterior and posterior cortices. Six regions of interest (ROI) were defined, each composed of four clustered electrodes in the 168-

channel montage. These ROIs were centered on 10-20 standard locations F3, F4, C3, C4, PO3 and PO4. We estimated phase-locking behavior across two ROIs by taking the difference between them, before performing the wavelet method, and computing the Rayleigh statistic. We considered a phase-distribution to be significantly non-uniform if the p-value was below the 0.05 level for more than two-cycles of the frequency of interest. The following pairs of ROIs were considered: (1) right-anterior and right-posterior ROIs, (2) left-anterior and left-posterior ROIs, (3) left-posterior and left-center ROIs, and (4) right-posterior and right-center ROIs. These last two phase-locking estimations were computed in order to rule out the possibility of coupling between anterior and posterior regions arising from volume conduction artifacts. Thus, if volume conduction played a significant role in phase-locking, then we expect to find greater coupling, as measured by the phase-locking value (PLV), across posterior and central ROIs in comparison to posterior and anterior ROIs.

For each individual subject and attending condition, we employed a bootstrapping technique across all accepted trials (n = 300). This yielded a total of 3600 trials. To estimate the magnitude of the source coherence we computed PLA[13] for each frequency of interest, at each time point, using the equations in Lachaux et al (1999), and Doesburg et al (2008a). To rule out that possibility that source coherence arises from a power fluctuation artifact, we computed four 2 x 2 repeated measures ANOVA between each pair of ROIs in each frequency of interest (i.e. alpha and gamma band). The ANOVA had factors of attention (attend auditory vs. attend visual) and ROI. The dependent measure

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[13] PLA computations were chosen because they are less sensitive to power fluctuations than standard source coherence measures

was computed by integrating the power values in each ROI for each frequency band and average across the time periods of interest (see above).

EEG & Behavioral Performance:

Late sustained preparatory processes and behavioral performance (Pre-target Alpha biasing, LSPOP and CNV broadband components)

To test for predictive links between the two late-sustained preparatory processes (i.e. pre-target alpha and LSPOP broadband component) and behavior, we derived single-trial measures and correlated them with d-prime and reaction time (RT) values. D-prime values quantify the sensitivity of identifying a deviant stimulus, independent of inter- or intra-individual variations in response criteria. We also tested the Contingent Negative Variation (CNV) ERP component (see Walter et al 1964), which is a broadband central negativity routinely observed between conditional (warning or cue) and imperative stimuli. This ERP component is thought to index generalized nonspatial alerting mechanisms over short intervals, and it has been linked to RT facilitation effects on the imperative stimulus (Jongen et al 2006).

D-prime values were derived from the hit and false alarm proportion rates from trials without eye movements or EEG artifacts. Ceiling and floor effects on hit and false alarms were corrected by assuming a 0.5 value. The prediction analysis was achieved by sorting trials into four equal-sized bins (i.e. quartiles) according to the magnitude of the pre-target measure (i.e. alpha, LSPOP, or CNV). For instance, bin one is comprised of the 25% of trials with the lowest magnitude indices, and bin four of the highest 25% magnitude indices. Two repeated-measures ANOVA with factors of Attention (auditory, visual) and bin-level (4 bin levels) were conducted, separately testing for effects of d-prime and RT. The independent measure was derived by collapsing across six clustered electrodes over right and left parieto-occipital cortices during the time period of 900 – 1100 ms post-cue onset, for both pre-target alpha and LSPOP component separately. For the CNV ERP component, the independent measure was derived by integrating activity across the time period of 900 – 1100 ms post-cue onset, and averaging across nine clustered electrodes over left right, and central regions in the center of the scalp.

4. RESULTS

Behavioral Analysis

A one-factor ANOVA with 4 levels of S2 stimulus-type (A-A_{att}, V-V_{att}, AV-A_{att}, AV-V_{att}) were computed for both the accuracy and RT data.

The ANOVA revealed a main effect of stimulus-type F(1,11) = 8. 26, $p < 0.01$, caused by a considerable decrease in performance for the AV-A_{att} type stimulus. The reader should recall that the auditory task is identical between the A-A_{att} and AV-A_{att} stimulus types, so it appears that the presence of a distracting visual stimulus has a large detrimental effect on performance. For the RT data, the ANOVA also revealed a main effect of stimulus-type F(1,11) = 9.523, $p < 0.01$. RTs were considerably slower in the AV-A_{att} stimulus-type.

Time Domain Analysis

Broadband activations

To statistically test for attention effects in the LSPOP component, we conducted a two-tailed paired sample t-test between attending conditions (auditory vs. visual) over the period 900-1100 ms after S1-cue onset. The t-test revealed a main effect of attention t(11) = -2.412, $p < 0.05$, indicating that attending to the visual modality elicited more positive amplitude in comparison to attending to the auditory modality (see Figure 3, upper left corner). This finding replicates those of Foxe et al (2005a).

Time-Frequency Domain Analysis

Alpha-band effects:

Figure 2 shows the alpha-band effects over parieto-occipital cortices. In order to statistically test whether the differential arises from an increase in the attend-Aud or decrease in attend-Vs, we conducted a 2 x 2 x 2 repeated measures ANOVA. The ANOVA had factors of attention (attend auditory vs. visual), hemisphere (left vs. right), and time (pre-cue = -300 to –100ms, post-cue = 900 to 1100 ms). The ANOVA revealed a main effect of attention, indicating that deploying attention to the auditory modality resulted in greater power in comparison to the visual modality, $F(1,11) = 6.15$, $p < 0.05$. Moreover, the ANOVA revealed a main effect of time $F(1,11) = 6.606$, $p < 0.05$, suggesting that alpha-power is higher during the pre-cue vs. the post-cue period. However, this main effect was mostly driven by a significant interaction between Attention and Time, $F(1,11) = 11.59$, $p = 0.006$. Multiple comparison t-tests revealed that this effect was due to differences between the pre-cue and post-cue times when subjects deployed attention to the visual modality, $t(11) = 3.031$, $p < 0.005$. That is, there was a significant drop in alpha-power, during the post-cue time, when subjects attended to the visual modality. Further, the $\eta^2 = 0.516$ indicated that this effect accounted for at least 52% of the overall variance.

Delta-band phase resetting:

The phase distribution across trials, for both attending conditions, was analyzed using the Rayleigh circular statistic test. Figure 3 shows the broadband ERP (Figure 3a), oscillatory power effects (Figure 3b) and the phase distributions for both attending conditions 1200 ms after the onset of the S1-cue in the delta-band (Figure 3c). The statistics revealed that, for both attending conditions, in the period preceding the presentation of the cue (500 ms preceding the S1-cue) the phase distribution is not significantly non-uniform ($p > 0.05$ attend auditory, $p > 0.05$ attend visual). However, after the presentation of the cue, the phase distribution ceased to be uniform for both attending conditions ($p < 0.01$ for both attending conditions, R = 0.08 attend auditory, and R = 0.07 attend visual). In order to assess whether this redistribution of phase indexes a 'pure' phase reset (i.e. a phase reset without a significant increase in power), we computed a 2 x 2 repeated measures ANOVA with factors of time (-500 to -250 ms pre-cue, and 600 – 1200 ms post-cue) and attention (attend-auditory vs. attend visual) in the delta-band (1 – 3 Hz) using oscillatory-power as our dependent measure. The results revealed no significant main effects of time $F(1,11) = .970$, $p > 0.05$ or attention condition $F(1,11) = .271$, $p > 0.05$. In addition, the ANOVA failed to reveal any interaction effect of time x attention condition, $F(1,11) = 1.92$, $p > 0.05$. The lack of power differences across time and conditions thus indicate a 'pure' phase resetting effect in the delta band.

To test for mean-phase differences between the attending conditions, we compared the two distributions using a nonparametric test for equality of circular means. There was a significant phase difference of 42º (164º attend-visual vs. 122º attend-auditory) between the two attention conditions, with the attend-visual condition leading the attend-auditory condition in the period immediately preceding the imperative stimulus ($p < 0.001$). We performed a subsequent analysis to validate the reliability of the statistical differences between the two circular means. This additional analysis was performed because the equations used to calculate differences between circular means are sensitive to the number of trials in each condition (see equations 1 and 2, Rizzuto et al 2006). To protect against this, we performed a bootstrapping procedure by random sampling five times (3600, 2700, 1800, 900, and 600 trials) from the entire population of trials. Although the p-values increased as the number of trials decreased, the statistics still produced highly robust effects ($p <$ *0.0001, 0.0001, 0.0005, 0.001,* and *0.04,* respectively).

Visual inspection of Figure 3c indicates that the delta-band phase distribution is bimodal. We performed additional analyses to characterize the underlying source(s) of this effect. First, we assessed whether a peak in the bimodal distribution is the result of trials composed of 'weak' and/or 'wrongly-executed' attentional deployments[14], while the other peak is composed of 'robust and correctly executed' attentional deployments. To investigate this we binned the delta-band phase of correctly-identified trials (e.g. hits) separately from trials where an incorrect response was executed (e.g. false alarms and misses). The data revealed similar effects as those observed in Figure 3c for both response-type distributions. Thus, these peaks do not correspond to 'weak' or 'robust' attentional deployments.

Alternatively, we hypothesized that this bimodal distribution is the result of a 2nd harmonic component occurring within the 1-3 Hz delta band. To test for this, we computed phase-distributions for a 0.83 Hz and its 2nd harmonic 1.66 Hz, which corresponds to the SOA between the S1 and S2 stimulus (e.g. 1200 ms). In addition, phase distributions were computed for a 1 Hz and its 2nd harmonic 2Hz, as well as for a

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[14] It is argued by this group that weak and/or 'wrongly executed attentional deployments are inherent in many of these S1-S2 experimental paradigms.

1.25 Hz component and its 2nd harmonic 2.5 Hz. These extra base-frequency components correspond to the middle time point of the duration of the S1-cue (e.g. 1 Hz, 200 ms) and the onset of the 800 ms inter stimulus interval (ISI) between the S1 and S2 stimulus (e.g. 1.25 Hz, 400 ms after S1 onset). The reason for performing the analysis on all of these different base frequencies (e.g. 0.83, 1 and 1.25 Hz) is because it is not clear whether the S1-cue will reset the phase of the ongoing oscillation at the starting point (e.g. 0 ms), during the processing of the cue (e.g. 200 ms), or after it has been presented (e.g. 400 ms).

Similar to the original observations, the data revealed significant non-uniform distributions for the 1st, 2nd and 3rd base frequency (0.83 Hz $p < 0.01$, 1 Hz $p < 0.01$, 1.25 $p < 0.01$). No significant non-uniform distributions for any of the 2nd harmonics were observed. Interestingly, the distribution of the 3rd base frequency (e.g. 1.25) was highly similar to that of the original phase-distribution (see supplementary figure 1). This is supported by the R-value (R-attend auditory = 0.08, R-attend visual = 0.05) and mean angles (159° attend-visual vs. 136° attend-auditory) of the distribution. This may indicate that the S1-cue resets the phase of the ongoing delta oscillation at or around the time of the S1 stimulus offset.

Alpha & gamma anterior/posterior phase-coupling:

Figure 4 illustrates statistically significant phase-coupling effects, resulting from the Rayleigh method, in the gamma and alpha bands for both attention conditions and in each ROI pair. The results revealed phase-coupling between ~510 – 600 ms in the gamma-band across central and posterior cortices when attending towards auditory inputs (left upper panel Figure 4). Phase-coupling was also observed between the same ROI pairs in the alpha-band (upper right panel Figure 4) when attention was apportioned to vision (~760 – 1100 ms) and audition (~975 – 1250 ms). Finally, the results revealed phase-coupling in the gamma band in the period between ~580 – 740ms across anterior and posterior cortices when attending to visual inputs only. All these statistically significant phase-couplings were observed in ROI pairs over the right hemisphere.

EEG & Behavioral Performance:

Pre-target alpha and behavioral performance:

Figure 5 (upper panels) plots d-prime and RT as a function of the binned index level for the pre-target alpha biasing. Two 2 x 4 repeated measures ANOVAs, with factors of attention (attend auditory vs. attend visual) and bin-level (four bin levels, ranging from lowest to highest amplitude) were conducted to test the pre-target alpha effect as a predictor of d-prime and RT. The independent measure was derived by averaging the alpha-band activity across six clustered electrodes symmetrically arranged over left and right parieto-occipital cortices during the timeframe 900-1100 ms post cue.

The d-prime ANOVA conducted on the pre-target alpha measure revealed a main effect of attention $F(1,11) = 8.976$, $p < 0.05$ indicating that d-prime values were greater for the attend-visual than attend-auditory condition. The ANOVA also revealed an interaction effect of attention by bin-level, $F(3,33) = 3.344$, $p < 0.05$. A test of within-subject contrast revealed that this interaction effect followed a cubic pattern, $F(1,11) = 5.11$, $p < 0.05$, as well as a trend towards significance for a linear distribution, $F(1,11) = 4.32$, $p =0.06$. Follow-up paired sample t-tests between the four bins in the attend-visual condition revealed that bin one (lowest alpha power) yielded significantly greater d-prime measures than bin two, three and four, t(11) = 2.33, $p < 0.05$, t(11) = 2.62, $p < 0.05$, t(11) = 6.42, $p < 0.01$, respectively. No other significant effects were found.

The RT ANOVA conducted on the pre-target alpha measure revealed a main effect of attention F(1,11) = 8.136, $p < 0.05$ indicating that attending to the visual modality resulted in significantly lower values of RT than attending to the auditory modality. No other significant effects were found.

LSPOP ERP component and behavioral performance:

Figure 5 (lower panels) plots d-prime and RT as a function of the binned index level for the LSPOP broadband ERP component. Two 2 x 4 repeated measures ANOVAs, with factors of attention (attend auditory vs. attend visual) and bin-level (four bin levels, ranging from lowest to highest amplitude) were conducted to test the LSPOP ERP component as predictor of d-prime and RT. The dependent measure was derived by averaging the LSPOP activity across four clustered electrodes symmetrically arranged over left and right parieto-occipital cortices during the timeframe 900-1100 ms post cue.

The d-prime ANOVA conducted on the LSPOP broadband component revealed a main effect of attention F(1,11) = 15.137, $p < 0.01$ indicating that d-prime values were significantly greater for attending to the visual than the auditory condition. The ANOVA also revealed a main effect of bin-level, F(3,33) = 10.479, $p < 0.001$. A within-subject contrast revealed that this effect followed a linear trend distribution, F(1,11) = 12.442, $p < 0.01$, thus indicating that bin one yielded the lower d-prime values, while bin four yielded the highest. Finally, the ANOVA also revealed a trend towards a significant interaction between attention and bin-level, F(3,33) = 2.263, $p = 0.09$. Post-hoc analysis revealed that this effect followed a trend toward a significant linear relationship, F(1,11) = 4.441, $p = 0.06$. No other significant effects were found.

The RT ANOVA conducted on the LSPOP ERP component revealed a main effect of attention F(1,11) = 8.492, $p < 0.05$ indicating that RT values were lower for the attend-visual than the attend-auditory condition. The ANOVA also revealed a main effect of bin-level, F(3,33) = 6.551, $p < 0.01$. A within-subject contrast revealed that this effect followed a linear trend, F(1,11) = 14.274, $p < 0.01$, indicating that bin one yielded the higher RT values while bin 4 yielded the lowest RT value. No other significant effects were found.

CNV ERP component and behavioral performance:

Two 2 x 4 repeated measures ANOVAs, with factors of attention (attend auditory vs. attend visual), hemisphere (9 clustered electrodes over central cortices – centered around C3,C4, and Cz) and bin-level (four bin levels, ranging from lowest to highest amplitude) were conducted to test the CNV ERP component as predictor of d-prime and RT. The dependent measure was derived by averaging the CNV activity during the timeframe 900-1100 ms post cue, across nine clustered electrodes symmetrically arranged over left and right central cortices

The d-prime ANOVA conducted on the CNV ERP component revealed a main effect of attention F(1,11) = 10.123, $p < 0.05$ indicating that d-prime values were significantly lower for attending to the auditory than the visual condition. No other significant effects were found.

The RT ANOVA conducted on the CNV ERP component revealed a main effect of attention F(1,11) = 8.656, $p < 0.01$ indicating that RT values were lower for attending to the visual than the auditory condition. The ANOVA also revealed a main effect of bin-level, F(3,33) = 3.742 , $p < 0.05$. However, this main effect was mostly driven by an interaction effect of bin-level by attention, F(3,33) = 4.565, $p < 0.05$. Paired sample t-tests revealed that when subjects deployed attention to the visual modality, bin one yielded significantly lower RTs than bin two, three and four, t(11) = 3.071, $p < 0.05$, t(11) = 3.816, $p < 0.01$, t(11) = 3.942, $p < 0.01$ - (Bin level RTs = 704, 723, 735, 748 ms). No other significant effects were found.

5. DISCUSSION

We investigated the oscillatory and broadband temporal dynamics during attentional deployments between the auditory and visual modalities. By using an S1-S2 cueing paradigm we were able to isolate the preparatory attentional mechanisms uncontaminated by the sensory processing of the S2 stimulus. Using single trial and broadband ERP analysis we uncovered a series of neurophysiological processes related to the deployment of attention to different sensory modalities. First, we replicated the pre-target alpha intersensory biasing effect (see Foxe et al 1998; Fu et al 2001), and found that it was mostly driven by a relative decrease when directing attention to the visual modality. We found that this decrease significantly predicted d-prime values. Second, we replicated the LSPOP ERP component (Foxe et al 2005a). That is, deploying attention to the visual modality results in a relative positivity over right parieto-occipital cortices in the period immediately preceding the arrival of the S2. We found that this LSPOP component significantly predicted d-prime and RT values, independent of attention condition. Third, we found that the symbolic S1-cue resets the phase of an ongoing delta-band oscillation during the attentional deployment period. This phase alignment was not accompanied by an increase in power, thus indicating that this effect reflects a ‘pure’ phase-resetting mechanism. Further, a significant phase difference was found between the two attention conditions. In addition, we found that high-frequency gamma-band oscillations synchronized activity between anterior and posterior cortical regions when attention was directed to vision. Taken together, this pattern of results indicates that a collection of band-specific and broadband neural oscillatory processes play a critical role in the orchestration of so-called biased attentional states to different modalities. In addition, the data indicates that top-down signals reorganize the ongoing oscillatory-phase dynamics, perhaps as a means to set the excitatory state of a local neural ensemble in sensory-specific cortices. Finally, we contend that pre-target alpha-band mechanisms enable processing in visual cortical areas that in turn facilitate discrimination of visual stimuli in the presence of auditory distracters.

Visual alpha biasing:

In support of previous findings, our results indicate that pre-target alpha activity plays an important role in the biasing of attention to different sensory modalities (see Foxe et al 1998; Fu et al 2001; Gomez-Ramirez et al 2007; Trenner et al 2008). We found that when subjects biased their attention to the visual modality a significant decrease, relative to baseline, is observed during the late stages of the preparatory attentional period (see Figure 2). In contrast, when subjects deployed attention to the auditory modality we failed to find any significant increase in alpha-power during the same time period. We take this pattern of results as evidence of a desynchronization effect, and suggest that the pre-target alpha biasing process operates, at least in part, by enhancing the relevant visual inputs in visual-related areas, and not just by suppressing visual input during auditory attention. Indeed, this finding is not in full agreement with the study of Fu et al (2001), where the authors found that allocating attention to the auditory modality resulted in a significant increase in alpha-power over parieto-occipital cortices relative to baseline activity (i.e. prior to the onset of the S1-cue stimulus). The reader should note however, that Fu and colleagues (2001) only tested for a synchronization effect when attention was apportioned to the auditory modality, thus leaving the question of a desynchronization effect unanswered. By carefully observing the findings in Fu et al (2001, Figure 2) one can appreciate that the deviation from baseline when attention is deployed to the visual modality is notably greater from that of deploying attention to the auditory modality. In fact, such a pattern of results indicates that this alpha process might function as a dual attentional mechanism of neural enhancement/suppression (i.e. a push-pull mechanism). This dual form of attentional gating has been documented in human and non-human primate studies of attention (see Motter 1993; Pinsk et al 2004; Moore and Armstrong 2003; Gazzaley et al 2005; Vuilleumier et al 2005; Quraishi et al 2007). Motter (1993) observed neurons in V1, V2 and V4 areas of macaque monkeys having an enhancement/suppression firing pattern when presented with simultaneously competing stimuli. These neurons however, ceased to exhibit this firing pattern once the competing stimuli were removed from their receptive fields. Further, Moore & Armstrong (2003) showed that neurons in V4 were enhanced when stimulated by their corresponding retinotopically-mapped neurons in the frontal eye fields (FEF). These authors showed that the magnitude response in these extrastriate neurons strongly depended on the presence of a competing stimulus outside the neurons’ receptive field.

The question arises, why did we fail to report a suppression-like effect, in the form of an alpha-synchronization, when subjects deployed attention to the auditory modality? While the answer is not apparent, a possible explanation could be found in the difference in experimental design between both studies. In Fu et al (2001) the paradigm was designed so that the visual stimulus was concurrently presented with the first auditory tone, while in the present experiment the visual stimulus was presented in conjunction with the 2nd auditory tone. Thus, a strong possibility is that subjects may have delayed any suppression-like effect until the presentation of the visual stimulus was nearer. This explanation however, should be treated with caution since there does not exist evidence for such a mechanism to be instantiated.

The results showed that this pre-target alpha-desynchronization effect was found to be a reliable predictor of d-prime measures. In particular, the data revealed an inverse relationship, whereby the highest d-prime values were grouped in the bin-level containing the lowest alpha-power measures (i.e. greatest desynchronization), while the lowest d-prime values were grouped in the bin-level containing the highest alpha-power measures (i.e. the lowest amount of desynchronization). Similar relationships have been observed in attention studies of spatial attention (see Thut et al 2006; Trenner et al 2008; Kelly et al (unpublished). The study by Thut et al 2006 found that left visual targets were detected most rapidly when the alpha-lateralization-index[15] (ALI; measured as difference between LH and RH normalized by the sum) was most negative, and slowest when the ALI was most positive. Conversely, they found that detection of right visual targets was fastest in trials where the ALI was most positive and slowest when the ALI was most negative.

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[15] An index of the pre-target alpha-biasing effect derived by subtracting the alpha-power in the left hemisphere from the alpha-power in the right hemisphere and dividing that difference by the mean of the alpha-power over left and right hemispheres.

Kelly et al (unpublished) observed similar relationships with regard to d-prime and RT measures. This pattern of results led Thut and colleagues (2006) to suggest that the pre-target alpha-biasing effect can serve as an indicator for the momentary visuospatial attentional vector, with more negative ALI values indicating a leftward attentional bias, and more positive ALI values signaling attention being directed to the right visual field. In this experiment however, a similar but unidirectional effect is observed. That is, greater alpha-desynchronization values indicate a biasing towards visual attention, perhaps as a means to enable visual-related cortices and in turn facilitate processing of visual stimuli in the presence of auditory distracters.

Broadband activity and behavioral performance:

Similar to the findings in the alpha-band, single trial prediction analysis performed on the LSPOP and CNV ERP components revealed systematic relationships with d-prime and RT values. Specifically, the LSPOP component predicted d-prime and RT values, independent of attention condition, while the CNV component was found to be a reliable predictor of RT across both attention conditions. This CNV effect however, was most prominent during attentional deployments to the visual modality. Similar findings were observed by Jongen et al (2006), where the authors found a systematic relationship between the CNV component and RT during neutral trials (e.g. trials where the cue has no predictability). Note however, that this relationship was only evident during trials where spatially selective attentional deployments were not executed.

Kelly et al (unpublished) found that the LDAP component reliably predicted RT during a visual-spatial attention task. As we previously mentioned, the LDAP is a late-sustained ERP component observed in many visuo-spatial attention studies that share very similar temporal, amplitude and topographical characteristics to the LSPOP. These two ERP components onset approximately 400 – 500 ms after cue onset, last for a relatively similar amount of time, have a similar differential-amplitude response with respect to the attending conditions, and are localized over lateral parieto-occipital scalp regions. It is highly intriguing then, that in addition to having very similar neurophysiological properties, they are both also predictors of certain behavioral measures. However, although there are many parallel characteristics between these two broadband potentials, there are some discrepancies that tip against the possibility of these potentials reflecting the same neurophysiological marker during different task scenarios. For instance, the findings from Kelly and colleagues (unpublished) clearly show that the LDAP has a selective behavioral prediction pattern across attention condition - stronger biasing towards one hemisphere predicts RT to targets appearing in the contralateral hemifield. In contrast, the findings in our present study showed that the LSPOP only predicts behavior in a unidirectional or non-selective manner across attention conditions. A second factor relates to retinotopic patterns of the LDAP that have yet to be replicated in the LSPOP component. That is, several spatial-attention studies have shown the LDAP having a reversed-polarity (i.e. an LDAN) when visual stimuli are presented below the horizontal meridian (see Griffin et al 2002; Grent-'t-Jong & Woldorff 2007; Dale et al 2008). To our knowledge this retinotopic pattern has yet to be tested in an intersensory study, but deem it essential if an indisputable relationship were to be made across both broadband potentials.

Delta band phase-reset and the LSPOP ERP component:

The original hypothesis was that the LSPOP component reflects a delta-band oscillation whose ongoing phase gets reset by the symbolic cue. This phase reset will cause the excitability state of the local neural ensemble to be in its ideal state at the arrival of the relevant S2-stimulus. Single trial analysis revealed a statistically significant reorganization of the oscillatory phase from pre-to-post S1-cue onset, in the same electrodes sites where the LSPOP component was found to be maximal. Furthermore, this phase redistribution was not accompanied by a significant increase in power, which indicates that this effect reflects a 'pure' phase resetting mechanism. Of utmost importance, the phase distributions of the attend-auditory and attend-visual conditions were statistically different from each other, which indicates that the S1-cue selectively alters the phase of an ongoing delta-band rhythm, perhaps as a means to set the firing state of a local neural ensemble. Similar findings have been observed in a non-human primate study during a temporally predictive intersensory attention task. Lakatos and colleagues (2008) found that top-down attentional signals reorganized the phase of a delta-band rhythm in primary visual cortex (V1) such that, when attention was apportioned to the visual modality, visual stimuli appeared at the excitatory-phase of the oscillation. However, when attention was apportioned to the auditory modality, these same visual stimuli appeared at the inhibitory-phase of the oscillation. We contend that in our experiment a similar mechanism is executed. That is, since the time interval between the onset of the cue and the target is fixed at 1200 ms, it is likely that when attention is deployed to the visual modality posterior cortices are placed in their most 'optimal' firing state, but when attention is deployed to the auditory modality they are placed in their least excitable state. Given the resolution of our methods however, we do not make claims as to whether the 'best' and 'worst' firing-states are in fact 42^o degrees out of phase with each other. We leave this issue to experiments that use more invasive recording techniques such as intracranial recordings in animals, where both dendritic (e.g. input states) and single/multi unit activity (e.g. output states) can be directly measured. Of interest, post-hoc analyses seem to indicate that the phase-reset might occur during the late-stages of the cue-decoding phase (~400 ms after S1-cue onset). However, further research is needed to fully validate this claim.

Another fascinating finding in Lakatos et al (2008) was the systematic relationship between delta phase and RT. The authors found that the fastest RTs occurred around the negative peak of the delta oscillation, while the slowest RTs occurred around the positive peak of the oscillation. This relationship between oscillatory-phase and behavioral performance has strong implications for these S1-S2 cueing paradigms. That is, since the S1-cue can reset the phase of the oscillation such that relevant stimuli appear at the 'high excitability' state, then a significant drop in performance should be expected during trials where the stimulus-onset-asynchrony (SOA) between the S1 and S2 stimuli is set at half the cycle of the delta-band rhythm. Note however, that for this effect to occur, the vast majority of trials need to have an SOA matching a full cycle of the driving delta rhythm.

Although the data revealed compelling differences in the phase-distributions between attention conditions, we point out that these differences only occurred for an approximate period of a delta cycle. Unfortunately, the experimental paradigm and the signal processing methods used herein disallow for longer testing periods of this phase-resetting effect[16]. This failure to report effects beyond a one-cycle period raises the question of whether this effect underlies a real physiological oscillatory mechanism, or whether the signal processing techniques masqueraded a non-oscillating process into a one-cycle delta-band rhythm. We believe however, that within the context of our experiment, this scenario is highly unlikely for the following reasons: (1) The data presented herein are only exclusive to processes in the delta-band, and are not prevalent in the surrounding frequency bands, theta (4 – 7 Hz) or alpha (8 – 14 Hz), (2) the data revealed a 'pure' phase-resetting mechanism between the periods before and after cue onset, thus indicating that this mechanism is purely phase-dependent, and (3) similar findings have been observed in intracranial studies in non-human primates (see Lakatos et al 2008).

Alpha & Gamma fronto-parietal phase coupling:

Our original hypothesis specified that anterior and posterior cortical regions would become phase-locked during the intermediate and late-stages of the attentional deployment phase in the gamma and alpha-band frequencies, respectively. During the timeframe of ~580 to 740 ms, the data revealed a phase-coupling effect in the gamma band across anterior and posterior right-hemispheric ROIs when subjects directed attention to vision, but not audition. It is not clear why this effect is unidirectional and not manifested during attentional deployments to auditory inputs. One possibility is that high-frequency activity emanating from auditory cortices may not propagate well to the scalp surface thus resulting in poor signal-to-noise ratios. Therefore, whether high-frequency oscillatory mechanisms mediate communication between so-called executive-control

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[16] There would be significant contamination in the EEG activity from the evoked sensory response of the S2 stimuli.

regions and task-specific auditory cortices still remains an open question, and should be investigated using more suitable techniques.

Activity in the alpha-band did not reveal phase-coupling between anterior and posterior cortices during the late-stages of the attentional deployment phase. The data only revealed a significant phase-coupling effect between central and posterior cortices. These phase-locking computations between central and posterior cortices were performed as a control condition, because of volume conduction concerns, for effects between anterior and posterior cortices. Possibly, this phase synchrony between these two neighboring areas might reflect the source that gives rise to the anticipatory alpha-band biasing effect. This however, is highly speculative and should be treated cautiously.

Indeed, our results are not in full agreement with previous findings by Doesburg et al (2007) and Brancucci et al (2008). Doesburg and colleagues (2007) found phase synchronization in the high-alpha band (~14 Hz) between widespread regions in visual cortex. The authors derived phase-synchronization/desynchronization values by computing PLA on a sample-by-sample basis and normalizing it with respect to the PLA during the pre-cue period. However, by assessing source coherence through the normalized PLA technique, it is not entirely clear whether these findings are strictly related to selective attention effects during the post-cue phase, or whether they reflect pre-cue expectancy effects. These pre-cue effects would definitely be instantiated if the inter-trial-interval (ITI) would not be randomized within a long-window but rather fixed at a particular time point. Unfortunately, in Doesburg et al (2007) there is no detail of whether the ITI was randomly varied or set to a particular rate. Further, it is recommended that before estimating the magnitude of a phase-coupling effect, one should first assess whether the phase distributions are non-uniform.

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7. FIGURE LEGENDS

Figure 1 (Sequence of Events): Each trial commenced with the presentation of an auditory symbolic cue (S1) whereby the abbreviated words “Aud” (attend auditory) or “Vis” (attend visual) were presented through headphones to the subjects. A delay period of 800ms followed the cue (i.e. 1200 ms SOA), after which an auditory stimulus alone, visual stimulus alone, ‘null’ trial (i.e. where no physical stimulus was presented), or compound audio-visual multisensory stimuli. Subjects were required to respond with a button push to targets within the cued modality only.

Figure 2 (Alpha-Band Synchronization vs. Desynchronization): Alpha band (8 – 14 Hz) wavelet transformed (WT) signals averaged across six clustered electrodes over left and right parieto-occipital cortices. A sustained divergence in the response is seen starting at ~350 ms post S1-cue onset and lasting until the presentation of the S2-stimulus. Alpha-band activity is significantly greater when subjects have been cued to attend to the auditory modality (blue trace) compared to the visual modality (red trace). However, the divergence from baseline (-300 to –100ms) is significantly greater for attend visual compared to attend auditory, thus indexing a desynchronization effect (bar graph)

Figure 3 (Oscillatory power and phase responses and LSPOP ERP component): The figure in the *upper left corner* shows the broadband ERP component associated with attending to the auditory modality (blue trace) versus the visual modality (red trace) over right-parieto occipital cortices. The findings revealed a statistical significance difference between both attending conditions, over the late-stages of the attention deployment period (900 – 1200 ms post-cue onset). The figure in the lower *left corner* shows nonbaseline corrected time-frequency power spectra from 1 to 50 Hz when attending to the auditory and visual modalities. The figures to the immediate right show baseline corrected (BC) power spectra, by dividing the post-cue activity by the average activity from –600 to –500 ms pre-cue in each frequency bin. The reader can appreciate that there is no significant differences in the delta-band power between both attending conditions. The figures in the *upper right corner* show the phase distributions (in radians) at 1200 ms post-cue onset for both attending conditions.

Figure 4 (Phase Coupling between anterior, central and posterior cortices – Evidence from the Gamma and Alpha Bands): Phase coupling effects across anterior, central and posterior regions. The data shows phase coupling between right central and posterior regions in the mid and late stages of the attentional deployment period (upper panels), as well as phase-coupling between anterior and posterior regions (lower panel). The upper left panel shows significant phase-locking activity between right central and posterior regions in the gamma-band between the period ~510-600 ms when attending for auditory inputs. The upper right panel shows significant phase-licking between the same ROI pairs in the alpha band when attending for visual (~760 – 1100 ms) and auditory (~975 – 1250 ms) inputs. The lower panel shows phase-coupling in the gamma band in the period ~580-740 ms when directing attention to the visual modality. Each ROI was composed of four clustered electrodes over posterior, middle and frontal regions in each hemisphere. The results only revealed phase-coupling effects over the right hemisphere.

Figure 5 (Preparatory EEG processes predict behavior): Behavioral measures of d-prime and RT plotted against the pre-target alpha-band mechanism (upper panel) and LSPOP ERP component (lower panel). X-axis indicates sorted average activity in quartiles levels. Attend auditory is depicted blue, while attend visual is depicted in red. The asterisk denotes a significant interaction of attention by bin-level. For both pre-target alpha and LSPOP ERP component, attend visual resulted in greater d-prime measure and slower RT. This effect was due to a significant drop in performance when subjects attended to the auditory modality and a bimodal stimulus was presented.

Supplementary Figure 1 (Oscillatory-phase distributions for sub and delta base-frequency components): The figure shows the phase distributions (in radians) at 1200 ms post-cue onset for both attending conditions (left panels attend auditory, right panels attend visual) in the 0.83 Hz (upper graphs), 1.00 Hz (middle graphs), and 1.25 Hz (lower graphs). The distribution of the 1.25 Hz frequency component bears high similarity to that of the original 1-3 delta-band distribution.

8. FIGURES

Figure 1

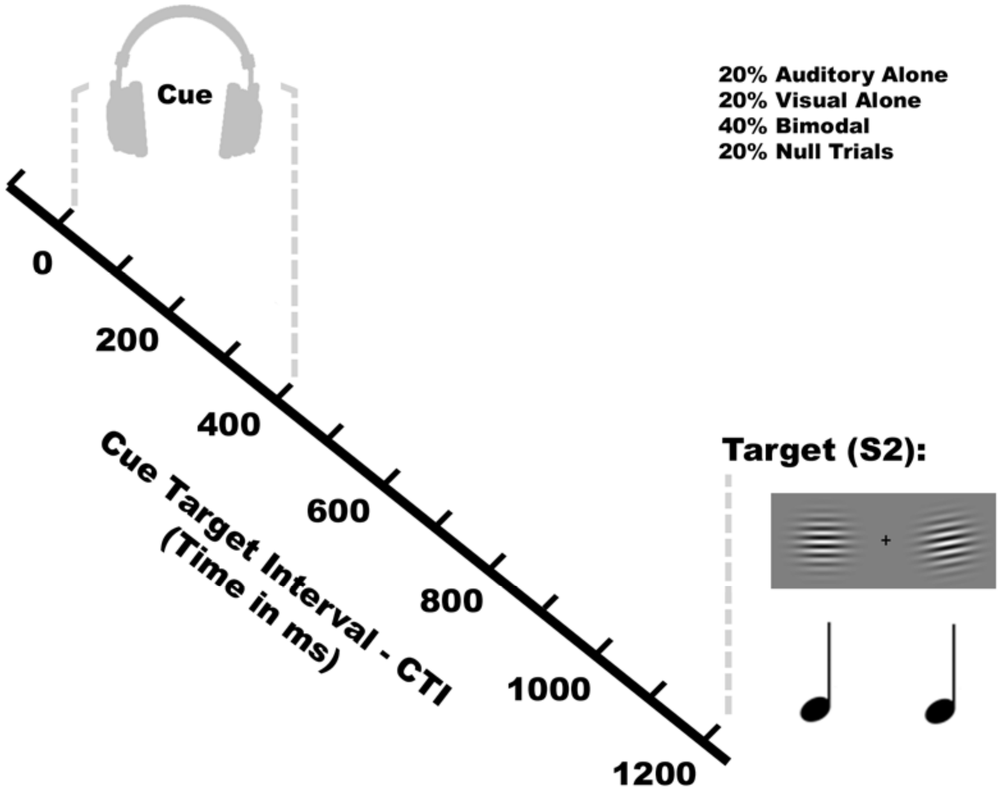


Figure 2

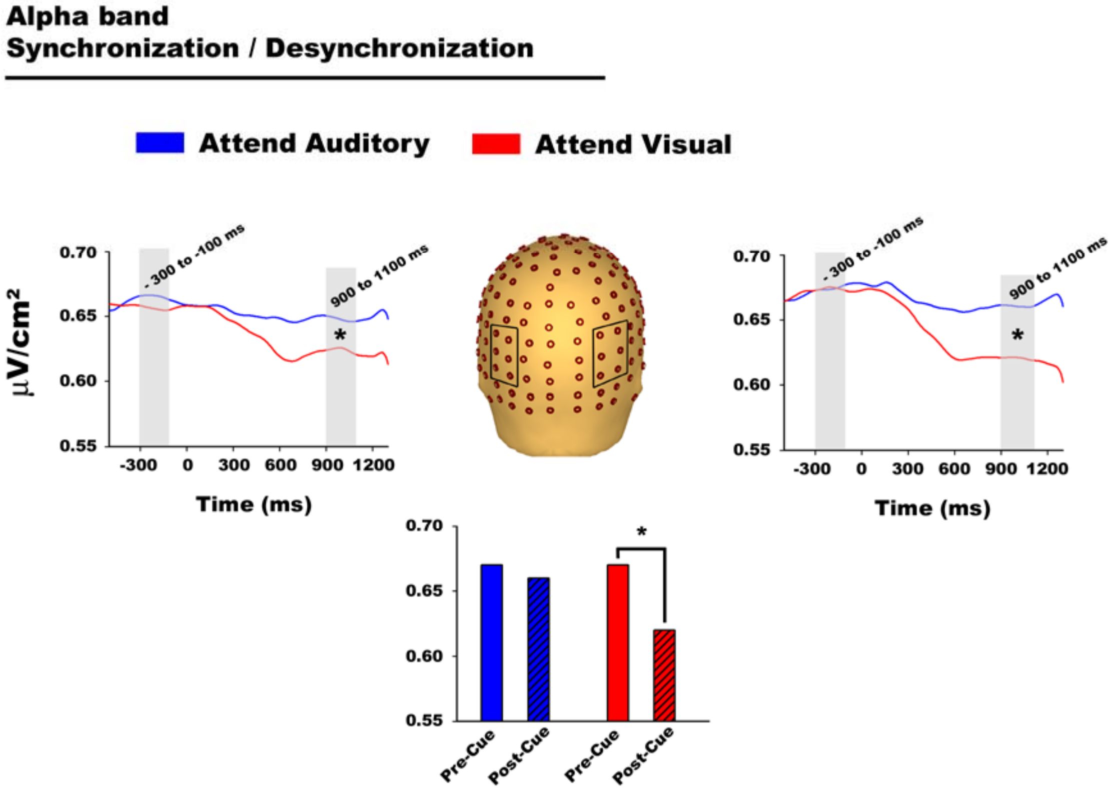

Alpha band
Synchronization / Desynchronization
Attend Auditory
Attend Visual
μV/cm²
0.70
0.65
0.60
0.55
- 300 to -100 ms
900 to 1100 ms
*
-300
0
300
600
900
1200
Time (ms)
0.70
0.65
0.60
0.55
- 300 to -100 ms
900 to 1100 ms
*
-300
0
300
600
900
1200
Time (ms)
0.70
0.65
0.60
0.55
*
Pre-Cue
Post-Cue
Pre-Cue
Post-Cue

Figure 3

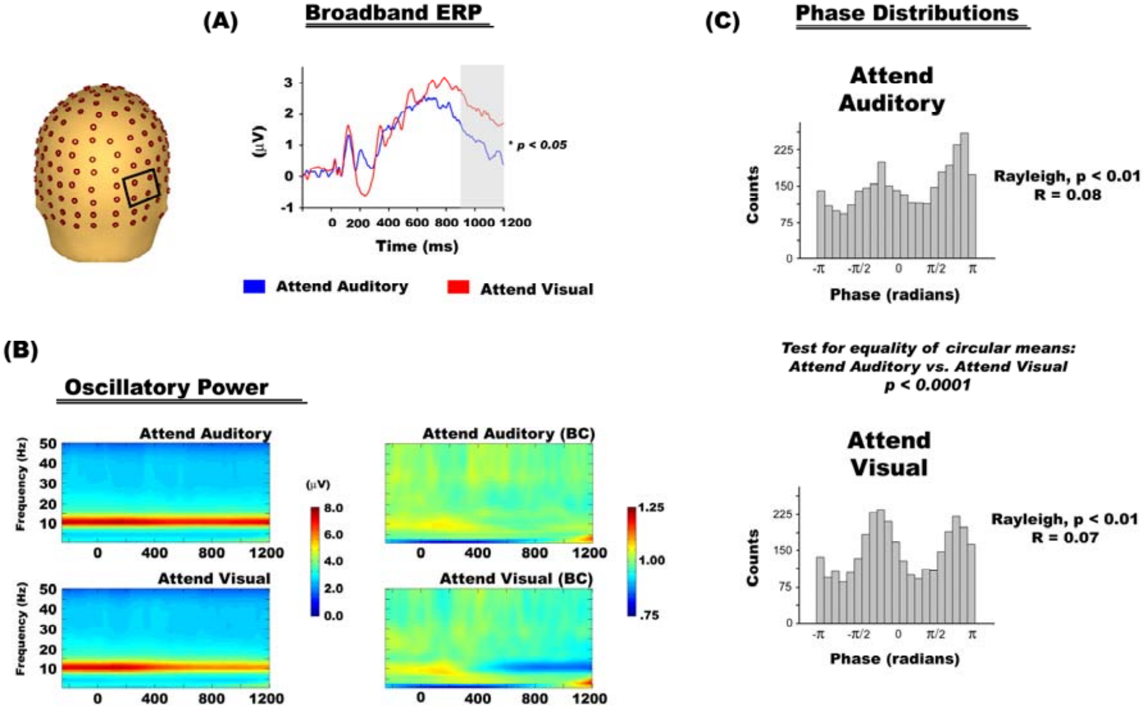

(A)
Broadband ERP
3
2
1
0
-1
(µV)
* p < 0.05
0 200 400 600 800 1000 1200
Time (ms)
Attend Auditory
Attend Visual
(B)
Oscillatory Power
Attend Auditory
Frequency (Hz)
50
40
30
20
10
0 400 800 1200
(µV)
8.0
6.0
4.0
2.0
0.0
Attend Auditory (BC)
1.25
1.00
.75
Attend Visual
Attend Visual (BC)
(C)
Phase Distributions
Attend Auditory
Counts
225
150
75
0
-π -π/2 0 π/2 π
Phase (radians)
Rayleigh, p < 0.01
R = 0.08
Test for equality of circular means:
Attend Auditory vs. Attend Visual
p < 0.0001
Attend Visual
Rayleigh, p < 0.01
R = 0.07

Figure 4

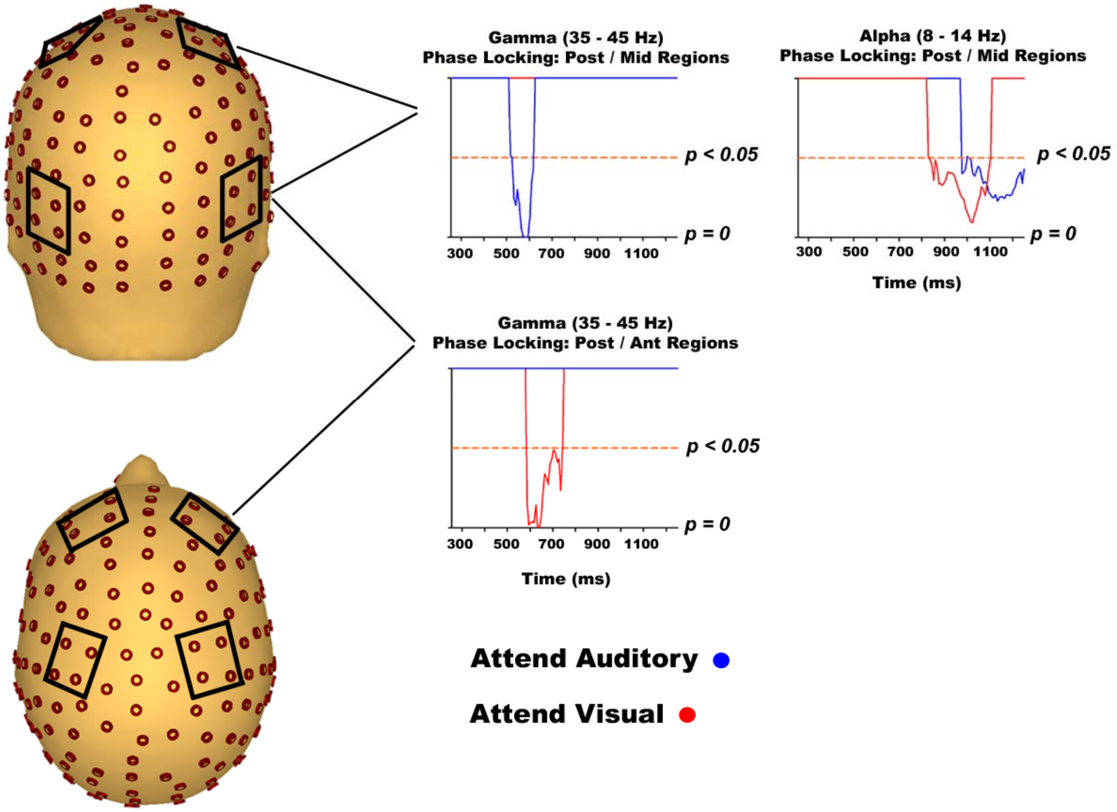
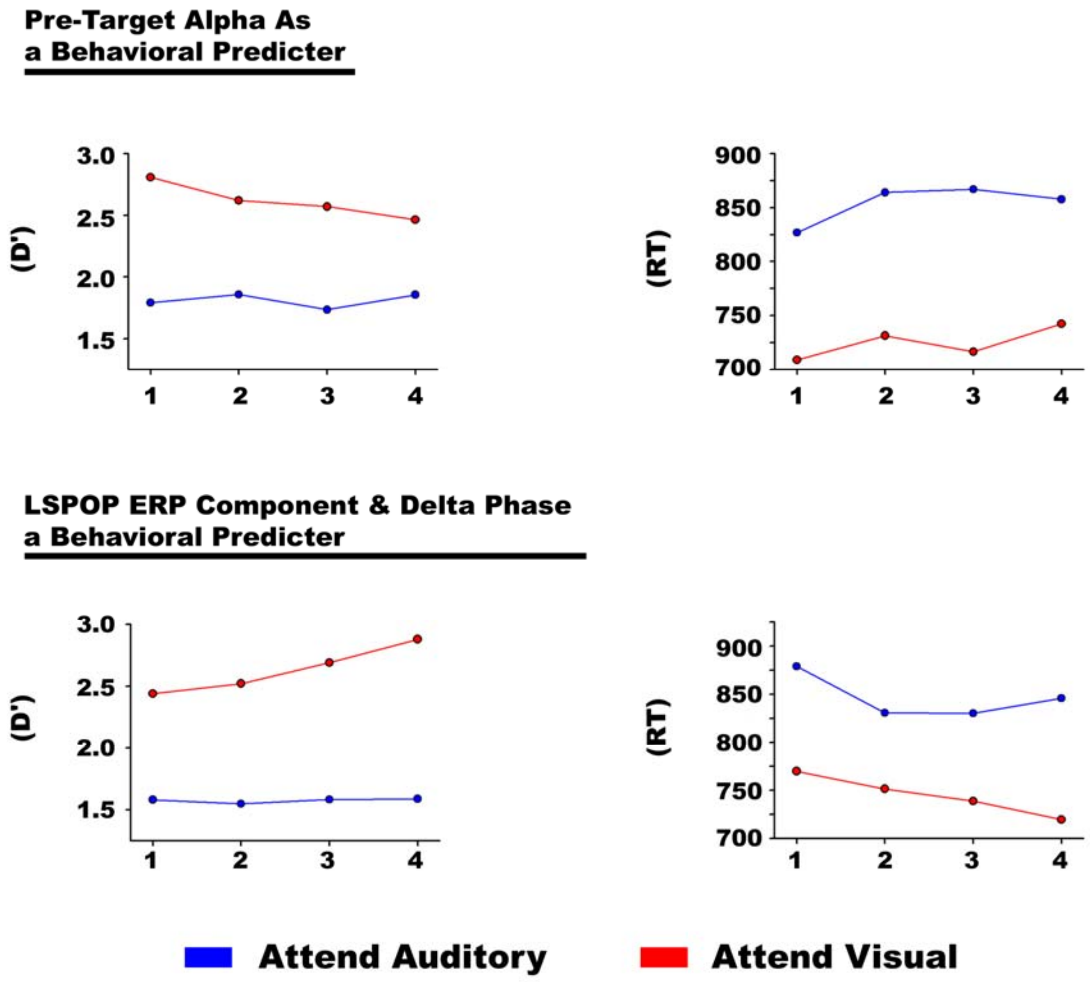
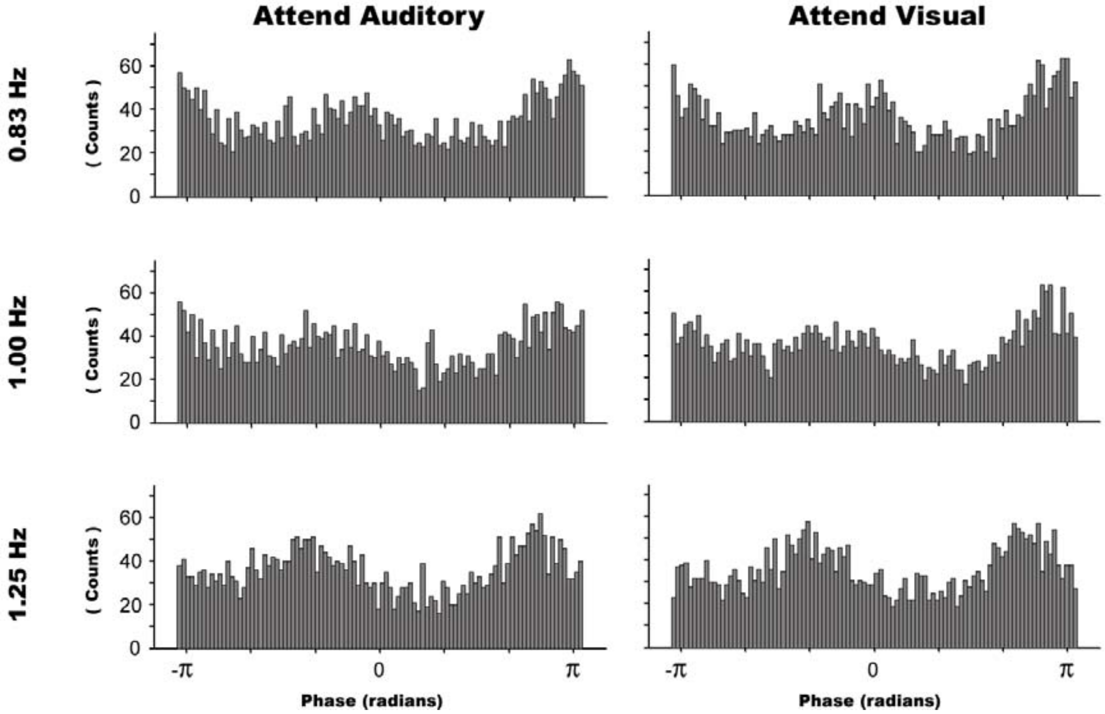

Gamma (35 - 45 Hz)
Phase Locking: Post / Mid Regions
p < 0.05
p = 0
300
500
700
900
1100
Alpha (8 - 14 Hz)
Phase Locking: Post / Mid Regions
p < 0.05
p = 0
300
500
700
900
1100
Time (ms)
Gamma (35 - 45 Hz)
Phase Locking: Post / Ant Regions
p < 0.05
p = 0
300
500
700
900
1100
Time (ms)
Attend Auditory ●
Attend Visual ●

Figure 5


Pre-Target Alpha As
a Behavioral Predicter
(D')
3.0
2.5
2.0
1.5
1
2
3
4
(RT)
900
850
800
750
700
1
2
3
4
LSPOP ERP Component & Delta Phase
a Behavioral Predicter
(D')
3.0
2.5
2.0
1.5
1
2
3
4
(RT)
900
850
800
750
700
1
2
3
4
Attend Auditory
Attend Visual

Supplementary Figure 1



CHAPTER 3

Oscillatory Sensory Selection Mechanisms Mediate Intersensory Attention to Auditory and Visual Inputs: A Human Intracranial Electrophysiological Study

1. ABSTRACT

We investigated whether entrainment mechanisms are instantiated at the earliest levels of auditory cortex during an audio-visual attention task. Electro-corticographic activity was recorded from electrodes localized to Brodmann-area 41 in two cognitively-normal patients undergoing invasive recordings for intractable epilepsy. Stimuli were presented every 1.5 seconds, and participants detected target stimuli in the attended modality only. We found evidence for oscillatory entrainment operating at twice the stimulation rate (1.33Hz). This was reflected in the cyclic modulation of alpha amplitude between stimuli, and in phase-amplitude coupling between delta-phase and alpha-power. Further, alpha-band amplitude was significantly greater during visual attention at the arrival of the auditory stimulus, thus further supporting the role of alpha-band activity as an active gating mechanism in early sensory cortex. These findings indicate that delta-band oscillatory entrainment is invoked endogenously, aligning its phase as a means for higher-frequencies to increase or decrease responsiveness to relevant or irrelevant stimuli, respectively

2. INTRODUCTION

Oscillatory neuronal activity is a pervasive phenomenon in the brain (Buszaki 2006) and is being increasingly viewed as playing a mechanistic role in sensory processing and cognition. Rhythms in various frequency bands have recently been implicated in attentional selection in particular. Recent studies have shown that higher-frequency rhythms (> 30 Hz) in local neural ensembles play a crucial role in the selection of relevant sensory inputs by enhancing the efficacy of signals located inside the locus of the attentional spotlight (Fries et al 2001; Fries et al 2002; Taylor et al 2005; Kayser et al 2006; Womelsdorf et al 2006; Fries et al 2007; Jacobs et al 2007; Jensen and Colgin et al 2007). Other studies have shown that oscillatory activity in the alpha-band (8 – 14 Hz) is associated with both enhancement and suppression mechanisms in visual cortex (see Mullholand et al 1983; Ray & Cole 1985; Foxe et al., 1998; Worden et al 2000; Fu et al 2001; Fries et al 2001; Sauseng et al 2005; Kelly et al 2006; Thut et al 2006; Rihs et al 2007). Slower oscillations (< 8 Hz), in contrast, seem to modulate neural processing through a different mechanism. That is, while sensory processing seems to be influenced by power fluctuations in the higher frequency bands, the momentary phase of an oscillation appears to be the important mediating factor in the operation of slower rhythms (see Bishop 1932; Fries 2005; Lakatos et al 2005; Canolty et al 2007; Jensen & Colgin 2007; Lakatos et al 2007; Lakatos et al 2008; Puig et al 2008). In fact, many studies have shown that the amplitude of faster rhythms (alpha, beta and gamma bands) modulates with the periodicity of slower oscillations (i.e. the delta or theta band). It is believed that these nested-frequency, or phase/amplitude cross-frequency coupling, phenomena provide coordination of neural activity on multiple time-scales and can selectively influence stimulus processing at different levels of the sensory hierarchy by controlling the excitability and stimulus-related responses in local neural ensembles, as well as across more distant cortical neural networks (see Csicsvari et al 2003; Buzsaki 2004; Jones & Wilson (2005); Fries 2005; Lakatos et al 2005; Canolty et al 2006; Lakatos et al 2007; Isler et al 2008; Lakatos et al 2008). Indeed, from a physiological perspective this interpretation is plausible because slow oscillations (< 8 Hz) are relatively robust to phase disturbances, an essential property for communication between large-scale neural networks. Phase disturbances can be expected from axonal conduction delays, which would be more likely for connections between more distant brain regions (e.g. Von Stein & Sarnthein 2000; Buzsaki & Draguhn 2004). Conversely, faster oscillatory rhythms are highly vulnerable to phase 'jitters', and thus they would be more suited for processes occurring at the local network level, where postsynaptic integration times are short. Conceivably, high frequency oscillations may also mediate temporal summation, and perhaps overall oscillatory mechanisms may mediate spatial summation.

A recent non-human primate study showed that during a rhythmic and predictable intersensory attention task, delta-band oscillations in primary visual cortex 'entrained' to the pace of the sensory inputs, which were delivered at a rate of ~1.5 Hz (see Lakatos et al 2008). This delta oscillation observed over supragranular layers was in opposite phase across two conditions where the visual versus auditory inputs of an alternating auditory-visual stimulus stream were attended. It was thus inferred that this type of entrainment forms the basis of a stimulus selection process whereby the relevant inputs occur during the excitable phase of the wave's cycle, while the irrelevant or distracting inputs fall within the inhibitory phase (see Schroeder and Lakatos et al 2009). An additional finding was that the amplitude of higher-frequency rhythms (theta and gamma band) modulated in accordance with the phase of the entrained delta oscillation. Similar cross-frequency coupling effects were observed by Canolty and colleagues (2006) humans while engaged in a wide range of sensory-motor and cognitive tasks such as passive and active auditory listening, mouth movement and articulation, visual search, and facial emotion recognition. Specifically, coupling was observed between theta phase (4 – 8 Hz) and gamma-power (80 – 150 Hz) in the anterior portion of the middle frontal gyrus (MFG).

The current study was primarily designed to investigate mechanisms of entrainment in humans and further establish their role in sensory selection. We recorded electro-corticographic (ECoG activity from electrodes placed subdurally on the cortical surface in two patients undergoing intracranial mapping due to intractable epilepsy. Participants were asked to bias attention on a block-by-block basis to a particular sensory modality (auditory or visual) and to detect a target stimulus in the attended modality only. The paradigm departs from that of Lakatos et al (2008) in two critical aspects. First, the vast majority of stimuli were a composite of auditory and visual inputs, with only few unisensory visual or auditory inputs presented unpredictably. This is an important distinction from the paradigm of Lakatos et al (2008), where the auditory and visual inputs were presented in a regular interdigitated sequence (i.e. A, V, A, V, A, …), directly promoting a regular alternation of intersensory attention. Given this regular alternation of inputs, it is possible that an anticipatory "set" was invoked on a trial-by-trial basis in early visual cortex on the basis of the knowledge of each upcoming stimulus modality. In order to establish the universality of entrainment as a tool of sensory selection, we must determine whether it operates in scenarios where sensory input is rhythmical, but the composition of the input is largely unpredictable. Second, we employ a fixed stimulation rate well below the delta-band (0.67 Hz, – i.e. a stimulus every 1.5 seconds). While entrainment has been observed for stimulation rates lying well within the traditionally-defined delta band (1-3 Hz; see Lakatos et al 2008), it is unknown whether and in what form oscillatory entrainment occurs for slower, sub-delta rates. It is possible that the rhythmic shifting of excitability can only operate within a delimited frequency-band around the delta rhythm (1-3Hz - i.e. that there are upper and lower limits on the period of an entrainment-rhythm cycle). If this is the case, entrainment may play out such that more than a single oscillatory cycle intervenes between successive stimuli. Alternatively, it is possible that delta-band activity is not malleable enough to precisely align with the frequency of the stimulation beat if that beat doesn't match the intrinsic delta period. If this is the case, then it would be expected that a more diffuse phase-ordering occurs since the phase of this rhythm incorporates an adequate temporal window for processing of relatively sparsely presented stimuli.

Here we employ various time-frequency analyses to characterize the operation of entrainment mechanisms during rhythmic multisensory stimulation bearing the above specific features. In particular, we test whether the phase of an entrainment rhythm is reversed across attention conditions (attend-auditory versus attend-visual), indicating an active role in sensory selection across modalities. A further question we test is whether the amplitude of higher-frequency rhythms modulate as a function of the phase of the entrained oscillatory cycle, similar to the phase/amplitude cross-frequency coupling reported by Canolty et al (2006) and Lakatos et al (2008).

We also assayed the involvement of alpha-band activity in sensory selection during the intersensory task. Several non-invasive EEG studies, from our lab and others, have shown that alpha-band activity over visual cortical areas selectively operates on relevant and irrelevant visual inputs during attentional operations in visuo-spatial and audio-visual intersensory tasks (see Foxe et al 1998; Worden et al 2000; Fu et al 2001; Kelly et al 2006; Thut et al 2006; Doesburg et al 2008; Gomez-Ramirez et al 2007). Here, we investigated whether similar mechanisms are instantiated at the earliest levels of auditory cortex. While there is evidence for an alpha-like rhythm generated within auditory regions from magneto-encephalography (Fujioka & Ross 2008), and from human intracranial recordings (see Niedermeyer 1990; Tiihonen et al 1991; Kaufman et al 1992; Lehtelä et al 1997), it is unknown whether it plays a role in sensory selection. The lack of evidence for attentional biasing of alpha in auditory areas may be because auditory alpha simply does not propagate well to the scalp surface given the relatively long trajectory to the fronto-central scalp from the auditory structures along the supra-temporal plane. Alternatively, this alpha selection mechanism may be exclusive to cortical regions coding for visual inputs only. We take advantage of the temporal and anatomical precision of the intracranial recording technique here to directly address this issue.

3. RESULTS

ECoG activity was recorded from two cognitively-healthy individuals while they were engaged in a highly demanding audio-visual intersensory task. A rhythmical stream of sensory input was induced by presenting an auditory sound every 1.5 seconds on 90% of the events. Visual stimuli were concurrently presented using five different stimulus onset asynchrony (SOA) values (0, 13, 25, 67, and 140). Participants were instructed to bias attention for an entire block of trials to the auditory or visual modality and to detect a target in the attended modality only. Behavioral performance was adapted online to ensure that participants were highly motivated and to equate for task-difficulty. We employed a set of time-frequency analysis techniques to characterize entrainment mechanisms during this rhythmical attention task between auditory and visual inputs.

Behavioral analyses:

D-prime measures were computed for each attention condition collapsed across stimulus-type and SOA variables. Participant MDJ had d-prime values of 2.49 and 2.36 for the auditory and visual conditions, respectively. Participant BD had d-prime values of 2.71 and 2.53 for the auditory and visual conditions, respectively.

Electrode Localization: MRI & ERC activity:

Figure 2 shows event-related current (ERC) activity, collapsed across attention conditions, for adjacent pairs of electrodes localized to regions in-and-around primary auditory cortex. We identified a single electrode in each participant that could be most clearly localized to primary auditory cortex (A1, or Brodmann area 41) on the basis of the MRI and neurophysiological activity. For participant MDJ this was electrode E14 (talairach coordinates 59, -25, 11) and for BD it was E10 (57, -20, 11). These A1-electrodes show an initial stimulus-locked ERC component peaking at ~45 - 55 ms (positive for MDJ, negative for BD; see Figure 2), followed by a substantial deflection of the opposite polarity peaking at around 80-100 ms past stimulus onset. The latter coincides with the timeframe of the typical auditory N1 ERP component observed in surface electrode recordings (Naatanen et al 1981; Naatanen et al 1982; Beer and Roder 2005; Molholm et al 2007).

Additional electrodes close to these A1-electrodes are also shown to illustrate the spatial resolution provided by the electrode grid and the clear dipolar field activity over early auditory sites. The MRI data indicated that electrode E15 in participant MDJ was located over Brodmann (BA) area 41 (59, -22, 5). Further, electrodes E19 and E21 in the same participant were placed over BA 22 (61, -38, 15 and 61, -24, 5, respectively), while electrodes E10 and E13 were placed over BA 43 and 40, respectively (53, -7, 13 and 58, -27, 20). Electrode E11 in participant BD was also localized to BA 41 (57, -12, 7). Furthermore, electrode E9 was located over BA 42 (57, -27, 14), while electrodes E3 and E16 in the same participant were located over BA 2 and 21, respectively (57, -22, 28 and 58, -22, 1).

Frequency spectrum

We first wished to examine oscillatory components present in the data that may have a hand in entrainment. Figure 3a (upper panels) shows the 6-second FFT spectrum from 0.33 to 100 Hz for both attention conditions in electrodes E14 in participant MDJ & E10 in participant BD. The inside graphs in Figure 3a zoom in on the spectrum in the range from 0.33 to ~4 Hz. During blocks where attention was deployed to the auditory modality, the FFTs show peaks in amplitude in the 0.67, 1.33, 2.67, and 3.33 Hz components, multiples of the induced 1.5-second rhythmic pattern (i.e. 0.67 Hz) in both participants. For the attend-visual blocks, the same pattern was observed for participant BD, but only a single peak was observed in the 1.99 Hz component for participant MDJ.

Histograms in Figure 3a show the phase distributions of the 0.67 Hz cycle in the same electrodes at 0ms (the onset of the auditory tone) for each attention condition. The Rayleigh test for non-uniformity showed that attention to both auditory and visual modalities elicited a significant phase organization (attend auditory R = .54, attend visual R = .21 participant MDJ – attend auditory R = .42, attend visual R = .36 participant BD). When testing for differences in phase-distribution across attention conditions, we found that they were statistically different from each other in participant MDJ (Yr = 6.989, $p < .05$) and in participant BD (Yr = 3.37, $p < 0.05$). Similar results were observed for the 1.33 Hz frequency component.

Figure 3b (upper panels) shows the 6-second FFT spectrum in the same electrodes from 0.33 to 5 Hz, with the mean ERC activity subtracted away in each single trial. The results revealed peaks in similar frequency components as in the FFT graphs of Figure 3a. However, the statistics derived from this subtracted-ERC analysis indicate that the phase-distributions of the 0.67 Hz component at 0ms are uniform in both attention conditions and in both participants (lower panel histograms in figure 3b). Similar results were observed for the 1.33 Hz frequency component (not shown in the figure). The mean ERC, residual and Hilbert-transformation of the residual activity is shown in supplementary Figure 1. Briefly, the data indicate that ERC activity was variable across trials, thus the average ERC did not completely remove the total power evoked by the auditory stimulus. This might explain why the ERC-subtracted FFT still exhibited peaks in the 0.67 frequency component and its harmonics.

Time-Frequency (TF) Domain: Attention effects in the ERC activity

Figure 4a shows the TF-spectrum from 1 to 70 Hz for both attention conditions, and their difference (attend auditory minus attend visual). Figure 4b shows the time-course of the alpha-band activity in both participants. Non-parametric statistical testing revealed an effect of attention in the alpha band (8 – 14 Hz) in both participants during the period between 0-400ms post stimulus onset (MDJ z-score = -1.19, $p < 0.05$; BD z-score = -.78, $p < 0.05$). Consistent with our hypothesis, attending to the visual modality resulted in greater alpha-band power than attending to the auditory modality. This effect is best captured in Figure 5c where the alpha-band trajectory for the visual-alone trials is presented. Alpha-band activity during the attend-visual blocks increased at the time the expected auditory stimulus would be presented. The reader should note that although the Montecarlo simulation revealed statistically significant effects, the z-score values associated with each participant's distribution are below the ±1.96 threshold level. We performed a 1-second FFT analysis (-500 to 500 ms relative to auditory stimulus onset) to show that an oscillatory rhythm in the alpha-band is present in auditory cortices. This data is presented in supplementary figure 2. Briefly, the FFT-spectrum revealed an amplitude-profile resembling those observed over visual cortices. Particularly, an increase in oscillatory power in the alpha band was observed in both attention conditions and in both participants. However, it is clear that these alpha-band peaks do not exhibit the same 'tuning' characteristics as seen in the alpha-band frequency components in visual-related areas.

The statistics also revealed attention effects in the upper beta-band (20 – 30 Hz) in the period between 0 – 120 ms after stimulus onset for both participants (MDJ z-score = 2.01, $p < 0.05$; BD z-score = 0.71, $p < 0.05$). The data showed that attention to the auditory modality results in greater upper beta-band power than attention to the visual modality. In addition, the data revealed attention effects in the lower gamma-band (45 – 60 Hz) in the period between 0 – 100 ms (MDJ z-score = -.67, $p < 0.05$; BD z-score = -.52, $p < 0.05$). In this case however, and similar to the findings in the alpha-band, the data showed that attention to the visual modality results in greater activity than attention to the auditory modality. No effects were observed over higher frequencies.

Cross-frequency coupling

Figure 5a (left panel) shows alpha band (8-14 Hz) amplitude sorted as a function of a delta (1.33 Hz) cycle for both participants. We found a phase-reversal of the alpha amplitude time-course across attention conditions with respect to a 1.33 Hz oscillatory cycle. The weakest alpha amplitude response was seen at approximately $-\pi/2$ in terms of the oscillatory-phase of the delta cycle when attention was directed to the auditory modality, while this $-\pi/2$ point was the phase of the strongest alpha response when attention was deployed to the visual modality. Similarly, when attention was deployed to the auditory modality, the strongest alpha-band amplitude value was observed approximately at the delta-phase point $\pi/2$, while this phase $\pi/2$ point resulted in the weakest alpha-band response when attending to the visual modality. Figure 5b (center panel) display the TF plots for the visual-alone stimuli (e.g. at time = 0 only a visual stimulus was presented) for both participants. The figure shows alpha-band amplitude modulating during this 3-s period (i.e. -1500 to 0 ms, and 0 to 1500 ms) in the absence of sensory evoked activity at time = 0. Figure 5c (right panel) displays the time-course of alpha-band activity for the visual-alone stimuli. Cross-frequency phase-amplitude coupling effects were not observed between the 0.67 or 1.33 Hz cycles and higher frequency band in the beta and gamma bands.

4. DISCUSSION

The present study investigated the effects of attention on oscillatory activity emanating from primary auditory cortex while participants engaged in a highly demanding intersensory attention task. A sound was presented every 1.5 seconds (e.g. 0.67 Hz) in order to induce a rhythmic sequence of events with predictable timing. Visual stimuli were presented simultaneously with or within 140ms of auditory stimuli. Participants were required to maintain attention to one sensory modality throughout the entire block of trials, and detect a target stimulus in that sensory modality only. Spectral analysis revealed amplitude peaks in a frequency component matching that of the stimulation rate (0.67 Hz), as well as peaks at multiples of this frequency. Further, the phase distribution of these oscillatory components was significantly different across attention conditions at stimulus onset. On the basis of this alone, however, it is difficult to infer the presence of oscillatory entrainment at either the stimulation rate or harmonics thereof. Time-frequency mapping of amplitude variations of higher-frequency rhythms provided more compelling evidence in this regard. Cyclic variations of alpha amplitude in particular were visible, with two cycles interposed between each consecutive stimulus in the sequence. Further, phase-amplitude cross-frequency coupling was found between the oscillatory-phase of a delta oscillation at this frequency (1.33 Hz) and power in the alpha band (8-14 Hz) in both attention conditions. Critically, alpha-band power was significantly greater at the arrival and during sensory processing of the auditory stimulus when attention was apportioned to vision compared to audition, and the phase/amplitude coupling occurred at opposite phases.

Attention effects on oscillatory amplitude were observed in the higher frequency bands alpha (8-14 Hz), upper-beta (20 – 30 Hz), and lower-gamma (45 – 60 Hz). In contrast, oscillatory-phase attention effects pertained to lower-frequency oscillations in the delta-band (e.g. 1.33 Hz), as reflected in the cross-frequency delta-alpha band effect.

Taken together, the data indicate that attention can exert its effects at relatively ‘early’ processing stages in-and-around primary auditory cortex, and that during a rhythmic and predictable task higher-order oscillatory mechanisms are instantiated, presumed to be involved in suppression and enhancement processes in early sensory cortex. Furthermore, the current dataset provides strong support for the hypothesis that higher-order oscillations (> 8 Hz) operate through power fluctuating mechanisms, while lower-order oscillations (< 8 Hz) influence neural activity through phase-dependent mechanisms. In what follows, we describe in detail the neurophysiological findings reported herein.

Oscillatory entrainment & hierarchical organization of oscillatory cycles:

The present study investigated whether oscillatory entrainment mechanisms are instantiated at temporal scales greater than the delta-band rhythm (i.e. below 1 – 3 Hz). Two possible scenarios were envisioned. First, lower-frequency oscillations may entrain precisely to the driving rhythm of the task, and it would be expected that a frequency component of 0.67 Hz be evidenced in both attention conditions. Furthermore, it was expected that the oscillatory-phase distributions across both attention conditions be significantly different from each other. Second, it could be that oscillatory entrainment only operates within a delimited frequency-band around the delta rhythm. If this was the case, entrainment played out such that more than a single oscillatory cycle (with a frequency matching a harmonic component of the stimulation rate) intervened between successive auditory stimuli.

Supporting previous theories of entrainment mechanisms, the present study suggests that in the presence of a detectable rhythmic pattern, neuronal oscillations ‘entrain’ to the temporal structure and top-down attentional signals reorganize the phase of these oscillations as a stimulus selection mechanism in early sensory cortex. Our data revealed amplitude peaks in the FFT spectrum of the 1st and subsequent harmonic components of the stimulation rate. Furthermore, the phase-distributions of both attention conditions were significantly non-random, and more importantly, significantly different from each other. It is not clear, however, whether these effects may have been mostly driven by the sensory evoked response of the auditory stimulus itself, rather than by top-down endogenous attentional mechanisms.

We conducted post-hoc analyses to ensure that the oscillatory peaks in the FFT and the significant non-random phase distributions were not an artifact of the evoked response elicited by the auditory stimulus. Indeed, phase-locking effects can occur by the evoked response of a sensory stimulus, by induced phase-resetting of ongoing oscillations, or by a combination of both (see Makeig et al 2004; Shah et al 2004). Although we found no significant differences in the power of the 0.67 Hz oscillation before and after the stimulus onset, we found that by subtracting the average ERC activity from each single trial, the oscillatory-phase distributions in both attention conditions were purely random. Similar findings were observed for the 2nd, 3rd and 4th harmonic of the base frequency component.

The results however, revealed a systematic relationship between lower and higher frequency oscillations, in that the phase of a delta cycle (1.33 Hz) modulated the power of an alpha-band (8 - 14 Hz) oscillation. This delta cycle corresponded to the 2nd harmonic component of the stimulation rate (e.g. 0.67 Hz). We observed a counter-phase relationship across attention condition within this cross-frequency coupling effect. That is, when attention was deployed to the auditory modality the highest peak in the alpha-band amplitude occurred at the approximate instantaneous phase point ‘π/2’ of the delta cycle. In contrast, when attention was apportioned to the visual modality that same instantaneous-phase point resulted in a close-to-zero value in the alpha band amplitude.

It is highly intriguing that the oscillatory-phase of this delta oscillation falls exactly within an integer multiple of the stimulation stream. This finding is in line with our second hypothesis that oscillatory entrainment operates within a delimited frequency-band around the delta rhythm and will align to a frequency matching a harmonic component of the stimulation rate in situations where the temporal beat is below the lower limits of the delta-band. It is also intriguing that we failed to find significantly non-random phase-distributions in this delta cycle in the post-hoc analysis stage (e.g. when the average ERC was subtracted from each single trial). This pattern of effects implies that this delta-band phase effect is not generated within ‘local’ cortices (i.e. auditory cortex) but most like originates from higher-order attentional control regions. These in turn, modulate the local sensory mechanics that either enhance or suppress the incoming sensory inputs depending on the stimulus relevance. Indeed, we contend that this represents a nice and somewhat comprehensive mechanistic model of sensory gain control in early sensory cortex.

The question becomes, why is the delta-band cycle the preferred oscillatory rhythm operating in this attention-based mechanism? While the answer is not clear, it is believed that many of the inputs generated in the external world occur at rates within this band. For example, several recent studies indicate that sensory inputs such as auditory rhythm and intonation, which are critical processes for speech perception, are conveyed at rates of 1-3 Hz (see Munhall et al 2004; Schroeder et al 2008). It is also argued that since facial gestures and head movements often coincide with these prosodic inflections that they may also carry significant energy in the 1-3 Hz range (see Schroeder et al 2008). In fact, a recent fMRI study showed that multisensory integration between audio-visual speech stimuli in the superior temporal sulcus (STS) was significantly greater when the SOA between stimuli were -300, 0 and +300 ms, in comparison to -150 and +150 ms (see van Atteveldt et al 2007). The remind the reader that the former SOA values correspond to time periods fitting a cycle of a 3.33 Hz oscillation, while the latter SOA values correspond to ½ a cycle of a 3.33 Hz wave. However, one should bear in mind that these are only a few examples, and they do not hold during other situations such as hand movements and certain visual-spatial exploration, just to name a few.

Alpha-band oscillations in human auditory cortex:

The second aim of this study was to investigate whether an alpha-band rhythm would be observed in an intersensory attention task in human auditory cortex, and whether it influences sensory processing, by enhancing and/or suppressing sensory inputs, at relatively ‘early’ stages in auditory cortex. Indeed, several non-invasive EEG studies have shown that alpha-band mechanisms selectively operate on relevant and irrelevant visual inputs during attentional operations in visuo-spatial and intersensory tasks over visual areas. By taking advantage of the superb temporal and anatomical resolution of our recording technique, we show that active suppression mechanisms operating within the alpha-band are also instantiated in ‘early’ regions of auditory cortex. We show that when attention is deployed to vision, greater alpha-band power is observed at the arrival and during stimulus processing of the auditory stimulus. These findings further support the role of the alpha frequency as an active gating mechanism in early sensory cortex.

To the best of our knowledge, this is the first account of an attentional modulating alpha-band effect in ‘early’ auditory cortex. Previous studies investigating auditory alpha aimed to characterize biasing attentional mechanisms in anticipation of a target stimulus. For instance, Bastiaansen and colleagues (2001) conducted a study to characterize event-related desynchronization (ERD) in the alpha-band in auditory and visual cortices during a temporal prediction task. The authors found enhanced alpha ERD (i.e. lower post-stimulus with respect to pre-stimulus power) over visual cortices in response to visual attention, but no evidence of an alpha-band effect over auditory cortices in response to auditory attention. In a separate study, Fu et al (2001) investigated preparatory alpha-band attentional mechanisms during an intersensory task to the auditory and visual modalities. The authors showed that when subjects biased their attention to the auditory modality an increase in the alpha-band power over parieto-occipital cortices is evidenced. As in Bastiannsen et al (2001), however, no evidence of an alpha-band effect was observed over auditory cortices.

Alpha-band, or so-called ‘tau’, rhythms in human auditory cortex have been reported in the literature (see Niedermeyer 1990; Tiihonen et al 1991; Kaufman et al 1992; Lehtelä et al 1997). Niedermeyer (1990) first reported this rhythm in auditory cortex in patients suffering from intractable epilepsy with implanted electrodes inside the skull. It was suggested that this cortical auditory rhythm exhibits very low signal-to-noise ratio (SNR) when recorded at the scalp level, and this might be the major reason why reports have been so scarce. Using MEG technology, which typically yields higher SNRs for activity generated in auditory cortices, Lehtelä and colleagues (1997) reported measuring a ‘tau’ rhythm (6.5 – 9.5 Hz) while subjects were passively stimulated with 500ms auditory pure tones. Our data further support the notion of an alpha-band oscillatory rhythm in auditory cortex, and more importantly, it demonstrates that this oscillation plays an active role during sensory amplification and/or attenuation of relevant and/or irrelevant inputs, respectively.

Oscillatory mechanisms in upper-beta and lower-gamma frequency bands:

We found that attention to the auditory modality resulted in greater upper-beta band (20 – 30 Hz) power than when attention was apportioned to the visual modality. This effect occurred within the early stages of stimulus processing (i.e. < 125ms after stimulus presentation). Previous studies have linked beta-band oscillations with behavior. For instance, Senkowski and colleagues (2006) found a systematic relationship between reaction time of multisensory trials and beta-band power across subjects. Further, Caplan & Glaholt (2007) found that beta oscillations co-vary with memory performance, while Leiberg and colleagues (2006) found a relationship between memory load and beta-band power. Thus, it seems that beta-band oscillations may play a more distributed role over general cognitive processes and performance, and less of a specific role in mechanisms of attentional selection. However, this notion should be regarded with caution until validated through further investigation.

We also found that attention to the visual modality enhanced activity in lower gamma (45 – 60 Hz) during the early periods of stimulus processing. This finding is highly intriguing and paradoxical since most attention studies have reported enhanced gamma-band activity in sensory regions matching those of the attended sensory modality (see Senkowski et al 2005; Karns & Knight 2008; Lakatos et al 2008). However, a previous study by Sokolov and colleagues (2004) found lower gamma activity (~ 33 Hz) in the neural regions coding for unattended inputs, and it was hypothesized that this reduced gamma activity might reflect an active suppression mechanism of the task-irrelevant sensory inputs. Indeed, similar mechanisms might have been instantiated during our task. It is plausible that several sub-bands operating within the gamma-band might operate through suppression-like mechanisms, while other sub-bands (e.g. higher-scale gamma-rhythms) might operate through enhancement mechanisms. However, that in our study we only find evidence of gamma-band rhythms operating through suppression-like mechanisms is an indication that this notion should be taken with prudence. Nevertheless, this is an issue that merits further investigation.

5. METHODS

Intracranial recordings were obtained from two patients (MDJ and BD, 40 and 37 year olds, respectively) suffering from intractable epilepsy. No seizure activity was observed in the cortical regions investigated herein. All participants were on anti-seizure medication at the time of recording, and all neuropsychological tests were within normal limits. Language was left lateralized as determined by Wada testing. Participants provided written informed consent and the procedures were approved by the Institutional Review Boards of the Nathan Kline Institute, Weill Cornell Presbyterian Hospital, and the City College of the City University of New York (CCNY).

Experimental Paradigm

The sequence of events in a typical block is illustrated in Figure 1a. We implemented a rhythmic task by presenting an auditory stimulus every 1500 ms (i.e. 0.67 Hz stimulus presentation rate). All visual stimuli were presented with a stimulus onset asynchrony (SOA), with respect to the auditory stimulus, of 0, 13, 25, 67, or 140 ms.

A central cross (black and ~1° angle) was presented on the screen throughout the experiment, and participants were instructed to maintain fixation at all times. Visual stimuli were displayed on a gray background, while all auditory stimuli were presented through headphones. Participants were instructed on a block-by-block basis to bias attention to the auditory or visual modality, and detect a deviant target in the relevant modality only. Each block contained a total of 120 trials, giving a block run-time of 3 minutes. Participant MDJ performed a total of 9 blocks (5 attend auditory and 4 attend visual), while participant BD performed a total of 18 blocks (9 attend auditory and 9 attend visual). Two attend-visual blocks of participant BD were excluded from analysis on account of poor performance (>10 misses and 10 false alarms) due to a self-reported lack of attentional focus or tiredness.

In a given block, 80% of the stimuli were bisensory, and the visual portion of the bisensory stimulus was delayed using five different SOAs (see above) relative to the onset of the auditory stimuli. Further, 10% of the stimuli where auditory-alone, and the remaining 10% were visual-alone. The auditory stimulus consisted of a binaural, continuous pure tone (1000 Hz, 80 dB SPL, 100 ms duration, 5 ms rise/fall, 5 ms interval between tones). The visual stimulus consisted of a pair of gabor patches (4.5° in diameter, centered 2.5° to the left and right of fixation, 100 ms duration, 10 cycles/degree). The audio-visual bisensory stimuli were a combination of the above-described auditory and visual stimuli. All visual stimuli were presented on a Dell Trinitron Ultrascan P780 17” Cathode Ray Tube Monitor, on a gray background running with a 60 Hz refresh rate. Eye position was closely monitored by the experimenters throughout the entire task.

On 85% of visual stimuli (standards), the two Gabor patches were identical and no overt response was required. On the other 15% (targets), the orientations of the left and right Gabor patches were slightly different (see below) and subjects responded to these targets with a button push during the blocks where attention was apportioned to the visual modality. For 85% of the auditory stimuli (standards), the tone had no discontinuity in the signal and no response was required. For the other 15% (targets), there was a slight discontinuity in the middle segment of the tone (a gap) and subjects were required to press a button upon detection during those blocks where attention was apportioned to the auditory modality. All combinations of incongruent (e.g. a deviant auditory stimulus paired with a standard visual stimulus, and vice versa) and congruent targets were presented.

The difficulty in detecting a target was adapted online based on the participant's performance. We implemented this adaptive task difficulty approach to minimize task difficulty differences across sensory modalities and to keep the participants highly motivated throughout the task. The difficulty levels in the auditory tone were achieved by attenuating the amplitude in the middle of the signal (i.e. 47 – 52 ms) by a particular value. The values were chosen using a logarithmic scale, with a 100% attenuation in the lowest difficulty level and a 5% attenuation in the highest level. In the visual modality, the level of difficulty was also adapted using a logarithmic scale. The lowest level of difficulty between the two Gabor patches was an angular difference of 54º, while the highest level of difficulty was an angular difference of just 1º (see Figure 1b for a visual illustration of the target stimuli). Neither participant reached the highest or lowest level of difficulty in either sensory modality.

Before the start of the experiment, participants performed several practice runs to set the initial target difficulty level, and to become familiar with the experimental setup. Thereafter, difficulty level was decreased in the event of either a single miss or two false-alarm responses in a row, and increased one level in the event of two hits in a row. Feedback on behavioral performance (i.e. amount of hits, misses, false alarms, and correct withholds) was given at the end of each block. The participant was also explicitly instructed that there would be a sound presented every second and a half, regardless of the attended block, as an additional effort to emphasize the rhythmic pattern of the task.

EEG Measurements

Continuous EEG from intracranial electrodes was acquired using a BrainVision amplifier system. The electrodes used here are highly sensitive to local field potentials (LFP) generated within ~4.0 mm3 area, and are much less sensitive to distant activity (Allison et al 1999; Lachaux et al 2005; Sehatpour et al 2008). EEG recordings were obtained using a multi-array grid electrode setup composed of 48 linear contacts (6 rows x 8 columns, 10mm inter-contact spacing), which covered a large portion of the surface of auditory cortex, including primary and secondary cortex. Both participants had the multi-array grid electrode placed over the right hemisphere. An electrode located over frontal cortex served as the reference. The data were bandpass-filtered online from 0.05 to 250 Hz and digitized at 1,000 Hz. The data were analyzed offline using a ±1200 µV artifact rejection criterion. Two notch filters at 60 and 120 Hz and a linear-detrend method were applied to the raw data offline. The EEG recordings were not obtained immediately before or after seizures. High-resolution pre-surgical MRIs were coregistered with post-surgery MRIs for the derivation of the electrode coordinates and reconstruction into 3D images.

Data Analysis:

Behavioral analysis

D-prime values were calculated for each participant. D-prime values quantify the sensitivity of identifying a deviant stimulus, independent of response criteria.

Data referencing: Event related currents (ERC)

Two-dimensional current source density (CSD) profiles were calculated using a five-point formula (see below) to estimate the second spatial derivative of voltage in the vertical and horizontal axis. CSD profiles provide an index of the location, direction, and density of transmembrane current flow, the first-order neuronal response to synaptic input (Nicholson & Freeman 1975; Mitzdorff 1985; Schroeder et al 1995; Schroeder et al 1998; Lakatos et al 2005; Chen et al 2007, see equation below).

$$\mathbf{CSD_{i,j} = 4 \times (V_{i,\,j}) - (V_{i+1,\,j}) - (V_{i-1,\,j}) - (V_{i,\,j+1}) - (V_{i,\,j-1})}$$

Where ‘$V_{i,\,j}$’ denotes the recorded field potential at row ‘i’ and column ‘j’ in the electrode grid. CSD profiles for electrode contacts located in the borderline of the grid were not calculated because of the lack of nearest neighbors.

Anatomical localization of electrodes based on MRI data

The BrainVoyager 4.9 software package was used to analyze the anatomical MRI data (Goebel et al 1998). High-resolution presurgical MRIs were coregistered with postsurgery MRIs using a method that lines up the anterior and the posterior commissures. These were reconstructed into three-dimensional (3D) images. Afterwards, the 3D coordinates of each electrode were calculated from the postsurgery MRI and mapped to the presurgery MRI. The MRI data were then transformed into Talairach space (see Talairach and Tournoux, 1988) for the localization of each electrode contact based on the Talaraich Daemon library (Lancaster et al 2000).

Anatomical localization of electrodes based on EEG data

Accepted trials were epoched from -100ms to 500ms post-stimulus onset. The baseline was defined as the mean current from 100ms to 0ms before the onset of the auditory stimulus. In order to characterize ‘pure’ sensory evoked activity, the ERC activity for all accepted audio-visual bisensory stimuli in both attention conditions were collapsed. The term ERC signifies ‘event related current’ and is similar to the event-related-potential (ERP) data, in that both are derived using the same algorithm. However, the ERC indexes activity in the current-domain, and is reference-independent, while the ERP indexes voltage activity and uses a reference location. Only trials where a non-target (in both modalities) bisensory stimuli was presented and no overt response was recorded were analyzed.

To characterize a sensory evoked activation, difference waveforms were calculated for each trial by subtracting the average activity from –100 to –50ms from the whole epoch. Statistical testing of sensory evoked effects was achieved by computing Montecarlo simulations on these difference waveforms and comparing the ‘observed’ z-score value against the simulated Montecarlo distribution (see Maris et al 2007 for non-parametric testing of neurophysiological processes). The ‘observed’ z-score was computed for each single time point in each electrode of interest (see Figure 2). The Montecarlo simulation was derived by computing the z-score of a random collection of the total sampled trials. This process was repeated 5000 times. We deemed a statistically significant effect when the following two criteria were met: (1) the observed 'z-score' value, in each dipolar moment, was less or greater than ±1.96, and (2) the observed z-score was situated above or below ±1.96 standard deviations away from the mean of the Montecarlo distribution.

Frequency domain analysis (FA):

To characterize the dominant oscillatory cycle, an FFT was performed on the CSD activity for each attention condition. This FFT was performed on a 6-second time window centered on the onset of each accepted trial (-3000 to 3000 ms). Such a broad time interval allowed for a 0.1667 Hz resolution in the FFT spectrum. Note that for all FA and time-frequency analyses, the first five observations in every block of trials were discarded in order to ensure that the rhythmicity of the task had been reestablished[17]

Time-frequency domain analysis (TFA):

Instantaneous power and phase activity was characterized on a single trial level by a Morlet wavelet decomposition method on the CSD measurements as implemented in the Fieldtrip MATLAB-based software version# 2008-04-05 (see http://www.ru.nl/fcdonders/fieldtrip/). This procedure provides an index of 'induced' activity (e.g. phase-locked and non-phased locked activity) as a function of time (see Tallon et al 1995; Sutoh et al 2000; Lakatos et al 2007). Before any time-frequency analysis (TFA) was conducted, the raw CSD signal was linearly de-trended. For each accepted epoch, the wavelet decomposition was computed from 0.67 to 115 Hz. In order to avoid edge filter artifacts, accepted trials were epoched separately (-2000ms pre-

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[17] The reader should recall that participants were explicitly told that the task had a rhythmical pattern by presenting an auditory stimulus every 1.5 seconds.

stimulus to 2000ms post-stimulus) time-locked to the onset of the auditory stimulus. The baseline was defined as the mean voltage from 100ms to 0ms before the onset of the auditory stimulus. Separate averages were made for the two attention conditions (Attend-Auditory, Attend-Visual).

To test for significant attention effects, the ‘observed’ z-score value was compared against a simulated distribution derived by a Montecarlo procedure. The ‘observed’ z-score was computed for each single time point in each of the electrodes of interest. The Montecarlo simulation was derived by computing the z-score of a random collection of the total sampled trials. This process was repeated 5000 times. To establish a statistically significant effect the same criteria as in the ‘*anatomical localization of electrodes based on EEG data*’ section was used.

Instantaneous phase statistics:

In order to estimate the phase distribution across trials, the mean angle and the resultant length of the mean vector (mean resultant length, R) were calculated at each frequency from each accepted EEG trial at the onset of the auditory stimulus. To estimate the mean resultant length ‘R’, each observation was treated as a unit vector (i.e. a normalized observation). A unit vector was computed by dividing each observation by its magnitude (i.e. the absolute value). R was then calculated by taking the mean across all observations. The mean resultant length ranges from 0 to 1; higher values indicate that the observations (i.e. phase at a given time point across trials) are clustered more closely around the mean than lower values. The distribution of phase (across trials) was analyzed using circular statistical methods, and the phase distribution was tested against the null hypothesis of uniformity using the Rayleigh statistic. A condition was deemed to elicit significant phase resetting if it exceeded a significance threshold ($p < 0.05$).

To test for differences across both attention conditions, pooled phase distributions were compared by a nonparametric test for the equality of circular means (see Fisher, 1993; Rizzuto et al 2003; Rizzuto et al., 2006; Lakatos et al 2007). The alpha value was set at 0.05 for all statistical tests.

Cross-frequency coupling:

We derived oscillatory amplitude in the delta, theta, alpha, beta and gamma bands as a function of oscillatory phase of the 0.67 Hz frequency cycle at time = 0 (e.g. the onset time of the auditory stimulus). Phase/amplitude cross-frequency coupling (or nested frequency) effects were also calculated for amplitudes of the theta, alpha beta and gamma bands and the phase of the 2nd, 3rd, and 4th harmonic of the 0.67 Hz component, as well as the delta (1 – 3 Hz) frequency band at time = 0. To accomplish this, we sorted the phase values obtained from the wavelet-transformed epochs from $-\pi$ to $+\pi$ radians. We then applied the permutation vector obtained from sorting the phases to the oscillatory amplitude values (see Lakatos et al 2005; Lakatos et al 2008).

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7. FIGURE LEGENDS

Figure One: Sequence of Trials

Each block consisted of 120 trials. A trial was composed of an auditory-alone (10%), a visual-alone (10%), or a bimodal (80%) stimulus. The inter-trial-interval (ITI) was set to 1500 ms. The SOA between the auditory and visual stimuli randomly varied between 0, 13, 25, 67, and 140ms. Subjects were required to respond with a button push to targets within the attended modality.

Figure Two: Reconstructed MRIs & Broadband Event-Related-Currents (ERC)

Figure 2. Individually reconstructed MRIs from each participant and ERC activity of electrodes placed over and nearby primary auditory cortex. MRI and ERC activity indicate that electrodes E14 & E15 in participant MDJ and electrodes E10 & E11 in participant BD are placed over primary auditory cortex (A1, BA 41). Waveforms illustrate ERC activity to standard bisensory stimuli, collapsed across attention conditions, in electrode pairs that capture dipolar moments during early sensory processing. The gray bars indicate the time interval chosen for testing significant evoked-sensory activity.

Figure Three: FFT & Oscillatory-Phase Distributions

Figure 3a. FFT spectrum between both attention conditions in Electrode E14 (MDJ) and Electrode E10 (BD). The results show peaks in the 0.67 Hz frequency component in the attend-auditory condition but not in the attend-visual condition for participant MDJ, while peaks in the same frequency component in both attention conditions for participant BD. The results also revealed peaks in the harmonic cycles of the 0.67 Hz during both attention conditions and in both participants. The histograms below illustrate the phase distribution of the 0.67 Hz frequency component at 0ms across both attention conditions in the same electrodes. The results revealed significant non-uniform phase distribution for both attention conditions in each participant. Further, the results revealed significant differences between the circular means across both attention conditions in each participant.

Figure 3b. FFT spectrum in the same electrodes as above but with the ERC activity subtracted away. Similar to Figure 3a, the results show peaks in the 0.67 Hz frequency component in both participants. The results also revealed peaks in the harmonic cycles of the 0.67 Hz. The histograms below illustrate the phase distribution of the 0.67 Hz frequency component at 0ms across both attention conditions in the same electrodes. In contrast to the results above, the results failed to reveal significant non-uniform phase distribution for both attention conditions in each participant.

Figure Four: Attention Effects in the Time-Frequency Domain

Figure 4a. Wavelet transform data in electrodes E14 (MDJ) & E16 (BD). The upper time-frequency (TF) plot shows data from 1.33 to 70 Hz (dominant 0.67 Hz component not shown for visual display purposes) when attention is apportioned to the auditory modality. The middle TF plot shows the data associated with attending to the visual modality. The lower TF plot shows the difference between the two attention conditions.

Figure 4b shows the time course of the alpha-band (8-14 Hz) activity in both attention conditions. Alpha-band activity is greater during the pre and post-stimulus interval when attention is directed towards vision. Blue traces correspond to activity when attention was directed to audition, while red traces indexes activity when attention was deployed to vision.

Figure Five: Cross-Frequency Coupling & Oscillatory Amplitude Responses in Visual-Alone Trials

Figure 5a (left panel). Cross-frequency coupling activity between both attention conditions during the bisensory trials. Cross-frequency coupling occurred between the phase of a 1.33 Hz delta cycle (e.g. the 2nd harmonic of the dominant oscillating frequency component) and the power of an alpha-band (8 - 14 Hz). *Figure 5b (middle panel).* Time-Frequency (TF) plots for the visual-alone stimuli at time 0. The figure shows alpha-band amplitude modulating during the inter-trial-interval in the absence of sensory evoked activity at time = 0. *Figure 5c (right panel)* displays the time-course of alpha-band activity for the visual-alone stimuli. Blue traces correspond to activity when attention was directed to audition, while red traces indexes activity when attention was deployed to vision.

Supplementary Material Figure One: ERC activity subtracted from FFT

Top waveforms in participants MDJ and BD illustrate the average ERC activity over 6 seconds that was subtracted from each individual trial when computing the FFT. Graphs 2 and 4 illustrate the residual mean computed from averaging the remaining activity across every trial in each participant. The 3rd and 6th graphs illustrate the Hilbert-transformed activity, on a trial-by-trial basis, of the residual activity. These last graphs indicate that ERC activity was variable across trials, thus the average ERC did not completely remove the total power evoked by the auditory stimulus. This might explain why the subtracted FFT still exhibited peaks in the 0.67 frequency component and its harmonics. Traces in blue show activity when attention is deployed to audition, while traces in red show activity when attention has been apportioned to vision.

Supplementary Material Figure Two: 1-second FFT spectrum (Alpha activity in auditory cortex)

1-second FFT-spectrum between 1- 30 Hz illustrating the presence of an alpha-band oscillation in electrodes over area A1 in both participants. The FFT-spectrum revealed an amplitude-profile resembling those observed over visual cortices. Particularly, there is increased oscillatory power in the alpha band, as indicated by the arrows that point to the frequency component with maximal power within this band. It is clear however, that these peaks do not exhibited the same ‘tuning’ as seen in the visual-related areas, which is interesting in itself. Traces in blue show activity when attention is deployed to audition, while traces in red show activity when attention has been apportioned to vision.

8. FIGURES

Figure 1

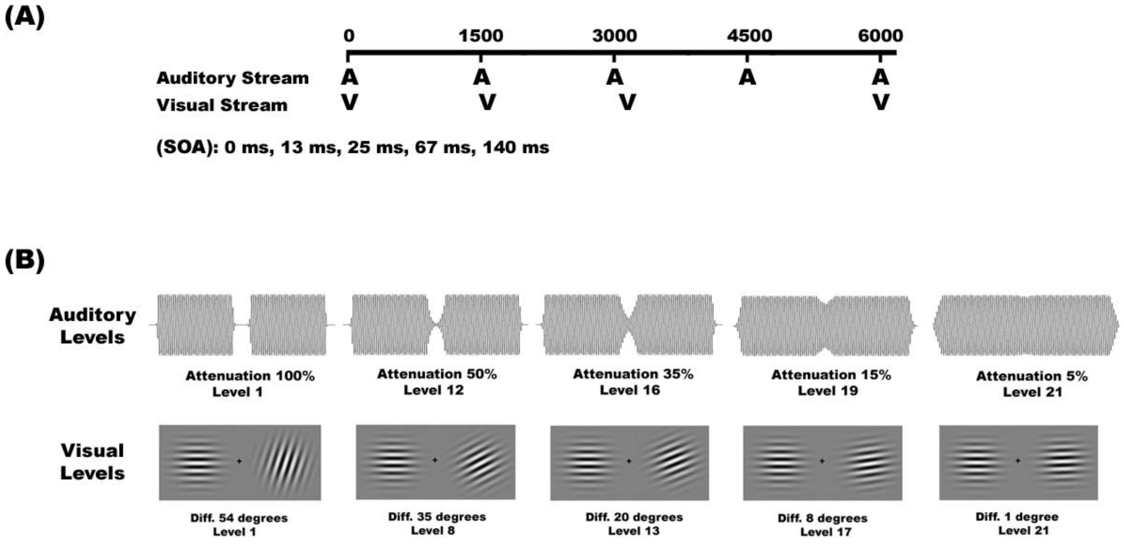


Figure 2

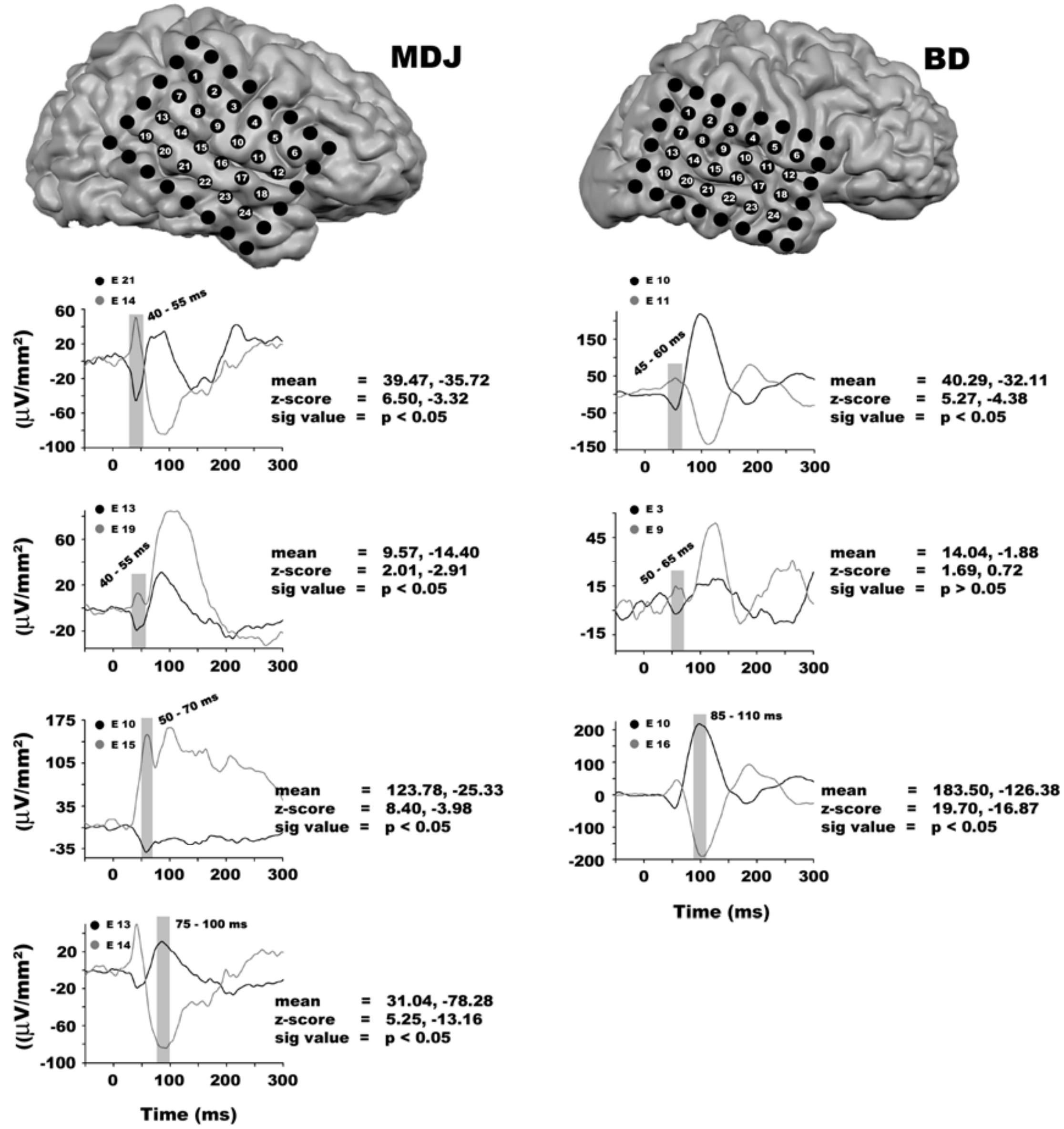

MDJ
BD
E 21
E 14
40 - 55 ms
(μV/mm²)
60
20
-20
-60
-100
0
100
200
300
mean = 39.47, -35.72
z-score = 6.50, -3.32
sig value = p < 0.05
E 10
E 11
45 - 60 ms
150
50
-50
-150
mean = 40.29, -32.11
z-score = 5.27, -4.38
sig value = p < 0.05
E 13
E 19
40 - 55 ms
mean = 9.57, -14.40
z-score = 2.01, -2.91
sig value = p < 0.05
E 3
E 9
50 - 65 ms
45
15
-15
mean = 14.04, -1.88
z-score = 1.69, 0.72
sig value = p > 0.05
E 10
E 15
50 - 70 ms
175
105
35
-35
mean = 123.78, -25.33
z-score = 8.40, -3.98
sig value = p < 0.05
E 10
E 16
85 - 110 ms
200
100
0
-100
-200
mean = 183.50, -126.38
z-score = 19.70, -16.87
sig value = p < 0.05
Time (ms)
E 13
E 14
75 - 100 ms
((μV/mm²)
mean = 31.04, -78.28
z-score = 5.25, -13.16
sig value = p < 0.05
Time (ms)

Figure 3

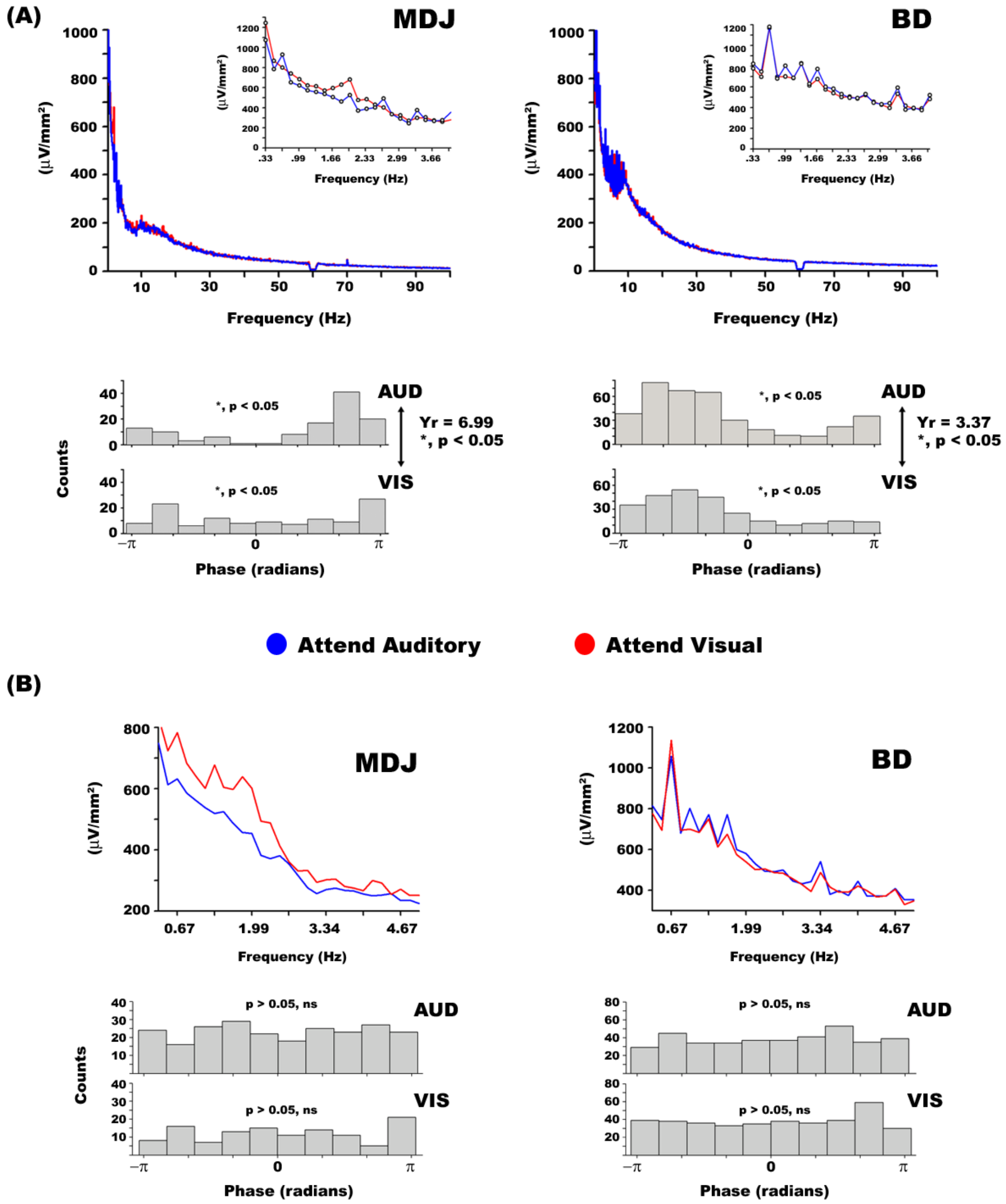
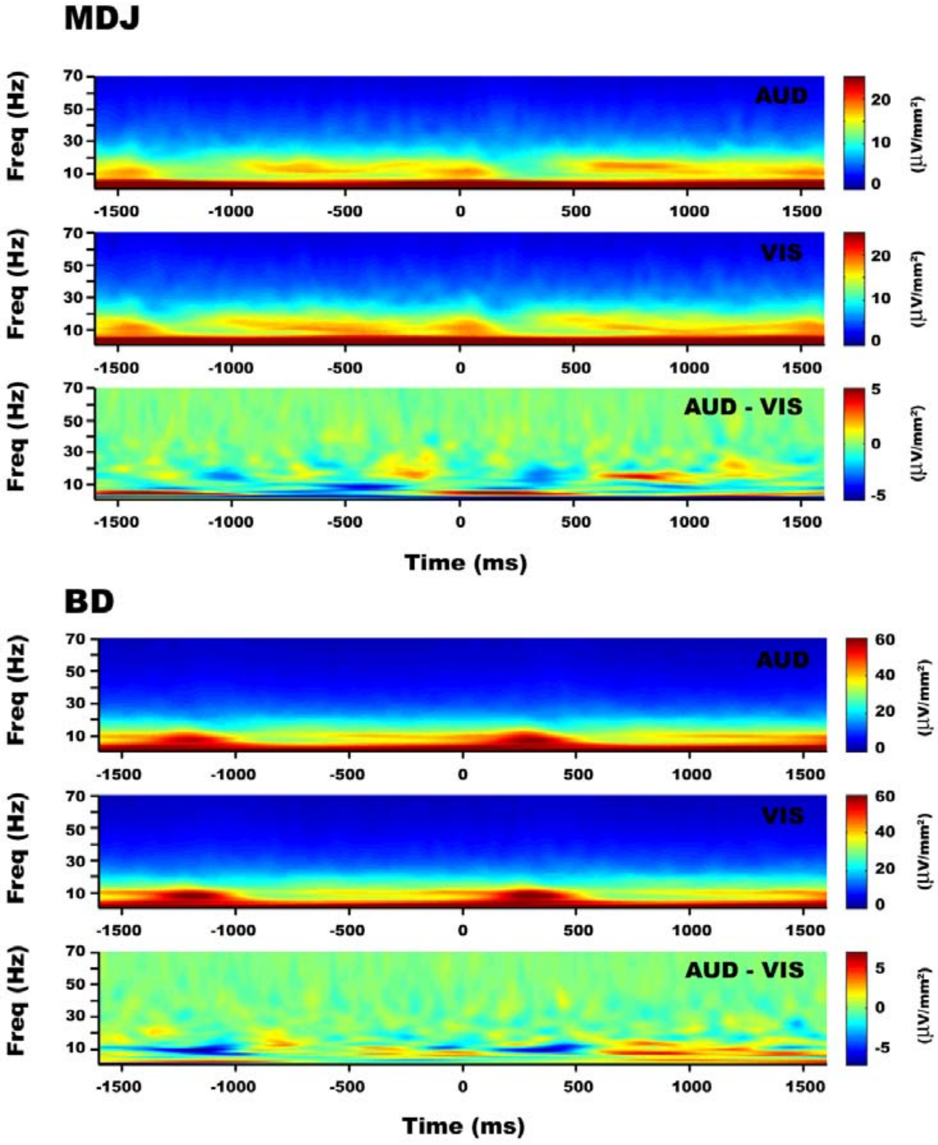

(A)
MDJ
BD
(µV/mm²)
Frequency (Hz)
1000
800
600
400
200
0
10
30
50
70
90
1200
.33
.99
1.66
2.33
2.99
3.66
Counts
AUD
VIS
*, p < 0.05
Yr = 6.99
*, p < 0.05
Yr = 3.37
*, p < 0.05
40
20
0
60
30
−π
0
π
Phase (radians)
Attend Auditory
Attend Visual
(B)
MDJ
BD
0.67
1.99
3.34
4.67
p > 0.05, ns
AUD
VIS
80
10

Figure 4

(A) Time Frequency Plots



(B) Alpha-Band (8-14 Hz) Power

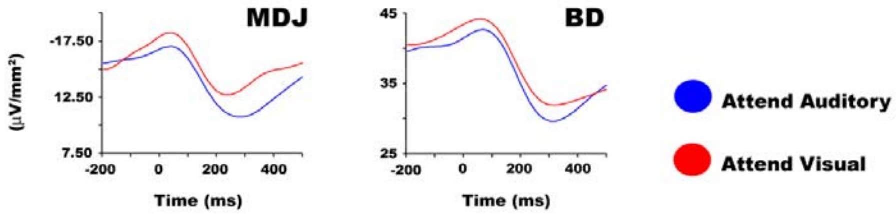
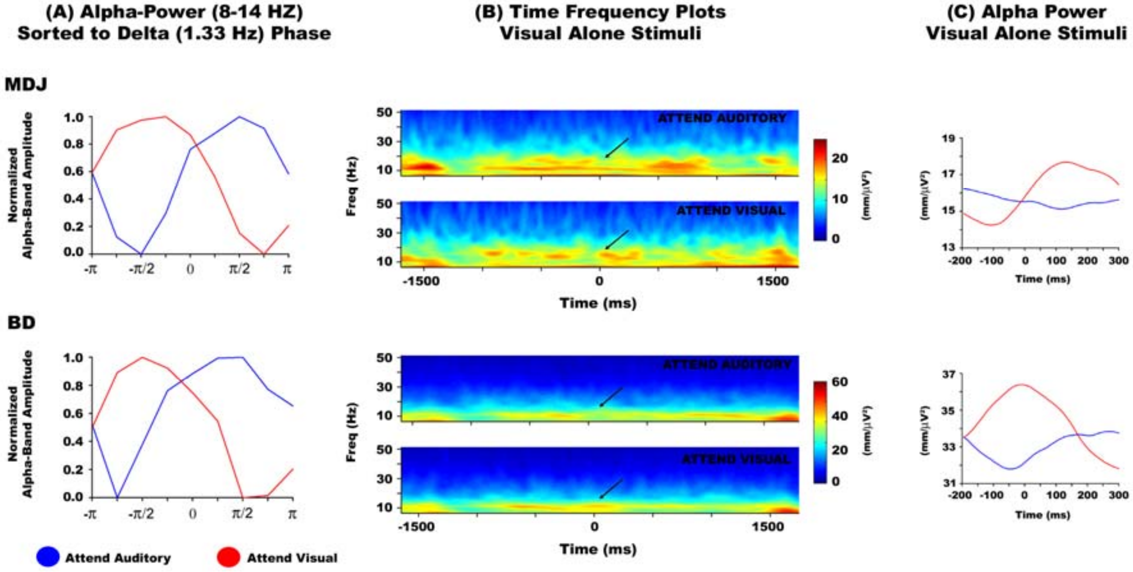
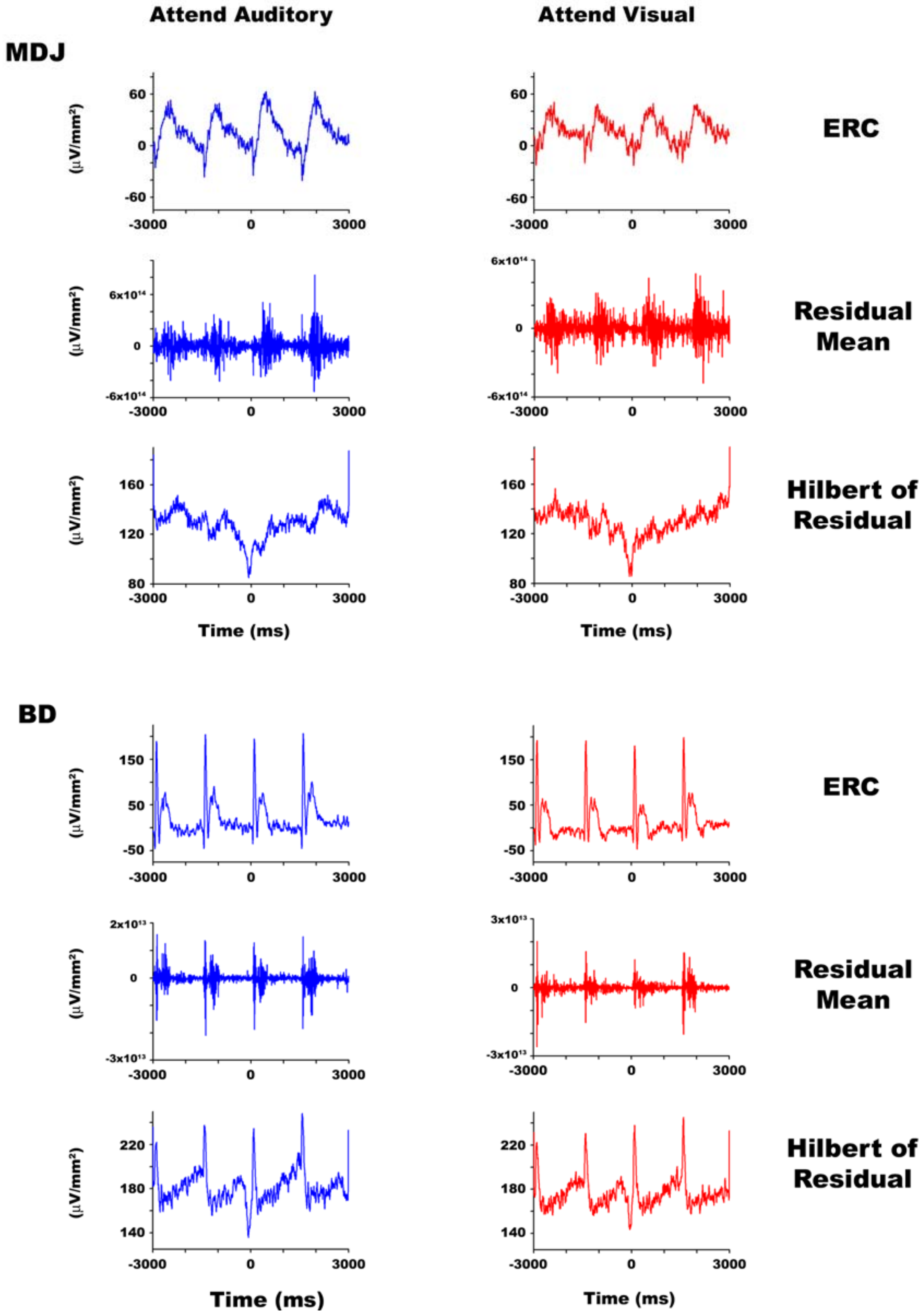


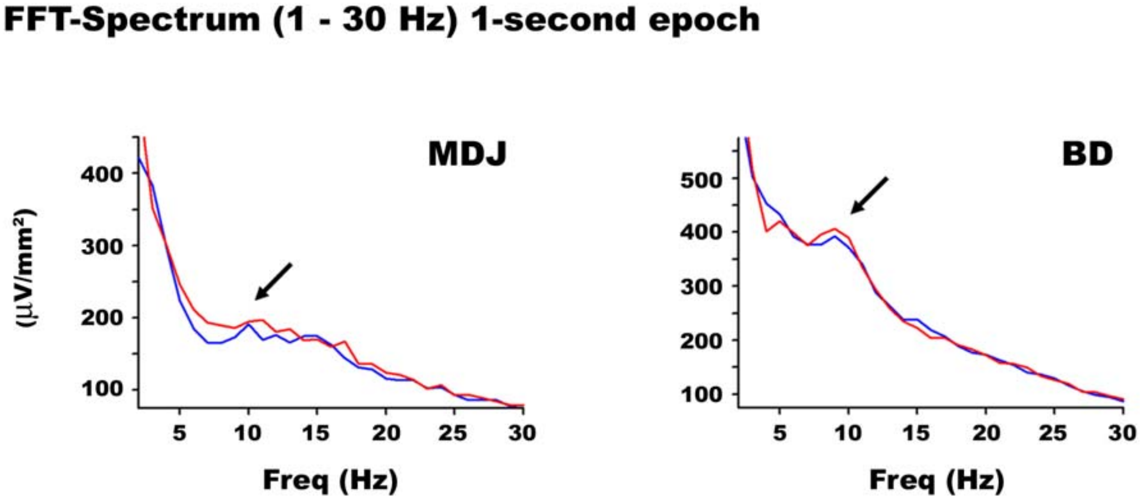
Figure 5


(A) Alpha-Power (8-14 HZ)
Sorted to Delta (1.33 Hz) Phase
(B) Time Frequency Plots
Visual Alone Stimuli
(C) Alpha Power
Visual Alone Stimuli
MDJ
BD
Normalized
Alpha-Band Amplitude
1.0
0.8
0.6
0.4
0.2
0.0
-π
-π/2
0
π/2
π
Freq (Hz)
50
30
10
ATTEND AUDITORY
ATTEND VISUAL
-1500
0
1500
Time (ms)
20
10
0
60
40
(mm/μV²)
19
17
15
13
37
35
33
31
-200
-100
100
200
300
Time (ms)
Attend Auditory
Attend Visual

Supplementary Figure 1



Supplementary Figure 2



CHAPTER 4

Returning the Reigns: Reconfiguration of Intersensory Attentional Mechanisms during Self-initiated Attentional Deployments

1. ABSTRACT

The present study was conducted to evaluate whether traditional attention-directing cueing paradigms represent efficient means of inducing endogenous attentional deployments. Half of the experimental blocks employed a symbolic cue to indicate the attended sensory modality (cue condition), while the remaining blocks had participants chose the attended modality by means of a button push (voluntary condition). Participants were instructed to detect the target in the attended modality and ignore all information emanating from the irrelevant sense. 168-channel EEG recordings were made from twelve neurologically-normal individuals, and the neural activity during the S2-processing period was assayed. The behavioral data revealed that participants' performance was better during the voluntary blocks, but at the expense of a slowing in reaction time. In addition, there was a substantial decrease in performance during the bimodal trials when attention was apportioned to audition in both cue and voluntary conditions (e.g. the so-called Colavita effect). However, during these trials, performance was significantly improved in the voluntary compared to the cue blocks. The neurophysiological data revealed a selection negativity (SN) effect over posterior and anterior cortices. Interestingly, in the voluntary blocks the SN effect over posterior cortices was significantly greater, but absent over anterior cortices. Taken together, the neurophysiological and behavioral data indicate that by allowing participants to voluntarily generate the attentional deployment, a reconfiguration of the attentional biasing signals is instantiated that might give rise to a more endogenous (or less automatic) attentional set.

2. INTRODUCTION

In many instances, efficient navigation through our multisensory environment depends on our ability to selectively extract relevant information from just one sensory modality while effectively ignoring distracting information from other modalities (e.g. Kristofferson 1967; Boulter 1977; Hillyard et al., 1984; Foxe et al., 1998; Teder-Salejarvi et al., 1999; Fu et al., 2001). One common example is to be found on the busy streets of any major city. Imagine yourself engaged in a visual search task where your current goal is to identify a landmark located on a given street. At the same time you are constantly being inundated by distracting auditory information such as car noises, people shouting, and myriad other environmental sounds. Obviously, allocating neural resources to these auditory inputs will not help your ability to accurately detect the visual target. If anything, allocating resources to these auditory inputs will hamper your performance. Therefore, the optimal strategy is to block-out all unwanted auditory information at the earliest stage possible and selectively attend to the apposite visual sources that will lead to the detection of the visual target.

The neural correlates mediating this biasing mechanism have been extensively investigated in laboratory settings, and are believed to be instantiated by a widespread network of frontal, parietal and subcortical regions. It is believed that this neural network influences neural activity by enhancing or suppressing baseline activity in early and/or midlevel sensory processing regions prior to the arrival of the imperative stimulus. That is, the biasing signals can give rise to enhanced neural responses in cortical areas responsible for ‘early’ sensory processing (see Desimone & Duncan, 1995; Kastner et al., 1999; Worden et al 2000; Yamagishi et al 2003; Kastner et al., 2004; Kelly et al 2006; Kelly et al 2008; Poghosyan & Ioannides 2008; Karns & Knight 2009).

Traditionally, to study the effects of these biasing signals upon stimulus processing, researchers have used so called “endogenous” cueing paradigms that are presumed to evoke ‘voluntary’ signals of attentional control (see Posner 1980; Heinze et al 1990; Fu et al 2001; Eimer et al 2002; Woldorff et al., 2004). These cueing paradigms use symbolic cues, which instruct participants to direct attention to a sensory modality, region in space, or stimulus feature, in anticipation of an upcoming imperative stimulus. Examples of such symbolic cues include the use of an arrow to direct attention to specific portions of visual space in the typical spatial attention task (i.e. the well-known ‘Posner’ task), or the presentation of an auditory sound to indicate which sensory modality is to be attended during an intersensory or crossmodal attention task (e.g. Fu et al 2001; Thut et al 2006; Gomez-Ramirez et al 2007). These cueing paradigms are also commonly referred to as “S1-S2 cueing paradigms” where the S1 (Stimulus 1) consists of the symbolic cue, while the S2 is the imperative to-be-attended (or ignored) stimulus.

While much has been learned from studies using these types of paradigms, an implicit assumption of such designs is that an abruptly and externally presented symbolic cue is an effective means of inducing endogenous deployments of attention. Although this is an entirely reasonable notion, at least to some extent, in many instances this assumption may represent something of an over-simplification and may not be fully justified on the following grounds. *First*, under these traditional designs, subjects are highly unlikely to optimally deploy attention on all trials. This is because over the relatively long periods of time that typical attention paradigms are conducted, there are frequent and usually regularly timed presentations of S1-S2 pairs[18], which due to fatigue and lapses in vigilance, may cause the subject to make weak attentional deployments, and in some cases to deploy attention to the incorrect modality (or location). *Second*, since the symbolic cue is an event generated in the external world, it is often difficult to separate the activity related to sensory processing and cue decoding from attentional deployment processes. That said, a number of studies have achieved a good level of success in separating these processes (see Nobre et al 2000; Van Velzen & Eimer 2004). Also, the presentation of a cue is by definition an exogenous attentional event and under explicit situations can come to evoke the modality shift effect (MSE). The MSE is a purely exogenous phenomenon that can be described as the automatic deployment of attention to the stimulated modality (Turatto et al 2002). It refers to the possibility that "regardless of any expectancy, there may be some cost in responding to targets when their modality changes successively, or some benefit in responding to a repeated sequence of identical stimuli" (Spence & Driver 1997). The MSE can occur even when stimulus and response uncertainty are removed and is primarily influenced by the sequence of imperative target stimuli (Spence & Driver 1997). Evidence for such effects has been repeatedly observed across a whole number of studies (e.g. Dinnerstein & Zlotogura, 1968; Robin & Rizzo, 1989, 1992; Ferstl et al., 1994; Spence, Driver, & Rogers, 1997). *Finally*, and perhaps more importantly, over the course of the experiment it is likely that the processes of cue decoding and consequent attentional deployment may together become a more automatic event. That is, after extensive practice, the cue might come to 'automatically' evoke

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[18] For instance, in Eimer (1993) subjects were presented with 60 Cue-S2 pairs per run, and each run lasted for just short of 3 minutes. There were 24 of these runs in the experiment. Such values are entirely typical for this field, including our own work. We remind the reader, that a Cue-s2 pair is a trial composed of the presentation of the symbolic cue (Cue), followed by an inter-stimulus-interval (ISI), then the presentation of the imperative stimulus (S2), and terminating with the inter-trial-interval (ITI).

activation of the relevant sensory system, thereby obviating the need for an endogenous attentional deployment.

In real-world situations however, attention tends to be deployed in a completely voluntary and independent manner. Thus there is a need for a more reliable and ecologically valid paradigm than the traditional cueing task used so far. Recently, there have been several paradigms developed that partially overcome these potential shortcomings of 'endogenous' cueing paradigms (Meiran et al 2002; Arrington & Logan 2004; Walton et al 2004; Arrington & Logan 2005; Forstmann et al., 2006). These studies assessed executive control functions by implementing a 'task-switching' design in which subjects choose which task to perform on every trial (Arrington & Logan 2004; Walton et al 2004; Arrington & Logan 2005; Forstmann et al., 2006) or choose when to initiate a trial without having any control over the type of trial (Meiran et al 2002). These studies found that the neural mechanisms underlying performance monitoring are strongly influenced when subjects themselves are able to decide what action to perform (Walton et al 2004; Forstmann et al 2005). This selection-type process inversely activated regions in the so-called 'frontal executive-function' areas (Walton et al 2004), and increased activation in the superior parietal lobule and the posterior intra-parietal sulcus (Forstmann et al., 2006), which are regions known to be critical nodes of the attentional circuitry in humans.

In the present study, we implemented an amalgamated design where on every trial participants chose when and to which sensory modality (auditory or visual) deploy attention to. We investigated whether similar attentional effects are observed when subjects are in complete control of task selection compared to when an externally presented cue instructs the to-be attended modality. In the blocks where participants had complete control of task selection (e.g. the voluntary condition), it was emphasized that they start a trial only when they "felt ready to make an effective attentional deployment." We believe that this paradigm goes some ways towards resolving the reservations outlined above, and constitutes a more effective means of investigating more endogenous, or less automatic, attentional control mechanisms.

The experimental paradigm used was highly similar to the ones employed in typical studies of intersensory attention. Participants were presented with unisensory and bisensory stimuli, and were required to detect a target in the attended modality only, while ignore all stimuli emanating from the irrelevant sense. We inspected activity time-locked to the imperative stimulus (e.g. the S2-stimulus) for the following two reasons: (1) we wanted to compared neural activity evoked by the same sensory stimulus but under different attentional control situations, and (2) previous studies have delineated the spatio-temporal effects of attention across the auditory and visual modalities, thus providing us with a template for assessing attention effects over stimulus processing.

3. METHODS

Participants:

Fourteen (seven females) neurologically normal, paid volunteers (mean age = 27.8, SD 6.5 years, age range 18 – 36 years) participated. All participants provided written informed consent, and the Institutional Review Board of the Nathan Kline Research Institute approved the procedures. Two of the participants, 1 male and 1 female, were removed due to excessive eye-movements and noisy data. All participants reported normal or corrected-to-normal vision and all were right-hand dominant as assessed by the

Edinburgh handedness inventory (Oldfield, 1971). All subjects received a modest hourly fee for their efforts.

Experimental Paradigm:

The sequence of events in a typical trial for each condition is illustrated in Figure 1A and B.

Cue Condition: Each trial commenced with the onset of the symbolic cue stimulus (S1) that instructed participants to deploy their attention to either the visual or auditory modality. After a stimulus onset asynchrony (SOA) of 1200 ms, a second stimulus was presented (S2, see below). Because the S1 was presented for 400 ms, the inter-stimulus-interval (ISI) was 800 ms. The inter-trial interval (ITI: i.e. the period between each S1-S2 pair) was uniformly randomized between 1400 and 2400 ms. A central, black fixation cross (1° visual angle) remained on the screen throughout the experiment and participants were instructed to maintain fixation at all times.

Voluntary Condition: A trial commenced with a left or right button push, which indicated the sensory modality the subject had chosen to deploy attention to. As in the cueing condition, the ISI (in this case, the time between the offset of the button push and the onset of the S2 stimulus) was 800 ms. The S2s were identical to those used in the cue condition and will be described in detail below. In contrast to the cue condition, the subjects themselves determined the ITI: they were instructed to take as much time as they needed in order to prepare for the forthcoming trial. Participants were instructed to maintain fixation at all times during the trial. Participants completed a minimum of 15 blocks of trials per condition. Each block contained a total of 100 S1-S2 pairs, and each condition was run on alternating blocks.

Stimuli:

All visual stimuli were displayed on a gray background, while all auditory stimuli were presented through headphones.

S1 (cue condition): The S1 consisted of one of two pseudo-words AUD or VIS presented in stereo over headphones (400 ms, 10 ms rise/fall, 80 dB SPL, Sennheiser TDH39 headphones). These pseudo-words (attend auditory = AUD, attend visual = VIS) instructed subjects of the task to engage in when the imperative stimulus (S2) occurred.

S1 (voluntary condition): Subjects cued themselves by means of a left/right button press. This button press indicated the task the subject was prepared to do on that trial (e.g. attend auditory = left button, attend visual = right button). The mapping of button to task was counterbalanced across subjects. Subjects were instructed that they were in full control on each individual trial, but were also requested to avoid adopting any stereotyped pattern of 'choice' across successive trials. The experimenter vigorously watched out for such stereotyped patterns, and queried the subject when any were detected.

S2: The S2 was one of four types: auditory-alone (pair of tones, 20%: 'A-A_{att}'), visual-alone (pair of gabor patches, 20%: 'V-V_{att}'), audio-visual compound (pair of tones and gabor patches, 40%, 'AV_{att}'), or a null (catch) stimulus ('no S2' stimulus, 20%: NULL). The A-A S2 stimulus consisted of a pair of binaural tones (e.g. 2000 Hz or 2100 Hz, 80 dB SPL, 100 ms duration each, 5 ms rise/fall, 5 ms interval between tones). The pair of tones was presented in a rapid sequence with auditory stimulation lasting for a total of 205 ms. The V-V_{att} stimulus consisted of a pair of gabor patches (4.5 $^{\text{o}}$ in diameter, centered 2.5 $^{\text{o}}$ left and right of fixation, presented simultaneously for 100 ms). The AV_{att}

compound stimulus consisted of a combination of the above-described A-A_{att} and V-V_{att} stimuli, where the pair of gabor patches (i.e. the visual component) and the second auditory tone was presented 105 ms after the onset of the first auditory tone. The NULL stimulus consisted of a period of fixation only. All visual stimuli were presented on an Iiyama VisionMaster Pro502 21" computer monitor, on a gray background.

On 85% of V-V_{att} S2 trials the Gabor patches were identical and no overt response was required (non-target standards). Similarly, on 85% of A-A_{att} S2 trials the tones were identical and no response was required. On the other 15% of V-V_{att} S2 trials, i.e. for visual targets, the orientations of the left and right Gabor patches were slightly different (see below) and subjects responded by pressing a button when they had been cued to the visual modality. On 15% of A-A_{att} trials, the two tones were of slightly different pitch and also required a response when the auditory modality had been cued. Importantly, the occurrence of a target in each modality was independent of the other modality, such that the probability of occurrence of a double target (i.e. a bisensory AV_{att} target) was approximately 1%.

This led to four possible target types:

1) Unisensory-auditory (A-A_{att}): the subject had deployed attention to the auditory modality and only an auditory S2 was presented.

2) Unisensory-visual (V-V_{att}): the subject had deployed attention to the visual modality and only a visual S2 was presented.

3) Multisensory-auditory (AV-A_{att}): the subject had deployed attention to the auditory modality and a compound, audio-visual S2 was presented, of which the auditory part was a target.

4) Multisensory-visual (AV-V_{att}): the subject was attending to the visual modality and a compound, audio-visual S2 was presented, of which the visual part was a target.

5) Rare double targets (i.e. targets in both modalities) were too few to be analyzed.

Our paradigm was designed such that when the S2 was unisensory the S1 cue was 100% predictive (e.g., an A-A S2 was always preceded by an attend-auditory S1 cue). We used this strategy to ensure that the cues were at least practically predictive, reasoning that subjects would deploy greater selective attention mechanisms under such circumstances. By this technique, we hypothesized that the fact that the cues were non-predictive with regards to the bimodal S2s, when subjects encountered these bimodal trials they would need to evoke stronger attentional deployments.

Procedure:

Participants sat in an electrically shielded and soundproofed booth, directly facing a computer monitor placed five feet away from them. They were encouraged to take breaks between blocks if they felt weary and needed to rest.

Prior to the start of the testing phase all participants performed a psychophysical test that titrated performance on the auditory and visual discriminations. We used this information to set the stimuli for each subject such that his/her accuracy was precisely 78%. This psychophysical test, know as the Up-Down Transformed Rule (UDTR, see Wetherill and Levitt 1965), is a rapid method that ensured the difficulty for each task was equivalent across all participants.

Measurements

Continuous electroencephalographic (EEG) data, digitized at 512 Hz, was acquired through the ActiveTwo Biosemi electrode system from 168 scalp electrodes. With the Biosemi system, every electrode or combination of electrodes can be assigned as the “reference”, and this is done purely in software after acquisition. A detailed description of the referencing conventions used by this active electrode system can be found at the following website: http://www.biosemi.com/faq/cms&drl.htm.

After acquisition, all data were re-referenced to an electrode on the nose. After each recording session, before the electrode cap was removed from the subject’s head, the 3D coordinates of the electrodes were digitized using a Polhemus Magnetic 3D digitizer, with reference to anatomic landmarks on the head (nasion, pre-auricular notches). EEG data were epoched and averaged off-line. Trials with blinks and large eye-movements, defined as continuous deviations of twenty milliseconds or more of at least $\pm$ 15 μV on both eye channels relative to a ten millisecond baseline period, were rejected offline. An artifact rejection criterion of ±100 microvolts was used at all other electrode sites to exclude periods of high EMG and other noise-transients.

Data Analysis Strategy

Accepted trials were epoched for the period surrounding the onset of the S2-imperative stimulus (-100ms pre-stimulus to 500ms post-stimulus). The baseline was defined as the mean voltage from –100 to 0 milliseconds before the onset of S2. Separate averages were made for all the possible variants of the S2 stimulus (A-A_{att}, V-V_{att}, AV-A_{att} and AV-V_{att}). We inspected event-related potentials (ERP) for each of the S2 stimulus types across both strategy conditions.

Separate repeated-measures analyses of variance (ANOVA) were used to statistically test for effects of attention across the cue and voluntary conditions. One ANOVA tested for effects of the so-called selection negativity effect (SN) or processing negativity (PN) in the visual modality during the time interval between 225 and 350 ms. The SN effect is an ERP component observed in many intersensory attentional designs, and it believed to index a ‘low-level’ stimulus selection mechanism in early sensory cortices (see Naatanen et al 1978; Näätänen et al 1981; Näätänen 1982; Näätänen et al 1988; Alho et al 1990; Oades et al 1997; Beer & Roder 2005; Molholm et al., 2007). The factors were Strategy (Cue vs. Voluntary), Attend-Sense (AV-A_{att} vs. AV-V_{att}) and Hemisphere (Center, Left and Right). The dependent measure was derived by calculating the average ERP response across six neighboring electrodes in three regions of interest (ROI) located over central parietal and bilateral parieto-occipital cortices. Another ANOVA tested for effects in the auditory modality during the time interval between 100 and 225 ms. The factors were Strategy (Cue vs. Voluntary) and Attend-Sense (AV-A_{att} vs. AV-V_{att}). The dependent measure was derived by calculating the average ERP response across six neighboring electrodes located over frontal cortices.

We tested effects on unisensory processing by computing separate ANOVAs with factors of Strategy (Cue vs. Voluntary) and hemisphere (Left vs. Right). One ANOVA tested for effects over frontal cortices during the period of 100 to 125 ms (e.g. the auditory N1 period of the first tone.) The second ANOVA tested for effects in the visual modality during the period of the visual N1 (i.e. 155 ms to 180 ms). The dependent measure was derived by calculating the average ERP response across four neighboring electrodes in two ROIs located in fronto-central and lateral occipital cortices.

4. RESULTS

Trial-by-trial task selection:

To ensure that participants adhered to the instructions during the voluntary blocks, we inspected each participant's task-selection pattern and assessed whether subjects preferred to select on average, a visual over an auditory task, or vice versa. A paired sample t-test was computed with factors of attention (attend auditory vs. attend visual) using the task selection as the dependent measure. The results did not reveal any statistical differences between attention selection criteria in the voluntary blocks, t(11) = 1.18, $p > 0.05$ (mean auditory = 49%, mean visual = 51%),thus indicating that subjects did not have a bias in attending to a particular sensory modality. We also computed a paired sample t-test to assess differences between repeat and switch trials during the voluntary blocks. Note that typical attention and basic sensory processing tasks are normally programmed such that repeat-trials outnumber switch-trials approximately 2 to 4 times (see Wylie et al 2003; DeSanctis et al 2008; Kelly et al 2008; Gomez-Ramirez et al 2007; Gomez-Ramirez et al 2008). The paired sample t-test revealed statistical differences between repeats and switch trials, t(11) = 6.85, $p > 0.0005$ (mean repeat trials = 67%, mean switch trials = 33%). The descriptive and inferential statistics indicated that subjects followed typical switch and repeat patterns similar to previous studies.

Behavioral results:

Behavioral performance and reaction time (RT) data for both experimental conditions are depicted in Figure 2. Separate 2 X 4 repeated measures ANOVAs with factors of strategy (cue vs. voluntary) and S2 stimulus-type ($A\text{-}A_{att}$, $V\text{-}V_{att}$, $AV\text{-}A_{att}$, $AV\text{-}V_{att}$) were computed for both the accuracy and RT data.

For the accuracy data, the ANOVA revealed a main effect of strategy $F(1,11) = 4.674$, $p < 0.05$, which was driven by an overall gain in hit responses in the voluntary condition. The ANOVA also revealed a main effect of stimulus-type $F(1,11) = 8.706$, $p < 0.01$, caused by a considerable decrease in performance for the AV-A_{att} type stimulus. The reader should recall that the auditory task is identical between the A-A_{att} and AV-A_{att} stimulus types, so it appears that the presence of a distracting visual stimulus has large detrimental effect in performance. Finally, an interaction of strategy and stimulus-type $F(1,11) = 3.87$, $p < 0.05$ was also found. Planned comparison tests revealed that this interaction effect was mainly driven by differences in the AV-A_{att} stimulus-type between the two experimental conditions (strategy) $t(11) = 2.38$, $p < 0.05$. Namely, participants performance on the AV-$_{Att}$ trials was significantly better during the voluntary blocks than the cue-blocks. No other significant effects were found for the accuracy dataset.

For the RT data, a main effect of strategy was found $F(1,11) = 5.268$, $p < 0.05$, mainly due to slower RTs in the voluntary condition (cue = 787 ms, voluntary = 916 ms). In addition, the ANOVA also revealed a main effect of stimulus-type $F(1,11) = 8.953$, $p < 0.001$. This was because RTs were considerably slower in the AV-A_{att} stimulus-type for both conditions (A-A_{att} = 894 ms, V-V_{att} = 786 ms, AV-A_{att} = 914ms, AV-V_{att} = 812 ms). No other significant effects were found.

We computed separate 2 X 4 repeated measures ANOVAs with factors of strategy (cue vs. voluntary) and S2 stimulus-type (A-A_{att}, V-V_{att}, AV-A_{att}, AV-V_{att}) to assess differences in signal sensitivity (e.g. d-prime) and response bias (beta). The ANOVA on d-prime revealed a main effect of stimulus-type $F(1,11) = 6.201$, $p < 0.001$, driven by a substantial decrease d-prime in the AV-A_{att} stimulus-type. The ANOVA on the response bias revealed a main effect of stimulus-type F(1,11) = 3.50, $p = 0.01$, caused by a substantial response shift in the AV-A_{att} stimulus type. No other significant effects were found.

Attention effects revealed by the ERP data time-locked to the imperative stimuli:

The attention-related effects over visual cortices are illustrated in Figure 3. Figure 3a Depicts averaged ERP waveforms across six electrode sites over the centro-parietal scalp and two bilateral regions over the parieto-occipital scalp for the AV-A_{att} and AV-V_{att} stimulus-types for both the cue and voluntary strategy condition. Figure 3b illustrates the SN effect in each of the ROIs, and difference topographical maps for both strategy conditions. The ANOVA computed on the SN effect over posterior cortices revealed a main effect of strategy condition F(1,11) = 6.5, $p < 0.05$, driven by a greater SN response during the voluntary condition. The ANOVA also revealed a main effect of hemisphere F(2,11) = 3.89, $p < 0.05$, caused by a greater amplitude response over the centro-parietal ROI. No other significant effects were observed.

The attention-related effects over auditory cortices are illustrated in Figure 4. Depicted are the average ERP waveforms across six electrode sites over the fronto-central scalp for the AV-A_{att} and AV-V_{att} stimulus-types across the cue and voluntary strategy condition. The ANOVA conducted during the SN period in auditory cortices did not reveal a main effect of strategy condition F(1,11) = .321, $p > 0.05$. However, the ANOVA revealed a significant main effect of attention F(1,11) = 5.874, $p < 0.05$, caused by a larger response when attention was directed towards audition. This effect was largely driven by an interaction effect of strategy x attention F(1,11) = 6.121, $p < 0.05$. A two-tailed paired t-test revealed that this interaction effect was mainly caused by a larger difference between stimulus-types in the cue condition $t(11) = 5.196$, $p < 0.01$. No other significant effects were found.

Unisensory processing Effects:

The ERP data to the unisensory stimuli are illustrated in Figure 4. Depicted are the average ERP waveforms across four electrode sites over frontal and posterior cortices for the $A\text{-}A_{att}$ and $V\text{-}V_{att}$ stimulus-types across the cue and voluntary condition. The ANOVA conducted on the period of visual N1 failed to reveal any main effects of condition or hemisphere. However, an interaction effect of strategy by hemisphere was found $F(1,11) = 7.6772$, $p < 0.05$. A paired two-tailed t-test revealed that this interaction was mainly due to a larger difference between hemispheres in the voluntary condition $t(11) = 2.694$, $p < 0.05$. No other significant effects were found.

DISCUSSION

The present study investigated attentional effects on stimulus processing when participants were in complete control of their attentional deployment in comparison to when an external cue indicated the attended modality. The ERP data triggered to the arrival of the imperative stimulus revealed differential attention effects across both strategy conditions during different periods of sensory processing. In particular, the data revealed a greater SN effect over posterior cortices during the voluntary blocks, but a significant reduction of effects over anterior cortices. Interestingly, during the voluntary blocks participants' performance improved but at the cost of a significant slowing in reaction time. These effects could not be accounted for by differences in task-selection, as this process during the voluntary blocks had a random pattern and was highly similar to selection patterns in previous studies. Taken together, the results suggest that by allowing participants to have full-control of their task selection, a reconfiguration in the attentional system is instantiated that leads to differential patterns of attentional effects during sensory stimulus processing. Further, this reconfiguration of attention might give rise to more endogenous or less automatic attentional sets. In what follows, we describe in detail the neurophysiological and behavioral findings between both strategy deployment conditions.

Attentional modulations in sensory specific regions

Typical attention effects were observed over posterior and anterior cortices in both strategy conditions during the stimulus processing period. Particularly, a SN effect starting ~125 ms after the onset of the visual stimulus was evidenced in both strategy conditions over posterior cortices. This SN effect was significantly more pronounced during the voluntary block trials. Naatanen and colleagues (1978) proposed that the SN reflects the basic principle of stimulus selection, and that this mechanism is a self-terminating matching process occurring between sensory input and a voluntarily maintained representation of the attended stimulus. The SN effect occurs in sensory-specific cortices under the control of higher-order executive control regions, and most likely underscore the neurophysiological correlate of the Broadbent's attentional filter (see Naatanen 1988).

Over anterior cortices, attentional signals generated in the voluntary blocks only began to influence neural activity after 300 ms or so. In contrast, in the cue-blocks attention influenced neural activity during much earlier stages. This was evidenced by a substantial SN effect, which started ~100 ms after stimulus onset. So, why are attention effects distributed so differently across these two strategy conditions? Unfortunately, the answer is not obvious, but the data provide strong evidence for fundamental changes in the way the attentional set is configured depending on how the attentional deployment is prompted. Further, this reconfiguration might explain why subjects exhibited a speed accuracy tradeoff effect during the voluntary blocks.

Visual interference during auditory processing: the Colavita effect

The behavioral data showed a substantial reduction in accuracy and a concomitant increase in RT for the auditory task when visual stimuli were concurrently presented. This effect was independent of strategy deployment condition, but it was less pronounced during blocks where participants signaled the attentional deployment. This effect, termed the 'Colavita-effect', reflects the ineffectiveness to detect auditory-relevant targets in the presence of distracting visual stimuli, albeit the visual distracting stimuli holds no categorical or feature relationship to the auditory stimulus and participants are explicitly instructed to ignore these visual distracting inputs (see Gomez-Ramirez et al 2007; Koppen & Spece 2007a; Koppen & Spence 2007b; Koppen & Spence 2007c; Koppen et al 2007d; Koppen et al 2008; Sinnett et al 2008). Indeed, similar relationships have been observed across the visual and somatosensory modalities during a visuo-tactile intersensory attention task (see Hartcher-O'Brien et al 2008), and also between the auditory and somatosensory modalities, where frequency-overlapping auditory irrelevant stimuli were shown to impair discrimination performance of vibratory-somatosensory stimuli (see Yau et al 2009).

Interestingly, this visual interference effect is not universal to intersensory attentional designs in humans. For example, Duncan et al (1997) conducted an attentional blink (AB) paradigm across and within sensory modalities, and showed that an interference effect, in the form of an AB, only exists during trials where attention is allocated within sensory modalities. That is, participants were able to detect all target stimuli during blocks where attention was divided to the auditory and visual modalities. Similarly, previous studies from our lab (see Foxe et al 1998; Fu et al 2001; Foxe et al 2005a; Foxe et al 2005b) showed that participants were able to reliably detect auditory stimuli in the presence of visual targets using an experimental design highly similar to the one here. So, why would an interference effect be observed in our study and not in our previous studies or in Duncan's? One possible explanation is that some form of an automatic multisensory integration (MI) effect, caused by the temporal co-registry of the auditory and visual constituents of the bimodal stimulus, occurred. Indeed, a difference in the sequence of stimulus presentation may have been the underlying cause for such different results. For example, in Fu et al (2001) the visual stimulus was presented in conjunction with the first auditory stimulus, and not with the second, where the auditory discrimination process occurred. Further, in Duncan's experiment (see Duncan et al 1997) although the auditory and visual streams occurred within the same block of trials, most of the individual stimuli themselves were not presented in temporal coincidence. In fact, the auditory stream started 125 ms after the onset of the first visual stimulus, and this temporal asynchrony may have been sufficient for the two sensory streams to be 'unhooked' from each other and performance be unaffected.

In our experimental design however, the auditory and visual stimuli did occur in temporal registry, and although they were presented from different spatial locations and had no natural relationship to each other, the temporal coincidence alone may have been sufficient for some form of MI to happen. Indeed, there is precedence in the literature for

MI across auditory and visual inputs to occur under similar conditions, and with such basic stimuli (see Molholm et al 2002; Foxe & Schroeder 2005; Schroeder & Foxe 2005; Koppen et al 2008).

In a series of studies, Koppen & Spence (see 2007a, 2007b, 2007c and 2007d) aimed to investigate the dependency of the Colavita effect on spatial, temporal, and congruity constraints. In one such study, Koppen & Spence (2007d) assayed the influence of temporal asynchrony between auditory and visual inputs during an audio-visual intersensory attention task. In a first set of blocks, participants completed a series of temporal order judgment (TOJ) runs between auditory and visual stimuli, and then continued to perform an audio-visual intersensory task using the same auditory and visual sensory stimuli. The findings revealed that the point at which the Colavita effect disappeared, during the intersensory attention task, correlated with the point at which participants started to reliably perceive the auditory stimulus as coming first in the TOJ task. There was no evidence of a Colavita effect when the visual stimulus was perceived as coming first. Thus, the data indicate that this audio-visual interference effect is a consequence of a MI effect, and its neural correlates most likely exist in the earliest levels of cortical processing.

6. CONCLUSION AND FUTURE DIRECTIONS

The neurophysiological and behavioral results provide compelling evidence that a different attentional biasing is instantiated during the voluntary blocks compared to the cue blocks. Further, the biasing signals generated during the voluntary blocks may be more representative neural correlates of endogenous attentional mechanisms. This claim is supported by the greater enhancement of attentional effects over visual cortices and behavioral performance. Indeed, so-called speed-accuracy tradeoff effects are believed to reflect a more endogenous and/or less automatic attentional state (see McCormick & Francis 2005). McCormick & Francis (2005) suggest that cueing effects in endogenous orienting could arise from a combination of an RT and response biased accuracy tradeoff, while cueing effects in exogenous orienting are primarily expressed as RT facilitation (see McCormick & Francis 2005).

A potential benefit of this novel voluntary paradigm pertains to the study of attention in clinical populations, especially in those that suffer from sensory processing deficits. It is argued that the this paradigm allows researchers to assess attentional deficits in clinical populations free of any sensory processing confound. The rationale is that since traditional attentional paradigms employ sensory symbolic cues as means to direct attention, then these cues have to be first processed and decoded before an attentional deployment is actually made. Therefore, one should consider the case when a schizophrenic patient is performing one of these typical cueing paradigms. Indeed, there have been many reports showing patients exhibiting severe attentional deficits (see Iwanami et al 1998; Kamio et al 2001; van der Stelt et al 2006; Wood et al 2007). By the same token, there have also been many reports indicating that patients have severe problems in the early stages of the sensory processing stream (cite Foxe et al 2001; Butler & Javitt 2005; Yeap et al 2006; Butler et al 2007; Leavitt et al 2007). Thus, it is entirely possible that the early sensory processing deficits in these patients may be consequently affecting their ability to make an effective attentional deployment. That is, if patients have problems with the processing of the sensory cue, which is a processing stage that necessarily precedes an attentional orientation process, then these sensory processing ‘errors’ might propagate throughout the attentional deployment stage and result in an ineffective, or suboptimal, attentional biasing set. By implementing this voluntary paradigm, where the presentation of a sensory symbolic cue is obviated, researchers can directly assess these attentional mechanisms in clinical patients without worrying about sensory processing confounds.

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8. FIGURE LEGENDS

Figure 1a. Schematic illustration of the paradigm (‘External-Cue’ Condition)

Each trial commenced with the presentation of an auditory symbolic cue (S1) whereby the abbreviated words “Aud” (for Auditory) or “Viz” (for Visual) were presented across headphones to the subjects. A delay period of 800ms followed the cue, after which one of the following four types of S2 stimuli would appear: auditory stimuli alone, visual stimuli alone, catch trials where no physical stimulus was presented, or compound audio-visual multisensory stimuli. Subjects were required to respond with a button push to targets within the cued modality.

Figure 1b. Schematic illustration of the paradigm (‘Voluntary’ Condition)

Each trial commenced with a left or right button push, which indicated the attended sensory modality. For example, a left button push indicated ‘attend-auditory’. The mapping of the button push and the attended modality was counterbalanced across subjects. A delay period of 800ms followed the button push, after which one of the following four types of S2 stimuli would appear: auditory stimuli alone, visual stimuli alone, catch trials where no physical stimulus was presented, or compound audio-visual multisensory stimuli. Subjects were required to respond with a button push to targets within the attended modality.

Figure 2. Behavioral Data

Upper graph illustrates hit rates for each stimulus-type in each strategy condition. Lower graph illustrates reaction time for each stimulus-type in each strategy condition.

Figure 3. Attention Effects In Visual-Related Cortices

Figure 3a: Attention effects over center, left and right hemispheres over posterior cortices. Upper three graphs illustrate activity during the cue blocks, while the lower graphs display activity during the voluntary blocks. Only bimodal trials are plotted. Attention to the auditory modality is plotted in red, while attention to the visual modality plotted in blue. The horizontal axis indexes time, relative to the onset of the S2-stimulus, while the vertical axis indexes the neural response in microvolt units. This is depicted in the middle-right x-y coordinate graph.

Figure 3b: Difference waveforms (attend-auditory minus attend visual) for each individual ROI tested over posterior cortices for both strategy condition. These difference waveforms illustrate a selection negativity (SN) effect occurring during processing of the visual stimulus. Also displayed are difference topography maps during the period of the SN effect. Note that the visual stimuli commenced at 105 ms after the first auditory tone.

Figure 4. Attention Effects In Auditory-Related Cortices

Attention effects over frontal cortices. Only bimodal trials are plotted. Attention to the auditory modality is plotted in red, while attention to the visual modality plotted in blue. The middle graph illustrates the selection negativity (SN) effect in the cue-condition. Notice the SN effect being absent in the voluntary-condition. Below the graphs are difference topography maps (attend-visual minus attend-auditory) during the SN period for both strategy conditions.

Figure 5. Unisensory Processing Effects

Sensory processing effects in the unisensory auditory-condition (upper graphs) and unisensory visual-condition (lower graphs). Unisensory stimuli in the cue-condition is plotted in blue, unisensory stimuli in the voluntary-condition is plotted in red. The right side of the figure illustrates difference topography maps (voluntary minus cue condition) for the auditory and visual unisensory stimulus condition.

9. FIGURES

FIGURE 1

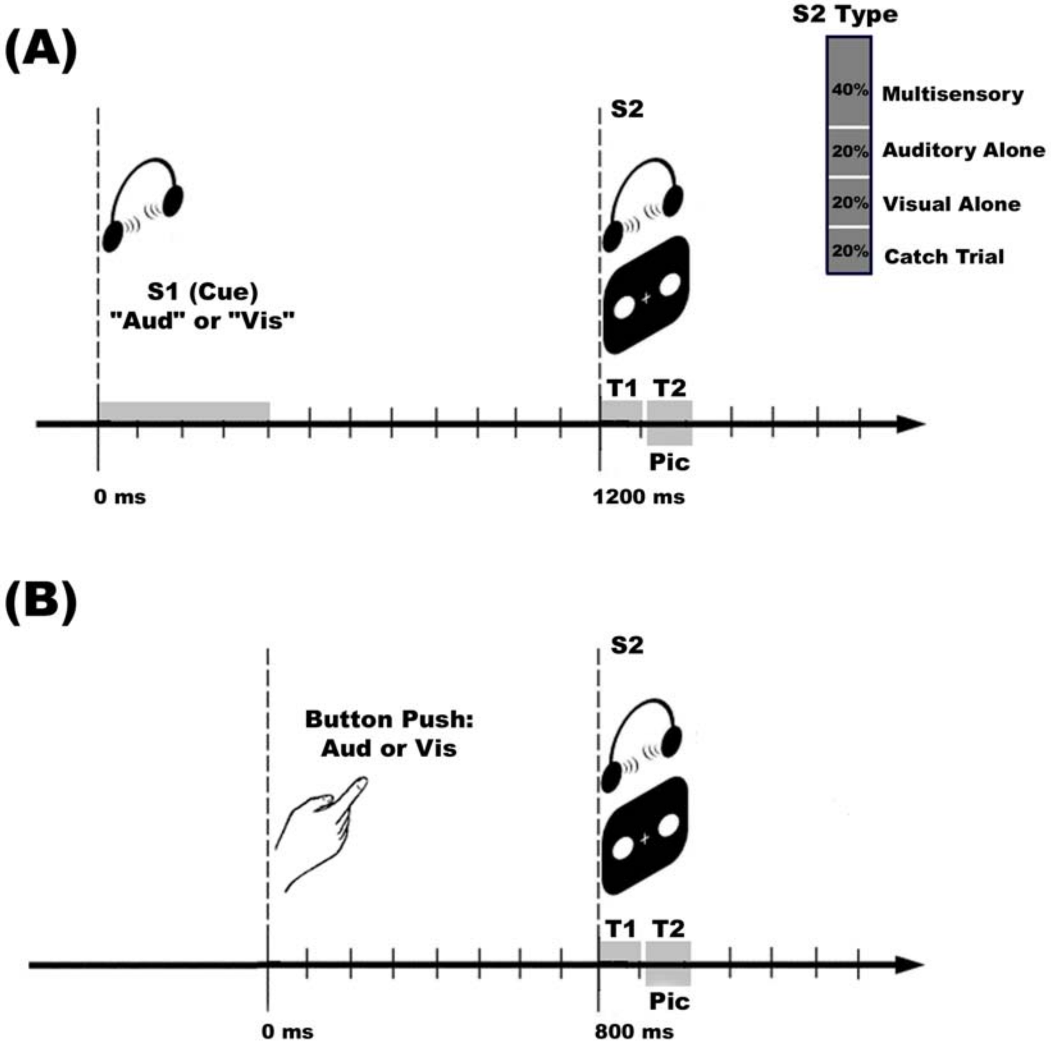


FIGURE 2

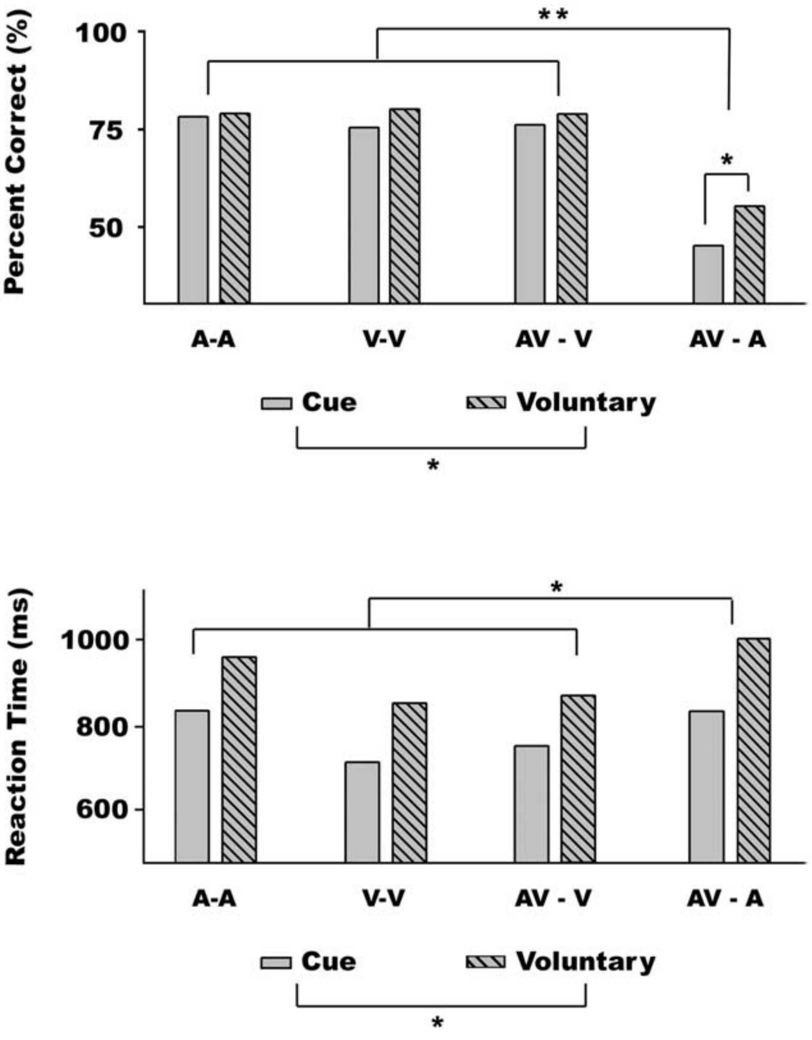

Percent Correct (%)
100
75
50
A-A
V-V
AV - V
AV - A
**
*
Cue
Voluntary
*
Reaction Time (ms)
1000
800
600
A-A
V-V
AV - V
AV - A
*
Cue
Voluntary
*

FIGURE 3

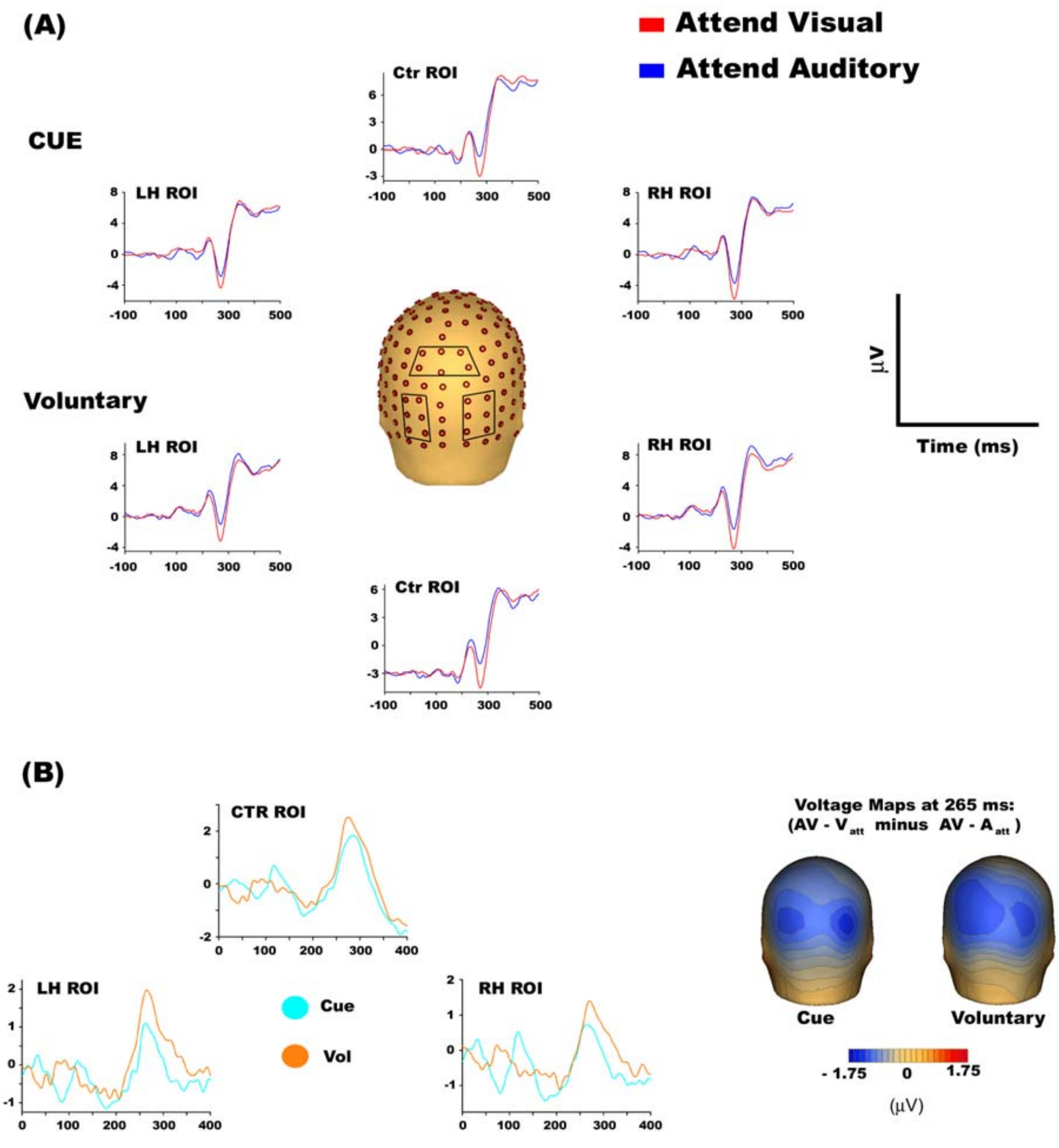
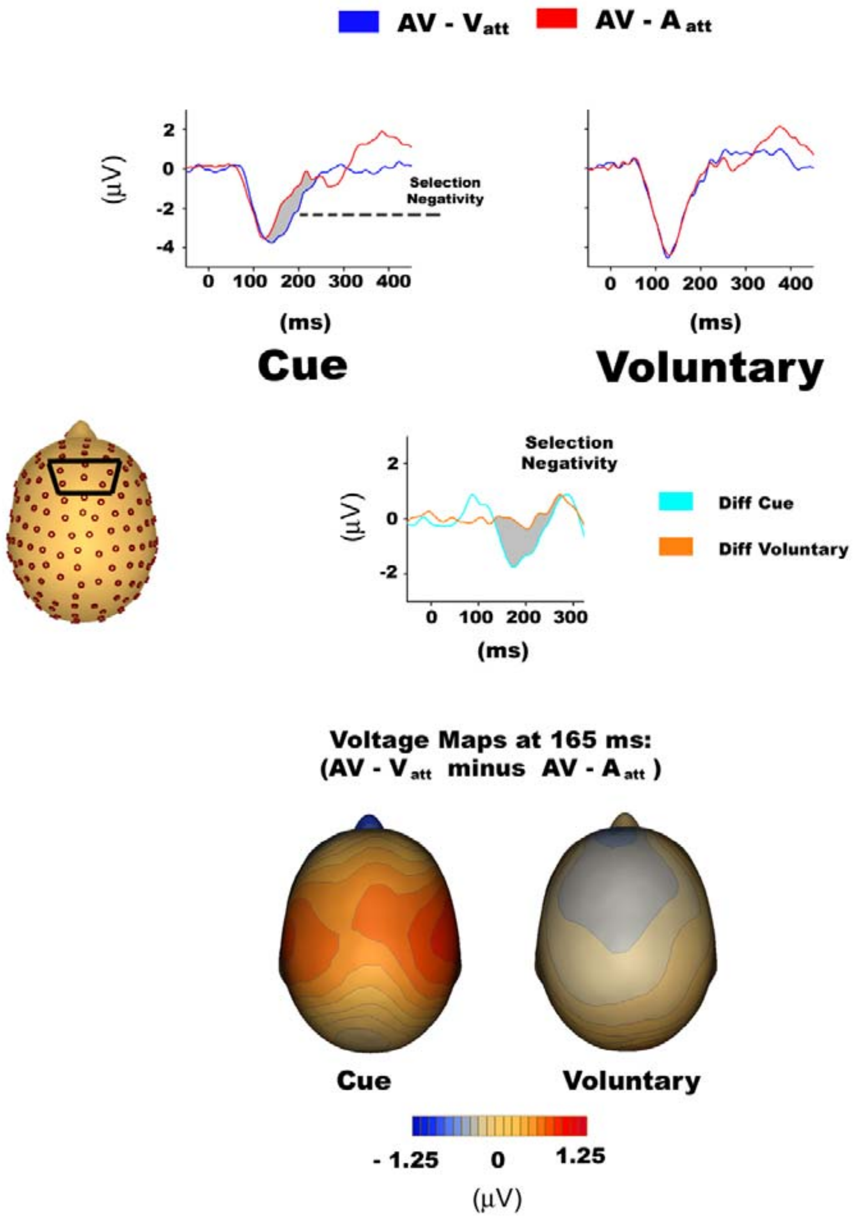
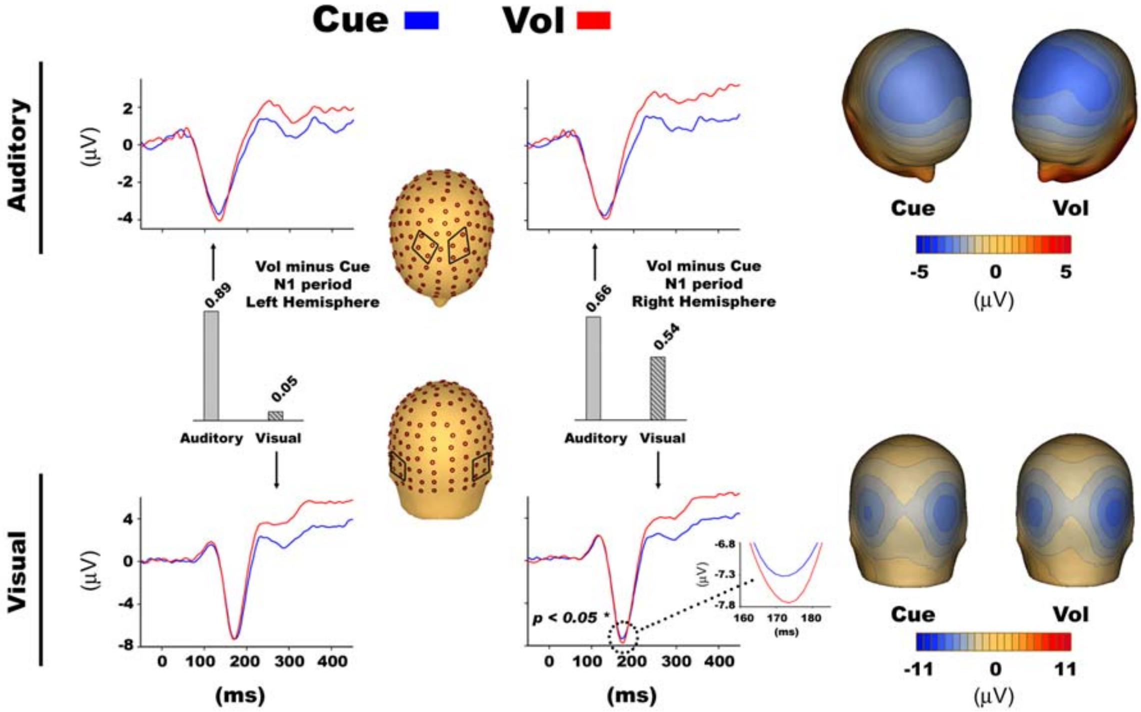

(A)
Attend Visual
Attend Auditory
CUE
Ctr ROI
LH ROI
RH ROI
Voluntary
LH ROI
RH ROI
Ctr ROI
μV
Time (ms)
-100
100
300
500
8
6
4
3
0
-3
-4
(B)
CTR ROI
LH ROI
RH ROI
Cue
Vol
0
100
200
300
400
2
1
0
-1
-2
Voltage Maps at 265 ms:
(AV - V$_{att}$ minus AV - A$_{att}$)
Cue
Voluntary
- 1.75
0
1.75
(μV)

FIGURE 4



AV - V_{att}
AV - A_{att}
2
0
-2
-4
(μV)
Selection Negativity
0 100 200 300 400
(ms)
Cue
Voluntary
Selection Negativity
Diff Cue
Diff Voluntary
0 100 200 300
Voltage Maps at 165 ms:
(AV - V_{att} minus AV - A_{att})
Cue
Voluntary
- 1.25
0
1.25
(μV)

FIGURE 5


Cue
Vol
Auditory
Visual
(μV)
2
0
-2
-4
4
0
-4
-8
0 100 200 300 400
(ms)
Vol minus Cue
N1 period
Left Hemisphere
Vol minus Cue
N1 period
Right Hemisphere
0.89
0.05
0.66
0.54
Auditory
Visual
p < 0.05 *
-6.8
-7.3
-7.8
160 170 180
(ms)
Cue
Vol
-5
0
5
(μV)
-11
0
11
(μV)

CHAPTER 5

The deployment of Intersensory Selective Attention: A high-density electrical mapping study of the effects of theanine.

Reprinted from Clinical Neuropharmacology, 30:25-38, Gomez-Ramirez M., Higging BH., Rycroft JA., Owen GN., Mahoney J., Shpaner M., & Foxe JJ., The Deployment of Intersensory Selective Attention: A High-density Electrical Mapping Study of the Effects of Theanine, Copyright (2007), with permission from Lippincott Williams & Wilkins.

1. ABSTRACT

Ingestion of the non-proteinic amino acid Theanine (L-N-ethylglutamine) has been shown to increase oscillatory brain activity in the so-called alpha-band (8-14 Hz) during resting EEG recordings in humans. Independently, alpha-band activity has been shown to be a key component in selective attentional processes. Here, we set out to assess whether theanine would cause modulation of anticipatory alpha activity during selective attentional deployments to stimuli in different sensory modalities, a paradigm in which robust alpha attention effects have previously been established. The present study replicated these studies in that it showed significantly greater alpha-band activity over parieto-occipital scalp for attentional deployments to the auditory modality than to the visual modality. Theanine ingestion resulted in a substantial overall decrease in background alpha levels relative to placebo while subjects were actively performing the demanding attention task. Despite this decrease in background alpha activity, the attention-related alpha effects were significantly greater for the theanine condition. This increase of attention-related anticipatory alpha over right parieto-occipital scalp suggests that theanine may have a specific effect on the brain's attention circuitry. Further, independent of treatment condition, behavioral results showed a substantial decrement in performance of the auditory task when visual stimuli were concurrently presented, a result that appears to contradict previous claims that supramodal attentional systems are not capacity-limited. In summary, we conclude that theanine has clear psychoactive properties and that it represents a potentially interesting 'naturally occurring' compound for further study as it relates to the brain's attentional system.

2. INTRODUCTION

Theanine (L-N-ethylglutamine) is a naturally occurring non-proteinic amino acid that, along with caffeine and cathecins, is one of the three major constituents of tea (*Camellia sinensis)*. Found only in tea and one rare mushroom variety (xerocomus badius), it is relatively easy to extract from tea, and it is not uncommon for it to be consumed in its purified form as a dietary supplement, with many of the commercial concerns proffering claims regarding beneficial psychological and physiological effects. Regrettably, the vast majority of these claims remain to be properly substantiated in clinical trials. One claim that appears to have some reasonable measure of physiological support, however, relates to potential effects on the resting brain state. That is, ingestion of theanine has been shown to increase oscillatory brain activity in the so-called alpha-band (8-14 Hz) when subjects are in a passive resting state (see Juneja et al., 1999). Indeed, this brain rhythm has traditionally been associated with a relaxed state (e.g. Pfurtscheller, 1992). This finding of increased alpha due to theanine ingestion was recently corroborated by Nobre and colleagues at the University of Oxford (personal communication). An increase in alpha activity implies that theanine or one of its metabolites is likely psychoactive and warrants further investigation.

Activity in the alpha-band has classically been associated with the general state of mental alertness or arousal (see e.g. Klimesch et al., 1998), implying in turn that theanine may exert effects on the level of alertness or attentiveness of humans. Indeed, anecdotal reports from tea drinkers often emphasize changes in general arousal and relaxation state. An open question, however, is whether the effects of theanine on oscillatory brain mechanisms are relatively non-specific, limited to more general arousal states during periods of rest or passivity, or whether this compound also operates in a more specific manner on attentional control systems of the brain when subjects are engaged in more demanding and mentally taxing tasks.

Previous studies have shown that oscillations in the alpha-band are not simply associated with brain arousal states but that these oscillatory potentials are also key components in selective attentional processes (see Vanni et al., 1997; Foxe et al 1998; Worden et al., 2000; Fu et al., 2001; Bastiaansen et al., 2001a, Bastiaansen et al., 2001b; Kelly et al., 2005; Sauseng et al., 2005; Thut et al, 2005; Yamagishi et al., 2005; Rihs et al., 2005). That is, directed deployment of alpha-oscillatory activity appears to underlie the suppression of distracting information in visual space during highly demanding attention tasks. For example, it has been shown that there is a highly specific pattern of alpha oscillatory activity when humans deploy their attention to stimulation in one sensory modality (e.g. audition) while attempting to exclude or suppress inputs from an interfering sensory modality (e.g. vision) (Foxe et al., 1998; Fu et al., 2001; Bastiaansen, 2001).

In one such study, Foxe et al. (1998) used symbolic cue stimuli to instruct subjects to attend to a given sensory modality (either audition or vision). After a one-second delay, a compound audio-visual multisensory stimulus appeared and subjects performed a very demanding task solely within the cued modality while attempting to suppress inputs from the other distracting modality. It was shown that deploying attention to impending stimuli in the auditory modality resulted in a robust increase in alpha power during the late phase of the cue-to-target-interval (CTI; i.e., the attentional deployment phase) over parieto-occipital scalp regions. It was proposed that this oscillatory alpha enhancement reflected anticipatory gating or suppression of visual processing by parieto-occipital structures known to be involved in attentional switching and disengagement within the visual modality (e.g. Posner et al., 1984; Posner and Petersen, 1990; Foxe et al 1998; Worden et al 2000). A subsequent study by Worden et al. (2000) showed that similar alpha processes were deployed to locations in space where distracters might appear during a demanding visuo-spatial selective attention task, reinforcing the role of alpha processes in attentional deployment and distracter suppression (see also Kelly et al., 2005; Sauseng et al., 2005).

The present study set out to assess whether theanine would cause modulation of anticipatory alpha activity during selective attentional deployments to stimuli in different sensory modalities. Here, subjects performed a task similar to that of Foxe et al (2005a, 2005b) in which they were instructed to deploy their attention to a given modality (auditory or visual), on a trial-by-trial basis. By inspecting the alpha-band activity during the cue-target-interval (CTI), the effects of theanine on intersensory attentional deployments were assessed. A simple hypothesis was tested. We reasoned that since theanine is now known to affect overall alpha-band activity during the resting state, it might also enhance (or indeed suppress) alpha-based attentional mechanisms. If the latter is the case, this would provide direct evidence that theanine does not simply have a general effect on arousal but can affect more specific attentional brain states. Further, if theanine is found to enhance attentional processes, this compound might well represent a potentially attractive, naturally occurring, intervention for attentional disorders.

3. METHODS

Participants

Fifteen (eight females) neurologically normal, paid volunteers (mean age = 27.8, SD 6.5 years, age range 18 – 36 years) participated. All participants provided written informed consent, and the Institutional Review Board of the Nathan Kline Research Institute approved the procedures. All participants reported normal or corrected-to-normal vision and all were right-hand dominant as assessed by the Edinburgh handedness inventory (Oldfield, 1971). Subjects were required to refrain from drinking any caffeine-based products (such as soft drinks, soda, coffee or tea) for at least 24 hours before the day of testing. Subjects' neurological status was determined by conducting a shorten version of the Structured Clinical Interview for DSM-IV-TR (SCID).

Experimental Paradigm

The sequence of events in a typical trial is illustrated in Figure one. A trial commenced with the onset of the cue stimulus (S1) instructing participants as to which modality they should attend. Stimulus onset asynchrony (SOA) between S1 and S2 (i.e. the Cue and the subsequent potential target) was 1200 ms. The inter-trial interval (ITI: i.e. the period between each pair of Cue-target stimuli) randomly varied between 1400 and 2400 ms. A central fixation cross (black and 1° angle) remained on the screen throughout the experiment and participants were instructed to maintain fixation at all times. All visual stimuli were displayed on a gray background, while all auditory stimuli were presented through headphones. Participants completed a minimum of 15 blocks of trials, on each of the 2 days of testing. Each block contained a total of 100 S1-S2 pairs, giving an average block run-time of 5 minutes. The specific details of the stimuli themselves follow.

S1 (Cues): The cue-stimulus (S1) was presented auditarily and was either the word 'AUD' or 'VIS', spoken by a male speaker and presented bilaterally via Sennheiser HD600 headphones (duration 400 ms, 10 ms rise-fall, 80 dB SPL). These word cues indicated the sensory modality (auditory or visual) to be attended when the second stimulus (S2) arrived. Specifically, the pseudo-word 'AUD' instructed participants to deploy their attention to the auditory modality, while the pseudo-word 'VIS' instructed the participants to attend to the visual modality. These cue-stimuli appeared in random order throughout the experiment.

S2 (Targets): The S2 consisted of either an auditory-alone (pair of tones, 20%), visual-alone (pair of gabor patches, 20%), audio-visual compound (pair of tones and gabor patches, 40%), or a null (catch) stimulus ('no S2' stimulus, 20%). The auditory S2 stimulus consisted of a pair of binaural tones (e.g. 2000 Hz or 2100 Hz, 80 dB SPL, 100 ms duration each, 5 ms rise/fall, 5 ms interval between tones). That is, the pair of tones was presented in a rapid sequence with auditory stimulation lasting for a total of 205 ms. The visual stimulus consisted of a pair of gabor patches (4.5^{o} in diameter, centered 2.5^{o} left and right of fixation, 100 ms duration). The audio-visual compound stimuli were a combination of the above-described auditory and visual stimuli. The null stimulus consisted of a period of fixation only. All visual stimuli were presented on an Iiyama VisionMaster Pro502 21" computer monitor, on a gray background. Subjects were instructed to maintain fixation on a 1^{o} black fixation-cross present at all times in the center of the screen.

On 85% of visual S2 trials, the pair of Gabor patches was identical and no overt response was required (i.e. these were non-target standards). On 85% of auditory S2 trials, the pair of tones was also identical and no response was required. On the other 15% of visual S2 trials, the orientations of the left and right Gabor patches were slightly different (see below) and subject responded with a button push (i.e. these were target stimuli) when they had been cued to the visual modality. On 15% of auditory trials, the two tones were of slightly different pitch and also required a response when the auditory modality had been cued. The reader should note that the occurrence of a target in each modality was independent of the other modality, such that the probability of occurrence of a double target (i.e. a bisensory target) was approximately 1%.

This scenario led to four possible target types:1) Unisensory-auditory (i.e. when the cue instructed the subject to attend to the auditory modality and only an auditory S2 stimulus occurred), 2) Unisensory-visual, 3) Multisensory-auditory (i.e. when the cue instructed the subject to attend to the auditory modality and an audio-visual compound multisensory S2 stimulus occurred), and 4) Multisensory-visual.

Procedure

At the beginning of each experimental day, all participants were given either a mixed solution of the theanine substance or a placebo drink. The mixed drink solution consisted of a mixture of 250 mg of powdered clear theanine with 200 ml of room-temperature water. The placebo drink consisted only of the 200 ml of water (i.e. approximately a cup of water). The day of drinking the theanine solution was counterbalanced across participants. Note that theanine is colorless and tasteless in a water solution and subjects were at chance in guessing whether they were taking the active compound or simply water.

On each experimental day, prior to the start of the testing phase, all participants performed a psychophysical test that equated the participant’s performance to an 80% level on both the auditory and visual tasks to be used herein. This psychophysical test, know as the Up-Down Transformed Rule (UDTR, see Wetherill and Levitt 1965), is a rapid method that assures the experimenters that the level of task difficulty for each task will be equivalent across all participants.

Measurements

Continuous electroencephalographic (EEG) data, digitized at 512 Hz, was acquired through the ActiveTwo Biosemi electrode system from 168 scalp electrodes. BioSemi replaces the "ground" electrodes used in conventional EEG systems with two separate electrodes; the so-called Common Mode Sense (CMS) active electrode and the Driven Right Leg (DRL) passive electrode. These 2 electrodes form a feedback loop, which drives the average potential of the subject (the Common Mode voltage) as close as possible to the ADC reference voltage in the AD-box (the ADC reference can be considered as the amplifier "zero"). With the Biosemi system, every electrode or combination of electrodes can be assigned as the “reference”, and this is done purely in software after acquisition. A detailed description of the referencing conventions used by this active electrode system can be found at the following website: http://www.biosemi.com/faq/cms&drl.htm.

All data were re-referenced to a midline prefrontal scalp-site (FPz) after acquisition. After each recording session, before the electrode cap was removed from the subject’s head, the 3D coordinates of the electrodes with reference to anatomic landmarks on the head (nasion, pre-auricular notches) were digitized using a Polhemus Magnetic 3D digitizer. This allowed the investigators to ensure that electrode locations were consistent between test days for all subjects. EEG was recorded continuously and epoched and averaged off-line. Trials with blinks and large eye-movements were rejected offline on the basis of horizontal and vertical electrooculogram recordings. An artifact rejection criterion of ±100 microvolts was used at all other electrode sites to exclude periods of high EMG and other noise-transients.

2.5 Data Analysis Strategy

Accepted trials were epoched for the period around the onset of the S1-cues (-300ms pre-stimulus to 1200ms post-stimulus). Note that only the S1 stimuli are analyzed for the present study. The baseline was defined as the mean voltage from 300ms to 0ms before the onset of S1. Separate averages were made for the two possible variants of the S1 stimuli (cue-AUD and cue-VIS). We inspected oscillatory activity in the alpha band (8-14 Hz[19]) during the CTI. Alpha band activity was characterized in this period by the temporal spectral evolution (TSE) technique, which provides an index of 'induced' alpha activity as a function of time (see Fu et al., 2001 for a full description of the method). All statistical analyses were performed on these induced alpha oscillations. The TSE waveforms are derived by the following method:

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[19] The exact band-pass that constitutes the alpha–band is not consistent across the literature and could be considered somewhat arbitrary. In fact, the centre frequency of alpha is quite variable across individuals and for most it tends to be in the 10-12 Hz range (see e.g. Doppelmayer et al., 1998). As such, the band-pass chosen here of 8-14 Hz nicely spans this range.

- Individual (single trial) stimulus-locked epochs are band-pass filtered after artifact rejection (Butterworth zero-phase, 8 – 14 Hz, 48 dB/octave).
- Filtered epochs are then full-wave rectified (i.e. all negative data points are made positive)
- Rectified waveforms are then averaged.

Repeated measures analysis of variance (ANOVA) was used to statistically test for effects. Factors were Attention Condition (Auditory vs. Visual), Treatment (Theanine vs. Placebo) and Electrode (four electrodes over the right parieto-occipito scalp were chosen, based on previous work, that best represented the maximal trajectory of the alpha oscillations). The epoch chosen for testing here (700ms to 1100ms) was also based on our previous work (Foxe et al., 1998; Worden et al., 2000; Fu et al., 2001) where it was shown that the alpha-effect was maximal in the latter part of the CTI in the period preceding the onset of the S2 (i.e. for approximately 400 ms). The dependent measure was an integrated area measure derived by calculating the difference across this 400ms epoch between the TSE waveform and the 0μV baseline.

A secondary analysis of the relative attentional differences between treatment conditions in induced oscillations was also performed. Specifically, we derived an attentional modulation index. This technique is a useful metric to normalize the data set with regard to background alpha levels. Modulation indices on the induced alpha oscillations were derived by the following method:

- Step 1: An average background alpha activity value was computed for each treatment condition across the 1200ms CTI.

- Step 2: After computing this average, the difference in alpha amplitude between the attend-auditory and attend-visual condition was divided by the appropriate mean value computed in step 1.

4. RESULTS

Performance Data

Percent correct hit responses (accuracy) and reaction time (RT) mean values are shown in Figure 2. Two 2 X 4 repeated measures ANOVAs with factors of Treatment (placebo vs. theanine) and S2 target type (unisensory-auditory, multisensory-auditory, unisensory-visual, multisensory-visual) were computed for both the accuracy and RT data.

For Accuracy, a main effect of stimulus type was found [$F(3,45) = 12.364$, $p < 0.01$], driven by the fact that a considerable performance decrement was seen for the 'multisensory-auditory' stimulus type during both treatment conditions. The reader will recall that the auditory task is identical between the unisensory-auditory and multisensory-auditory conditions, so the presence of distracting visual information in the latter case had a large impact on performance accuracy. No other effects reached significance – that is, accuracy was not found to be different in any condition between treatments (i.e. placebo versus theanine).

For the RT data, a main effect of stimulus type was found [$F(1,14) = 12.23$, $p < 0.01$] due mainly to faster RTs to the 'unisensory-visual' stimuli, again observed during both treatment types. An interaction of treatment X stimulus type [$F(3,45) = 5.96$, $p < 0.05$] was also seen. This was because RTs were considerably slower during the theanine treatment than placebo for both the ‘unisensory-auditory’ and ‘multisensory-auditory’ stimulus types. No other significant effects were found.

Induced Alpha-Band Activity

Alpha band activity during the attentional deployment phase is illustrated in Figure 3. Depicted are the derived 8-14 Hz TSE waveforms for just one representative electrode site over the right parieto-occipito scalp region. It can be seen that the divergence in the alpha-band activity starts to occur at approximately 400 ms and is sustained until the onset of the S2 stimulus at 1200 ms, where the largest difference is observed.

A repeated measures ANOVA performed on these TSE waveforms revealed a main effect of Treatment, $F(1,14) = 9.112$, $p < 0.01$, indicating that overall alpha activity in the late sustained period is significantly reduced by the theanine solution. Figure 3 shows that this drop in the alpha power is present across the whole CTI, not just in the late sustained period.

The ANOVA also revealed a main effect of Attention, $F(1,14) = 9.774$, $p < 0.01$). A trend toward an interaction of Treatment x Attention was also observed [$F (1,14) = 3.056$, $p = .1$]. No other effects reached significance.

In the second phase of our analysis, we derived an attention modulation index. Following the computation of these indices, a 2 X 4 repeated measures ANOVA was computed with factors of Treatment (placebo vs. theanine) and Electrodes (as above). A main effect of Treatment was revealed [$F(1,14) = 6.075$, $p = 0.027$], indicating that the overall amplitude of the alpha attention effect as a function of background alpha, was significantly greater for the theanine treatment day than the placebo day.

To investigate the topographical distribution of the induced alpha effect, the TSE response of the attend-visual condition was subtracted from the TSE response to the attend-auditory condition. This subtraction results in a derived response representing only the differential activity between attention conditions. Following this subtraction, the resulting waveform was modeled using the minimum norm solution technique of the BESA 5.01 software (Brain Electric Source Analysis - www.besa.de).

The topographic analysis of the induced alpha-band oscillatory effect reveals a distribution over bilateral parieto-occipital regions, with a predominance of activity over the right hemisphere (see Figure 4). The theanine treatment condition elicits a greater differential and sustained alpha effect over the period.

5. DISCUSSION

The present study showed that theanine consumption caused substantial effects on the brain's generation of the alpha oscillatory rhythm (8–14 Hz) while subjects performed a demanding intersensory selective attention task. First, theanine consumption resulted in a substantial decrease in overall background alpha power regardless of which sensory modality was being attended. Second, theanine caused a relative amplitude increase of a previously defined alpha-attention effect associated with the deployment of intersensory selective attention (Foxe et al., 1998; Fu et al., 2001). These earlier studies showed that cueing attention to the auditory features of an imminent compound audio-visual stimulus resulted in significantly higher alpha amplitude in the period preceding onset of this stimulus than when attention was cued to the visual features. Here we found that this difference in anticipatory alpha activity was relatively greater when subjects had ingested the theanine, suggesting that theanine may have enhanced this well-characterized attention effect. This anticipatory alpha activity is generated within the right parieto-occipital cortex, a critical node of the brain's attention circuitry, further suggesting that theanine, rather than having a more general effect on arousal levels, may be having more specific effects on the brain's attention circuitry. These and other implications of the present data are discussed in what follows.

A Resting versus "Active" Alpha paradox:

The motivation for the present study was the fact that theanine has been shown to increase ongoing tonic alpha power during the resting or passive state. That is, the two previous studies of the neurophysiology of theanine in humans have simply recorded ongoing EEG while subjects sat passively and were not performing any cognitive task (e.g. Juneja et al 1999). That theanine might enhance alpha activity is of real interest as increased alpha amplitude may have implications for general cognitive performance abilities. For example, Schmid et al. (2002) have shown that children with an impoverished educational background and low reading and writing scores show generally reduced resting alpha power. The same appears to be true of children with attention deficit hyperactive disorder (ADHD) who show generally reduced alpha power (Clarke et al., 2005), and evidence also suggests that this reduction can be normalized through medication (Clarke et al., 2003; Song et al., 2005). Smith et al. (1999) showed a relationship between increasing alpha across practice sessions and improved performance on a verbal working memory task. Most recently, Thut et al. (2005) showed that performance on a visuo-spatial attention task was predicated on the amplitude of preceding anticipatory alpha. In a design closely modeled on the original one used by Worden et al. (2000), subjects were cued by a central arrow to attend to either the left or right hemifields for an impending visual target. Reaction times to detected targets were faster on the attended side, and for both left and right targets RT varied as a function of the amplitude of anticipatory alpha, with faster RTs to right targets when alpha was greater over the right hemisphere (lower on the left) and faster RTs to left targets when alpha was greater on the left (lower on the right). Overall, there appears to be growing evidence that increased tonic alpha power (ie. during the resting state) may be related to better cognitive performance abilities and that the strength of alpha processes during more active tasks, may be a predictor of performance on demanding attentional tasks.

While the present study was designed to specifically assess alpha-attention effects, one surprising and apparently paradoxical outcome was that overall background power was significantly lower in the theanine treatment condition compared to placebo. It is important to point out that this reduction in alpha power is only seen while subjects are engaged in a very demanding cognitive task, so in this sense, our study is entirely different from the previous EEG studies. Unfortunately, in the present study, a measure of tonic alpha was not taken during a resting condition as in the two previous studies, so a direct comparison between these results and previous work is not possible. It should also be noted that despite the overall drop in background alpha observed here, it was also the case that this had no effect on subjects' ability to effectively deploy alpha-attention mechanisms, since the differential alpha effect was greater in the theanine condition. That is, while background alpha dropped in amplitude, concurrent attention-related alpha processes were enhanced. As such, these results may suggest that overall background alpha and attention-related alpha processes represent distinct cognitive functions, a possibility meriting further investigation.

Another consideration here is the makeup of the subject group in our study relative to the previous studies, which were carried out in Japan (Juneja et al 1999) and England (Nobre laboratory) respectively. The young American adults who served in our study were not regular tea-drinkers, and as such, had little to no previous exposure to theanine. This is unlikely to have been the case in the previous studies as tea-drinking is considerably more prevalent in both countries than it is in the United States. Levels of previous and ongoing exposure to theanine are factors that will have to be accounted for in future studies of this compound.

Visual Dominance during Multisensory Target Trials:

One dramatic effect seen here in behavioral performance (for both the placebo and theanine conditions) was a substantial reduction in performance accuracy for the auditory task when visual stimuli were concurrently presented – that is, during the audio-visual multisensory target condition. The reader will recall that both the auditory and visual tasks were psychophysically equated before any recordings were made, with performance calibrated such that all subjects detected exactly 80% of targets in both sensory modalities. However, this pretest psychophysical calibration was only conducted for the unisensory stimulus conditions. Behavioral results show that the manipulation was fully effective as performance remained at or very close to 80% for the both unisensory stimulus conditions across both treatment days. The same result extends to the multisensory-visual targets where subjects also achieved about 80% accuracy, indicating that the presence of simultaneous distracting auditory inputs had no effect on performance of the visual task. The reverse was not the case. Subjects' performance dropped substantially for the auditory task when concurrent distracting visual inputs were present (from 80 % to approximately 50%).

This finding has implications for one prominent view in attentional theory. A central tenet of modern theory is that selective attention is necessary because of the limited informational processing capacity of the brain (Broadbent, 1958). That is, selective attention functions to filter the overwhelming quantity of information constantly impinging on our senses, allowing for preferential processing of a subset of these inputs. Implicit in this construct is the notion that stimuli that are not in the attentional focus receive reduced processing. The existence of a limited capacity is seen in divided attention tasks, where subjects monitor two streams simultaneously and clear deficits in performance within a given stream are seen due to interference from the second stream (e.g. Posner et al., 1980; Duncan, 1993). However, some have claimed that this capacity limitation only occurs when the two streams of information are within a single sensory modality and that no such capacity limit is present when the streams of information occur within separate sensory systems. For example, in a seminal paper, Duncan and colleagues (1997) used the so-called “attentional blink” (AB) paradigm to show that there was no interference between modalities. In the AB paradigm, subjects are typically required to respond to two target stimuli that occur in relatively close temporal proximity within a stream of distracters. Identification of the first target in the sequence produces a sustained reduction in the ability to identify the second target stimulus when the two targets are presented within a single modality – that is, when all stimuli are only visual (or only auditory). In contrast, Duncan et al (1997) showed that when a pair of targets was presented in two different modalities, one auditory and the other visual (or vice-versa), no such interference effects were found. Similar results for audio-visual pairings were found by Potter et al. (1998) and Soto-Faraco & Spence (2002)[20]. This finding led Duncan and colleagues to propose that "visual attention to one simple target does not restrict concurrent auditory attention to another" and to conclude that there was no restricted attentional capacity between sensory modalities.

The present results argue otherwise. Concurrent visual stimulation, despite being completely irrelevant to the task at hand, caused a substantial decrement in subjects' abilities to perform the auditory discrimination task, suggesting that supramodal attentional systems do in fact have a limited capacity. In this respect, our results are reminiscent of early work by Colavita (Colavita, 1974, Colavita and Weisberg, 1979; see also Sinnett et al 2005).

The question becomes why such a strong interference effect is seen in these data but not in the attentional blink paradigms of Duncan and others. One possible explanation is that a degree of automatic multisensory integration of the simultaneous auditory and visual constituents of our multisensory targets occurred. Indeed, Duncan explicitly pointed out that their auditory and visual stimulation streams were clearly separable and they were careful to specify that other circumstances might apply for the case where the auditory and visual events emanated from the same object (i.e. when multisensory integration might occur). Our auditory and visual stimuli did occur in temporal register although it should be emphasized that they were presented in different spatial locations (headphones versus computer screen) and they had no natural relationship with each other. Further, subjects were required to explicitly treat them as separate stimulus streams

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[20] Note that an attentional blink was in fact found by Soto-Faraco et al. (2002) between the visual and somatosensory modalities, suggesting capacity limitations may vary across sensory combinations.

to be attended differentially, and this separability would have been reinforced by the fact that only 40% of the S2 stimuli were actually bisensory. Nonetheless, some degree of automatic multisensory integration of the auditory and visual components of S2 may well have occurred and there is precedence in the literature for integration of even such basic stimuli (e.g. Molholm et al., 2002, 2004; see Foxe and Schroeder, 2005; Schroeder and Foxe, 2005).

Another obvious question that arises is why the interference effect is found to be unidirectional, only affecting performance on the auditory task when targets were bisensory, with visual performance remaining unaffected. A striking phenomenon in the study of perceptual models of multisensory stimuli is the tendency of visual information to dominate other competing sensory stimuli. Jordan (1972) and Posner et al. (1976) have argued that visual dominance phenomena arise from brain mechanisms designed to compensate for the "low alerting capability of visual signals". The premise is that because of this intrinsically lower state of alertness in the visual system, the attentional system is biased towards vision when there is a probability that reliable information will be provided in this modality. As a consequence, this visual biasing would result in the withdrawal of processing resources from other senses. It should be pointed out though that Posner and colleagues proposed that this general attentional biasing would only occur when the subjects are likely to receive reliable inputs from the visual modality. In order to test this, Klein (1974) presented subjects with random trials of visual, somatosensory, or multisensory somato-visual stimuli. He found that subjects responded fastest to the multisensory stimuli and slowest to the visual-alone stimuli. These results led Posner et al (1976) to propose that in a conflict situation (i.e. when vision, proprioception and/or audition provide discrepant information), visual inputs will tend to dominate the brain's attentional system unless the subject is aware that responses based on visual information will be disadvantageous. Both Jordan (1972) and Posner et al (1976) predicted that visual dominance would "no longer prevail" under circumstances where vision doesn't provide adequate information.

The present results simply do not align with this view. A strong visual dominance effect persists, even when the visual stimuli are known by subjects to be immaterial to the task at hand, suggesting that endogenous attentional processes cannot fully supersede exogenous attentional capture by visual inputs. Our data suggest that there is indeed an attentional capacity limit for streams of information occurring across two sensory modalities. The contention that there is no attentional capacity limit between sensory modalities is also not supported by data from patients with spatial neglect syndrome. For example, Mattingly et al. (1997) have shown cross-sensory extinction between vision and touch in neglect patients, again suggesting a central supramodal attentional bottleneck (see also Rapp & Hendel, 2003; Bueti et al., 2004). Similarly, extinction between audition and touch has also been described (Ladavas et al., 2001).

Theanine Slows RTs to Auditory Stimuli:

Our results also showed a marked slowing of RTs for all auditory conditions when subjects had ingested theanine (by as much as 60ms), although there was no change in performance accuracy. This fairly dramatic slowing of responses was unique to the auditory modality, as RTs to all visual stimuli remained unaffected by theanine. One possibility is that theanine may cause subjects to be more deliberate when confronted with such stimuli although why this would only occur for the auditory stimuli is not clear and if subjects have become more deliberate, they certainly haven't benefited in terms of accuracy from such a change. Whatever the case, and this needs more study, theanine appears to differentially affect the auditory and visual sensory modalities, causing a measurable slowing of performance in the auditory domain. One possibility is that theanine may increase susceptibility to visual dominance as described above.

6. CONCLUSIONS

High-density electrical mapping showed that theanine ingestion had robust effects upon alpha-oscillatory activity in the cortex of healthy adult subjects while they performed a highly demanding intersensory attention task. We found a robust decrease in background alpha activity but a concomitant increase in attention-related alpha effects. That is, over the late sustained period of an attentional deployment phase, while subjects prepared to attend to either the visual or auditory modality for an impending multisensory target, differential alpha deployments were observed with greater amplitude than was seen during a placebo control condition. Topographic mapping confirmed that these alpha processes were generated in the posterior parietal cortices, especially over the right hemisphere. Thus, theanine, as well as affecting more general brain rhythms associated with cortical arousal, was found to have more specific effects on known nodes of the visual attention circuit. We conclude that theanine has clear psychoactive properties and that it represents a potentially interesting 'naturally occurring' compound for further study as it relates to the brain's attentional system.

7. ACKNOWLEDGMENTS

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9. FIGURES & FIGURE LEGENDS

Figure 1. Schematic illustration of the paradigm

A. Each trial commenced with the presentation of an auditory symbolic cue (S1) whereby the abbreviated words “Aud” (for Auditory) or “Viz” (for Visual) were presented across headphones to the subjects. A delay period of 800ms followed the cue, after which one of the following four types of S2 stimuli would appear: auditory stimuli alone, visual stimuli alone, catch trials where no physical stimulus was presented, or compound audio-visual multisensory stimuli. Subjects were required to respond with a button push to targets within the cued modality.

B. An example of a visual target trial. A pair of Gabor patches were presented bilaterally with the orientation of one slightly different to the other. Target trials occurred on only 20% of visual S2s. On the other 80% of trials, the orientation of both patches was identical. The orientation difference was psychophysically calibrated on an individual subject basis such that subjects could only identify 80% of targets correctly.

Figure 2. Behavioral Data

Hit rates are plotted for each treatment in the upper graph. Mean reaction times for correct responses are plotted in the lower graph.

Figure 3. Alpha-band oscillatory activity is selectively modulated by deployment of anticipatory attention to different sensory modalities.

TSE waveforms from one electrode over the right parieto-occipito scalp are plotted for the placebo (upper panel) and theanine conditions (lower panel). A sustained divergence in TSE amplitude is seen starting at approximately 400 ms post-cue. In both treatment conditions, alpha-band activity is significantly greater when subjects have been cued to attend selectively to impending auditory stimulation (blue trace) compared to visual stimulation (red trace). However, this sustained divergence is significantly greater during the theanine condition compared to the placebo condition.

Figure 4. Topographical Analysis

Topographic analysis using the minimum norm solution reveals a clear predominance of alpha oscillatory activity over the right parieto-occipito region. The theanine treatment condition (lower field) elicits a greater differential and sustained alpha effect compared to placebo (upper field).

10. FIGURES

FIGURE 1

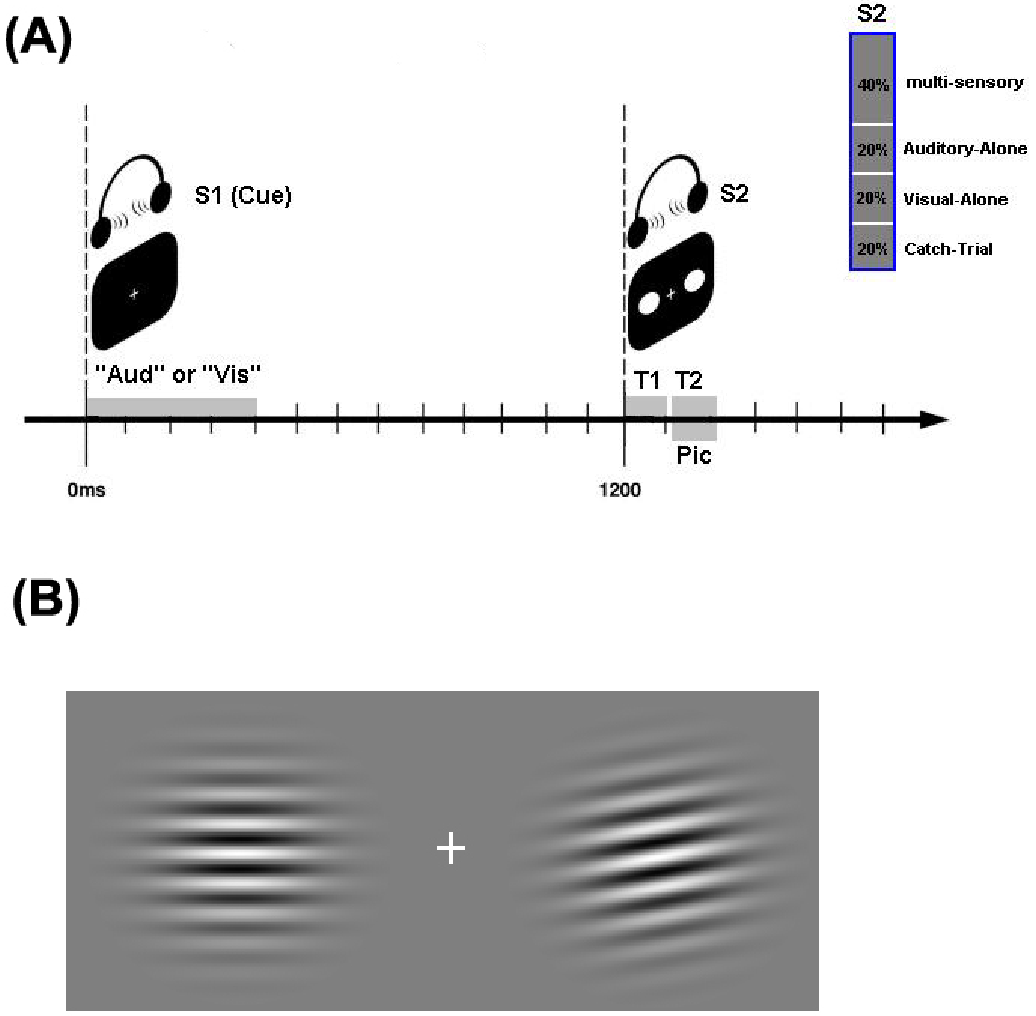
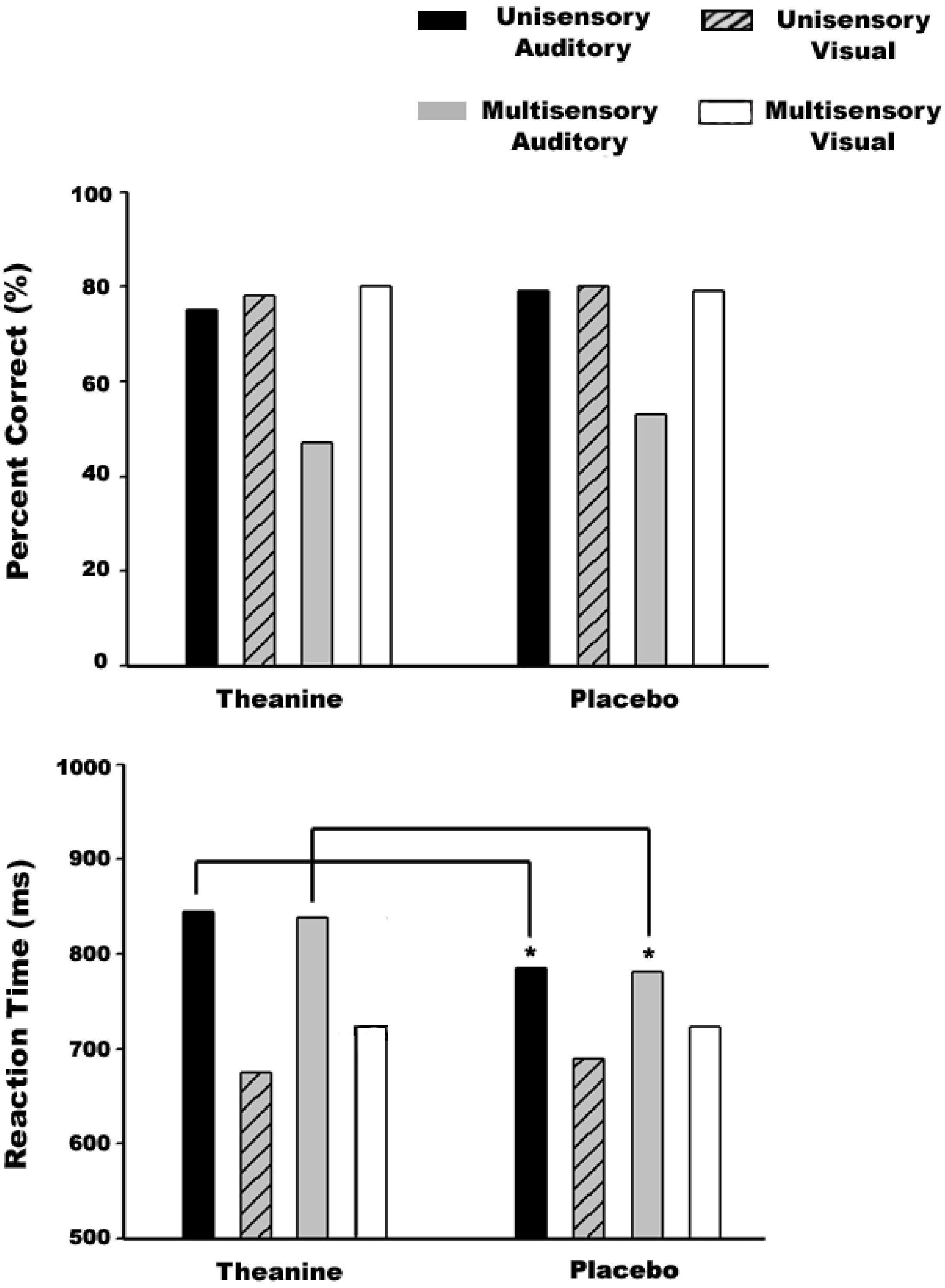


FIGURE 2


Unisensory Auditory
Unisensory Visual
Multisensory Auditory
Multisensory Visual
Percent Correct (%)
100
80
60
40
20
0
Theanine
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Reaction Time (ms)
1000
900
800
700
600
500
*
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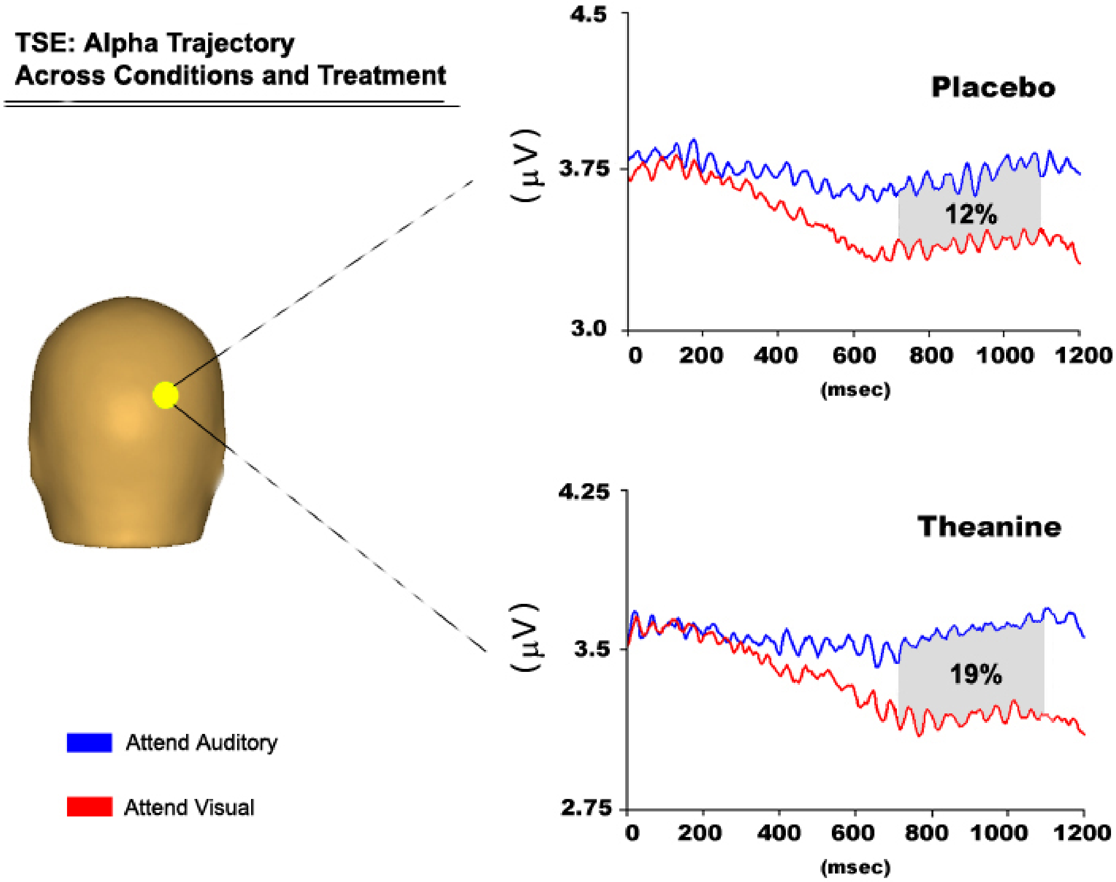
Theanine
Placebo

FIGURE 3


TSE: Alpha Trajectory
Across Conditions and Treatment
Placebo
4.5
3.75
3.0
(µV)
12%
0
200
400
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800
1000
1200
(msec)
Theanine
4.25
3.5
2.75
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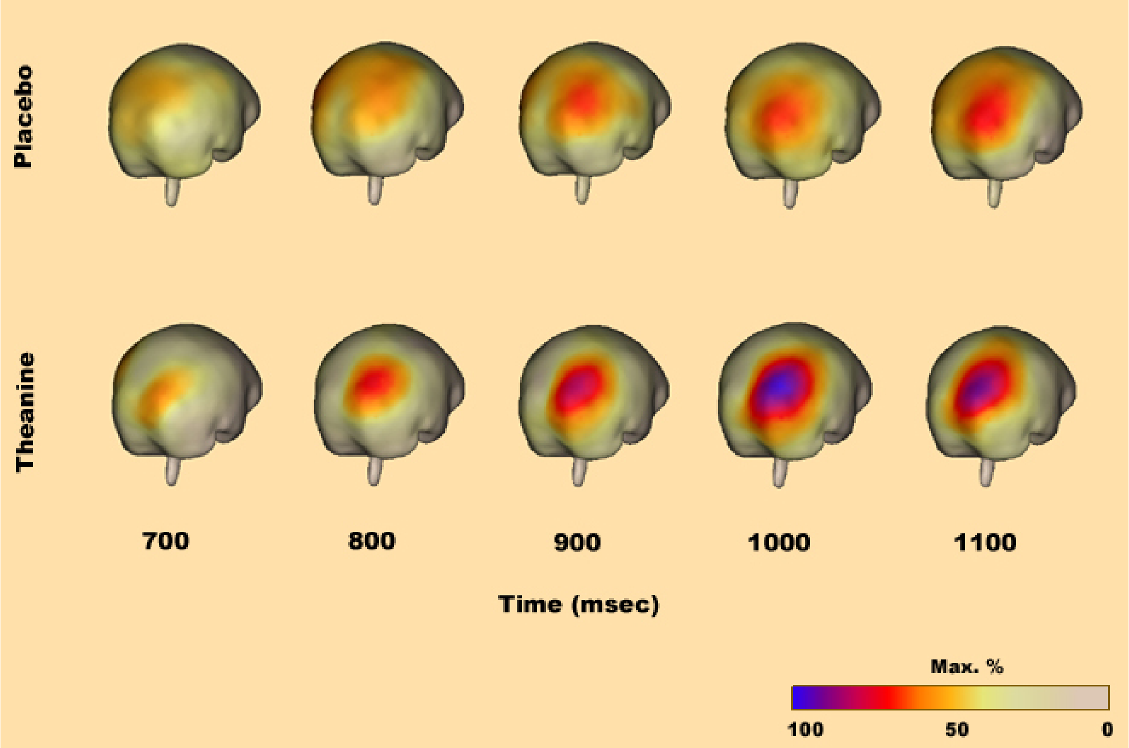
FIGURE 4



CHAPTER 6

The effects of L-theanine on alpha-band oscillatory brain activity during a visuo-spatial attention task

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1. ABSTRACT

Background/Objectives: Ingestion of the non-proteinic amino acid L-theanine (γ-glutamylethylamide) has been shown to influence oscillatory brain activity in the alpha band (8-14 Hz) in humans during resting electroencephalographic (EEG) recordings and also during cognitive task performance. We have previously shown that ingestion of a 250-mg dose of L-theanine significantly reduced *tonic* (background) alpha power during a demanding intersensory (auditory-visual) attentional cueing task. Further, cue-related *phasic* changes in alpha power, indexing the shorter-term anticipatory biasing of attention between modalities, were stronger on L-theanine compared to placebo. This form of cue-contingent phasic alpha activity is also known to index attentional biasing within visual space. Specifically, when a relevant location is pre-cued, anticipatory alpha power increases contralateral to the location to be ignored. Here we investigate whether the effects of L-theanine on tonic and phasic alpha activity, found previously during intersensory attentional deployment, occur also during a visuospatial task.

Subjects/Methods: 168-channel EEG data were recorded from thirteen neurologically normal individuals while engaged in a highly demanding visuo-spatial attention task. Participants underwent testing on two separate days, ingesting either a 250-mg colorless and tasteless solution of L-theanine mixed with water, or a water-based solution placebo on each day in counterbalanced order. We compared the alpha-band activity when subjects ingested L-Theanine vs. Placebo.

Results: We found a significant reduction in tonic alpha for the L-theanine treatment compared to placebo, which was accompanied by a shift in scalp topography, indicative of treatment-related changes in the neural generators of oscillatory alpha activity. However, L-theanine did not measurably affect cue-related anticipatory alpha effects. **Conclusions:** This pattern of results implies that L-theanine plays a more general role in attentional processing, facilitating longer-lasting processes responsible for sustaining attention across the timeframe of a difficult task, rather than affecting specific moment-to-moment phasic deployment processes.

2. INTRODUCTION

With a history of consumption stretching over thousands of years, tea is now the most commonly consumed beverage in the world after water, and continues to grow in popularity. Consumers often associate tea with subjective effects on "state of mind" and mood, as much as the obvious factor of taste. Anecdotal testimony regarding these effects has recently been borne out in experimental investigations, with findings of increased relaxation ratings, stress relief, and alertness resulting from placebo-controlled tea studies (e.g. Hindmarch et al 2000; Steptoe et al 2007). Several recent studies have focused their investigation on the non-proteinic amino acid L-theanine (γ-glutamylethylamide), a substance found almost exclusively in tea and known to elicit neurochemical effects in the brain within 1 hour of consumption (Terashima et al 1999).

Previous studies in healthy humans have suggested that ingestion of L-theanine can affect oscillatory brain activity in the so-called alpha-band (8-14 Hz) when subjects are in a passive resting state (Kobayashi et al 1998; Juneja et al 1999). This brain rhythm has traditionally been associated with a relaxed state (Pfurtscheller 1992), and has also been linked to general states of mental alertness and/or arousal (e.g. Klimesch et al 1998). More recent research has shown that alpha activity is not simply associated with brain arousal states but indexes the operation of selective attention mechanisms (Vanni et al 1997; Foxe et al 1998; Worden et al 2000; Fu et al 2001; Bastiaansen & Brunia 2001; Bastiaansen et al 2001; Kelly et al 2005; Yamagishi et al 2005; Sauseng et al 2005; Kelly et al 2006; Thut et al 2006; Rihs et al 2007; Kelly et al 2008). For example, several studies from our lab have shown that alpha activity is highly involved in distracter suppression mechanisms during visuo-spatial and intersensory attentional deployments (see Worden et al 2000; Fu et al 2001; Kelly et al 2006). Furthermore, this oscillatory alpha activity has been found to predict both the accuracy level and reaction time in detecting a visual target stimulus (see Thut et al 2006; Kelly et al 2007 – *Abstract Presentation at the Cognitive Neuroscience Meeting in NY, 2007*)

Following up on a series of experiments on alpha-mediated attention mechanisms, we recently investigated the effects of a 250-mg dose of L-theanine on alpha activity during a highly demanding intersensory attention task (Gomez-Ramirez et al 2007). In this study, a symbolic cue stimulus instructed subjects to attend to either the auditory or visual modality, thus preparing to preferentially process an imperative stimulus that may appear ~1 s later in that modality, and to disregard any information emanating from the uncued modality. Previous studies of this paradigm revealed that attention deployments to the visual modality result in a decrease in parieto-occipital alpha power in the anticipatory period prior to imperative stimulus presentation, while deploying attention to the auditory modality results in an increase (Foxe et al 1998; Fue et al 2001). This differential in phasic (event-related) alpha-band activity is proposed to reflect anticipatory gating of visual processing by parieto-occipital structures known to be involved in attentional switching and disengagement within the visual modality. The data of Gomez-Ramirez and colleagues (2007) showed an enhanced differential alpha effect when subjects ingested L-theanine compared to placebo, suggesting that L-theanine may have a specific facilitatory effect on the brain's attentional deployment mechanisms. In addition to this effect on phasic deployment processes, a significant overall drop in tonic (background) alpha-band activity was observed, i.e. alpha amplitude appeared reduced across all trial periods, in all conditions.

The aims of the present study were twofold. First, we wished to investigate whether a similar enhancement in the cue-related, phasic alpha differential as seen in Gomez-Ramirez et al 2007 would be observed during a visuospatial attention task, for which analogous, retinotopically specific cueing effects are routinely observed (Worden et al 2000, Kelly et al 2006; Thut et al 2006). Second, we wished to test for the finding of decreased tonic alpha on L-theanine as was observed in our previous study (see Gomez-Ramirez et al 2007).

3. METHODS

Participants:

Thirteen (five females) neurologically normal, paid volunteers (mean age = 23.5, SD 3.25 years) participated. Two participants were excluded from the analyses due to excessive eye movements during the task. All participants provided written informed consent, and the Institutional Review Board of the Nathan Kline Institute approved the procedures. All participants reported normal or corrected-to-normal vision and all were right-hand dominant as assessed by the Edinburgh handedness inventory (Oldfield 1971). Subjects were required to refrain from drinking any caffeine-based products (such as soft drinks, soda, coffee or tea) for at least 24 hours before the day of testing. Subjects' neurological status was assessed via a shortened version of the Structured Clinical Interview for DSM-IV-TR (SCID).

Treatment:

At the beginning of each experimental day, all participants were given either a mixed solution of the L-theanine substance or a placebo drink. The mixed drink solution consisted of 250 mg of powdered clear L-theanine with 200 ml of room-temperature water. The placebo drink consisted only of the 200 ml of water (i.e. approximately one cup). The day of drinking the L-theanine solution was counterbalanced across participants. Note that L-theanine is colorless and flavorless in a water solution. Anecdotally, subjects were at chance in guessing whether they were taking the active compound or simply water.

Experimental paradigm:

The sequence of events in a typical trial is illustrated in Figure 1. A trial commenced with the onset of a visual cue stimulus (S1) indicating the location to which attention was to be deployed in anticipation of an imperative stimulus (S2) appearing 900 ms later. The inter-trial interval (ITI, i.e. the time between S2 offset and following S1 onset) was 1500 ms. A central fixation cross (white; 1° of visual angle) remained on the screen throughout the experiment and participants were instructed to maintain fixation at all times. All visual stimuli were presented on an Iiyama VisionMaster Pro502 21" computer monitor, on a black background.

The S1 (cue) consisted of a white arrow (duration 100 ms, 1° visual angle; see Fig 1) pointing leftward or rightward with equal probability toward one of two marked peripheral locations in the upper hemifield. Cue stimuli appeared in random order throughout the experiment.

The S2 (imperative stimulus) consisted of the letter T rotated at either 0°, 90°, 180° or 270° (white, 60 ms duration, 0.66° visual angle) constructed from two orthogonal line segments, and surrounded by four equally spaced distracter circles (0.66° visual angle). The S2 appeared inside a square outlined by 4 white dots (3.33°, centered at 4.1°

eccentricity) placed in the left and right visual fields, which were permanently present throughout the experiment (see Fig 1).

At the beginning of each block, one specific ‘T’ orientation was assigned as the target stimulus for that block. On 20% of trials the target stimulus appeared and subjects were instructed to make a speeded button push if it appeared at the cued location only. On 60% of the trials, the orientation of the ‘T’ stimulus was different than the target, and subjects were instructed to withhold any response. The remaining 20% of trials were “catch trials”, where no S2 was presented. The subject was instructed to attend to the stimuli appearing at cued location only, and to ignore any information appearing in the uncued location. Participants completed a minimum of 14 blocks of trials, on each of the 2 days of testing. Each block contained a total of 100 S1-S2 pairs, giving an average block run-time of less than 5 minutes.

Data Acquisition:

Continuous electroencephalographic (EEG) data, digitized at 512 Hz, was acquired through the ActiveTwo Biosemi electrode system from 168 scalp electrodes. With the Biosemi system, every electrode or combination of electrodes can be assigned as the “reference”, and this is done purely in software after acquisition. A detailed description of the referencing conventions used by this active electrode system can be found at the following website: http://www.biosemi.com/faq/cms&drl.htm.

All data were re-referenced to an electrode placed on the nose (Nz) after acquisition. After each recording session, before the electrode cap was removed, the 3D coordinates of the electrodes with reference to anatomic landmarks on the head (nasion, pre-auricular notches) were digitized using a Polhemus Magnetic 3D digitizer. The average location across all subjects was computed and used as the ‘electrode file location’ and supplied to the BESA software for 3D voltage source mapping. EEG was recorded continuously and epoched and averaged off-line. Trials with blinks and large eye-movements, defined as continuous deviations of 20 ms or more of at least ± 15 µV on both eye channels relative to a preceding 10-ms baseline period, were rejected offline. Before epoching and averaging, the continuous EEG of an electrode site was linearly interpolated, using the data from the four nearest ‘good-standing’ electrodes, if the standard deviation of amplitude over the whole block at that electrode was 50% greater than that of at least three of the six neighboring channels. Thereafter, epoched trials on which activity exceeded ±100 µV on at least four electrodes were rejected. In all subjects, an acceptance rate of greater than 90% was observed.

Data Analysis:

Accepted trials were epoched separately for the S1 (-300ms pre-stimulus to 900ms post-stimulus) and the S2. Only the S1 stimuli were analyzed for the present study. The baseline was defined as the mean voltage from 200ms to 0ms before the onset of S1 (i.e. two full cycles of a 10 Hz oscillation). Separate averages were made for the two possible variants of the S1 stimulus (cue-Left and cue-Right). We inspected oscillatory activity in the alpha band (8-14 Hz[21]) during the cue-to-target interval (CTI). Alpha band activity was characterized in this period by the temporal spectral evolution (TSE) technique, which provides an index of ‘induced’ alpha activity as a function of time (see Foxe et al

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[21] The exact band-pass that constitutes the alpha–band is not consistent across the literature and could be considered somewhat arbitrary. In fact, the centre frequency of alpha is quite variable across individuals and for most it tends to be in the 10-12 Hz range (see e.g. Doppelmayer et al., 1998). As such, the band-pass chosen here of 8-14 Hz nicely spans this range.

1998). All statistical analyses were performed on these induced alpha oscillations. The TSE waveforms are derived by the following method:

- Individual (single trial) stimulus-locked epochs are band-pass filtered after artifact rejection (3rd Order IIR-Butterworth, zero-phase, 8 – 14 Hz).
- Filtered epochs are then Hilbert transformed.
- The absolute value of the Hilbert transformed epoch is computed. This computation is equivalent to a full-wave rectification and enveloping technique that results in robust measures.
- Enveloped waveforms are then averaged.

Two repeated-measures analyses of variance (ANOVA) were used to statistically test for effects over the baseline period (-200 – 0 ms) and the late-stage of the CTI (650 – 800 ms) relative to the S1 cue. The first ANOVA tested effects over the baseline period, with factors of Treatment (Theanine vs. Placebo) and Region of Interest (ROI – Left, Right, and Center). The ROIs were defined as 6 clustered electrodes over the parieto-occipital scalp region of both the left and right hemispheres, and 5 clustered electrodes over the centro-parieto region. The dependent measure was calculated by integrating the amplitude across the baseline period and averaging across electrodes in each ROI. We collapsed across attention condition (attend left, attend right), since there should be no differential activation between these conditions prior to the onset of the cue.

The second ANOVA tested effects over the late-stage of the CTI, with factors of attention condition (Left vs. Right), Treatment (Theanine vs. Placebo) and Hemisphere (Left vs. Right). The dependent measure was calculated by averaging the integrated amplitude measures across a cluster of six electrodes over the left and right parieto-occipital scalp respectively. SPSS for Windows (version 12.0) was used for all statistical analyses.

4. RESULTS

Behavioral performance:

We calculated the d' values for each participant and computed a repeated measures ANOVA with factors of treatment (L-theanine vs. Placebo) and attention (attend left vs. attend right). The ANOVA did not reveal any main effects of treatment or attention, as well as no interaction effect of treatment by attention. The mean d' values for the L-theanine and placebo conditions were 0.66 and 0.73, respectively.

Tonic Alpha-Band Activity (Baseline Period):

Illustrated in Figure 2a are the average TSE waveforms plotting the time course of alpha-band activity for both treatment conditions, collapsed over both attention conditions and within the ROIs chosen for statistical testing. The baseline period (-200 – 0ms) relative to the instructional cue onset is highlighted by the gray-shaded area. Consistent with the previous study of Gomez-Ramirez et al (2007), an overall drop in tonic alpha activity is evident over posterior regions on ingestion of L-theanine relative to placebo.

A repeated-measures ANOVA conducted on tonic alpha measured in the baseline period revealed a main effect of treatment ($F(1,10) = 5.57$, $p < 0.05$), driven by the reduction of tonic alpha-power for the L-theanine condition (see Fig 2b). The ANOVA also revealed an interaction effect of treatment x ROI ($F(2,20) = 4.897$, $p < 0.01$) which suggests that the overall drop in tonic alpha is topographically specific. Planned comparison t-tests revealed that this interaction was driven by a significant drop in alpha over the right hemisphere for L-theanine ($t(10) = 3.487$, $p = 0.006$), but a trend towards greater alpha for L-theanine over the center ROI ($t(10) = -1.957$, $p = 0.07$). No other significant differences were found.

Illustrated in Figure 2b is the scalp distribution of tonic alpha for both treatment conditions during the baseline period. A topographical shift in the focus of tonic alpha is apparent, with a more dorsal/superior focus in the L-theanine condition relative to placebo.

Phasic Alpha-Band Activity (Late-Phase CTI):

Illustrated in Figure 3 is alpha-band activity during the period between the instructional cue and the subsequent imperative stimulus (-200 – 900ms). Depicted are average alpha-band TSE waveforms over left and right parieto-occipital cortices for the L-theanine and placebo conditions.

A repeated-measures ANOVA conducted on the TSE amplitude integrated over the pre-target period 650 – 800 ms revealed a main effect of treatment ($F(1,10) = 5.873$, $p < 0.05$), indicating that the reduction in tonic alpha persists throughout the trial epoch. The ANOVA also revealed a main effect of hemisphere ($F(1,10) = 7.507$, $p < 0.05$), driven by a substantial drop in alpha-power over right-hemisphere cortices. There was also an attention x hemisphere interaction ($F(1,10) = 7.030$, $p = 0.022$), reflecting the typically-observed differential attention effect across hemispheres (see 10,15,18). Planned comparison t-tests revealed that this interaction effect was mostly driven by differential attention-directing effects over the left hemisphere; $t(10) = 2.498$, $p < 0.05$. That is to say, directing attention to the left visual field evoked significantly greater alpha-band activity over the left hemisphere than directing attention to the right visual field. No other significant effects were observed.

5. DISCUSSION

The present study set out to investigate the effects of a 250-mg dose of L-theanine on alpha-band oscillatory activity while subjects were engaged in a highly demanding visuo-spatial attention task. Primarily, we conducted this study to verify and extend the results of Gomez-Ramirez et al (2007), in which we uncovered effects of L-theanine on two aspects of alpha-band activity that we have here termed *tonic* and *phasic*. The distinction between these forms of attention-related alpha activity deserves further elaboration. Ongoing alpha oscillatory activity is evident in the EEG regardless of the task in which a subject is engaged at a given time. This so-called tonic alpha activity varies over periods of many seconds to minutes, with a typical topography over parietal and parieto-occipital scalp. It represents the baseline level of activity that is not immediately related to particular events and it is considered to be an EEG correlate of sustained attentional processing or overall engagement in a given task (see Dockree et al 2007). Phasic alpha, in contrast, refers to changes in activity over much shorter timeframes on the order of 100-1000 ms that occur in response to specific stimuli. Of most relevance to the current discussion, phasic alpha has been clearly related to selective deployments of intersensory (e.g. Foxe et al 1998) and visuo-spatial attention (e.g. Kelly et al 2006; Kelly et al 2008). In the case of visuo-spatial attention, cued phasic increases in alpha are observed over retinotopically-specific regions reflecting the gating of irrelevant input, whereas phasic decreases are observed over regions preferentially primed to process relevant input. This differential alpha effect is proposed to arise from posterior structures known to be involved in attentional switching and disengagement within the visual modality (e.g. Posner & Petersen 1990; Foxe et al 1998; Worden et al 2000). Demonstrating its importance to behavior, this mechanism has been shown to be positively correlated with detection performance (Thut et al 2006). Thus, separately measuring tonic and phasic varieties of alpha activity enables the assessment of both long-term sustained attentional factors and short-term moment-to-moment phasic deployments[22].

Gomez-Ramirez et al (2007) found that L-theanine enhanced the differential effect of cue information on anticipatory phasic alpha activity compared to placebo, and found an overall decrease in tonic background alpha, which was evident even before the presentation of any cue and throughout the trial period. This would suggest that L-theanine brings about an enhancement in both sustained attention across the timeframe of the task, and in the effectiveness of phasic attentional deployments. In the present study, however, we again find a substantial drop in tonic alpha indicating facilitated sustained attention but find no evidence of effects upon phasic alpha deployments.

The present data indicate that L-theanine does not globally reduce tonic alpha-power but exerts its influence more selectively over distinct brain regions. That is, L-theanine caused a substantial drop in tonic alpha-power over posterior visual regions, mostly right-lateralized, whereas a trend towards enhancement was seen over midline centro-parietal scalp. This may reflect specific targeting of task-critical visual areas for sustained

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[22] Although phasic and tonic alpha mechanisms clearly relate to separable attentional factors, it has not yet been explicitly tested whether these mechanisms rely on the same or different neural generators. Nonetheless, the scalp topography of tonic alpha typically shows a distribution over central parieto-occipital scalp sites. In contrast, the distribution of phasic alpha rhythm, observed in these visual spatial-attention studies, shows a clear bilateral and lateralized topography. That is, when deploying attention to the left visual field, the alpha-power distribution is highly biased to right parieto-occipital cortices, and conversely, when attention is deployed to the right visual field, the distribution is biased to left parieto-occipital cortices. We take this voltage topographical dissimilarity as evidence for at least partially distinct neural generators although a subset of common neural generators is still a likelihood.

facilitation, rather than a nonspecific modulation of more generalized aspects of arousal. In this context, it is interesting that the sustained alpha modulation is lateralized to the right hemisphere, where phasic processes appear to be instantiated somewhat equally for attentional deployments towards left and right hemifields. A fair degree of caution is warranted, however, as this was an unexpected finding and will bear replication.

While the present study was designed to replicate our previous findings (see Gomez-Ramirez et al 2007), it is important to point out that the reduction in tonic alpha power observed in this and our previous study occurs while subjects are engaged in a highly demanding cognitive task, and not in a ‘passive resting state’ as in previous studies purporting to show enhanced alpha power for L-theanine (Kobayashi et al 1998; Juneja et al 1999). Though our tonic alpha measure was taken over an interval where no attentional deployment was taking place, subjects were still highly engaged in the task. Thus, it may well be the case that our results are addressing completely different brain processes from those in the Kobayashi et al (1998) and Juneja et al (1999) studies.

Although the finding of modulated tonic alpha may be taken to reflect an effect on sustained attention based on previous work related to the alpha rhythm, the failure to find an accompanying behavioral effect casts some doubt on whether the result can be interpreted in a wholly positive light. However, in attempting to induce strong attentional shifts, the task was titrated to a very high difficulty level, which may have compromised its sensitivity to detect changes in performance across treatments due to a floor effect. Thus, it remains to be seen whether L-theanine can exert effects on behavior, or whether it modulates phasic attentional deployment within the visual modality, during a less difficult task. Whatever the case, the current pattern of results suggests that L-theanine modulates the activity of the attentional system when deploying attention to different sensory modalities, but not when deploying attention in space. In the latter case, L-theanine may exert its influence on attentional processing at a more general level, facilitating longer-term sustained attentional processing across the timeframe of a difficult task, rather than affecting specific moment-to-moment phasic deployment processes.

6. ACKNOWLEDGEMENTS

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8. FIGURE LEGENDS

Figure 1: Schematic illustration of the paradigm

Each trial commenced with the presentation of a visual symbolic cue (S1). The visual cues were either a left or right pointing arrow, which indicated which side of fixation to deploy attention. A delay period of 800ms followed the cue, after which the imperative stimulus appeared. Subjects were required to respond with a button push to targets within the cued side.

Figure 2. Alpha-band oscillatory activity baseline

(A) TSE waveforms from six electrodes averaged over the left and right parieto-occipito scalp and five electrodes over the central-parieto scalp are plotted for the placebo (blue trace) and theanine conditions (red trace). The factor of directing-attention is collapsed across both treatment conditions. Alpha-band activity during this baseline period is significantly reduced when subjects ingest L-theanine compared to placebo. (B) Topographical voltage maps for both treatment conditions, and their difference, during the baseline period (-200 – 0 ms relative to the instructional cue). The maps show a difference in the topographical distribution between both treatment conditions, suggesting that L-theanine can have differential effects on specific brain regions.

Figure 3. Alpha-band oscillatory activity during the late phase of the CTI

TSE waveforms from six electrodes averaged over the left and right parieto-occipito scalp separately are plotted for the placebo (upper panel) and theanine conditions (lower panel). Red traces indicated attention deployed to the Left visual field, while blue traces indicate attention deployed to the right visual field. Alpha-band activity is significantly depressed when subjects ingest L-theanine compared to placebo.

9. FIGURES

FIGURE 1

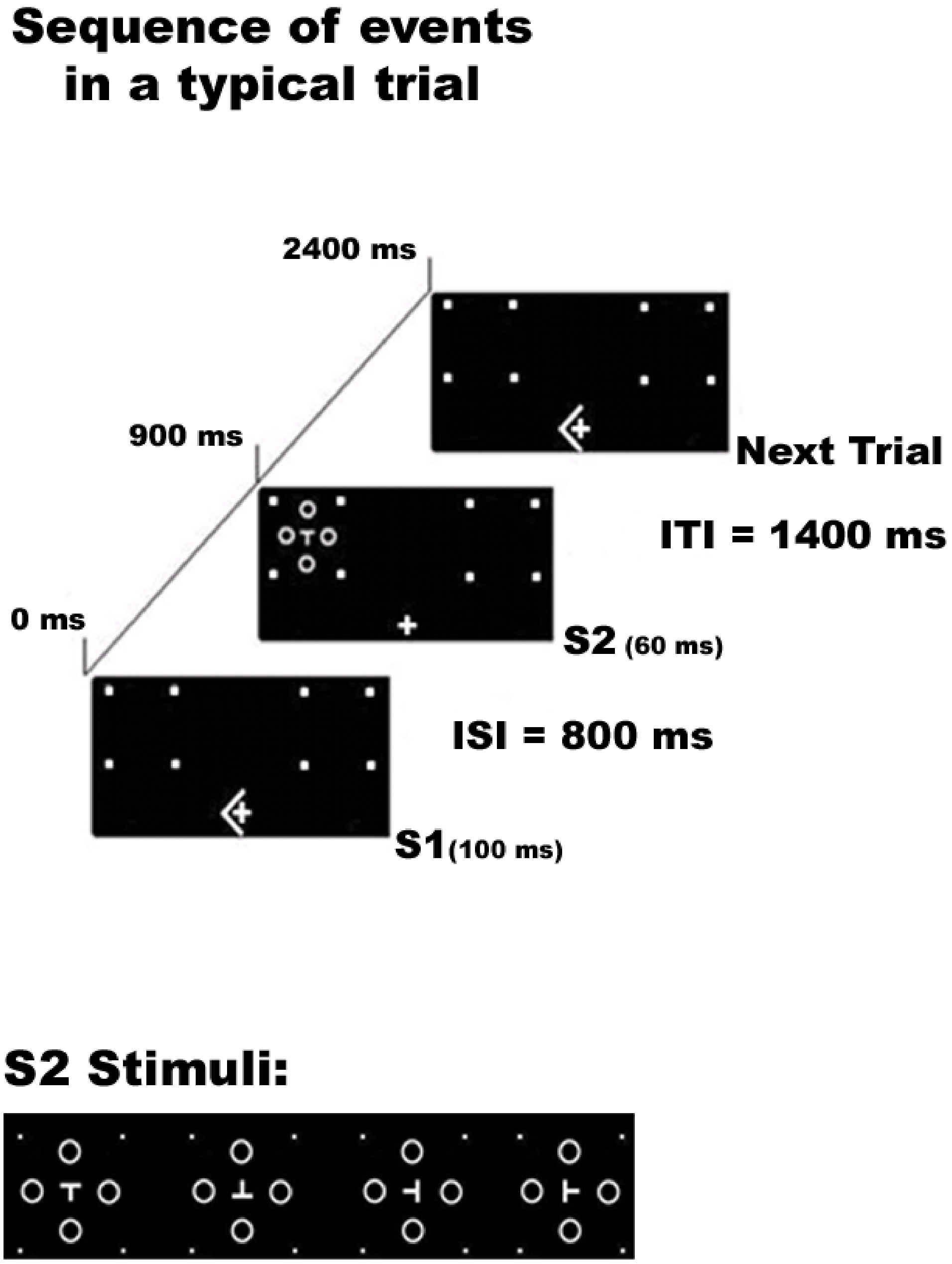


FIGURE 2

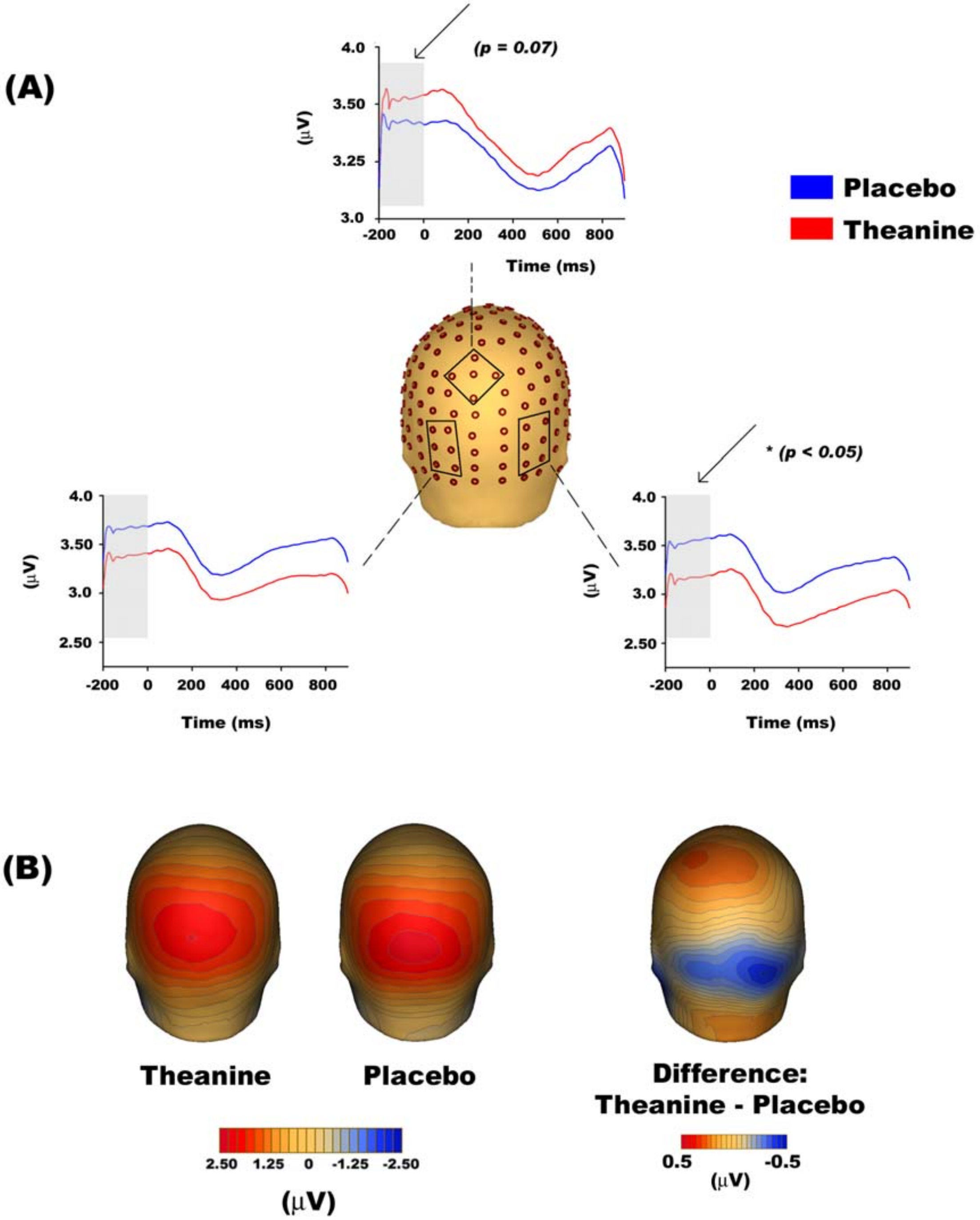
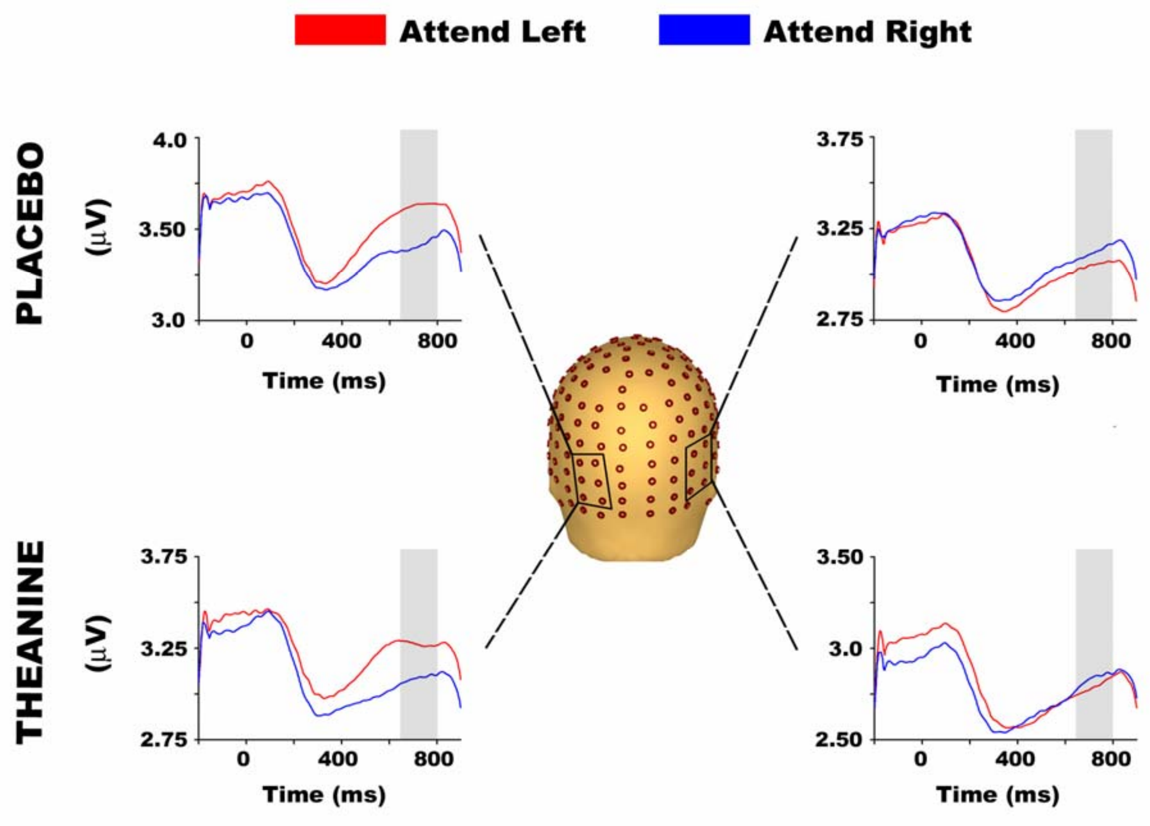

(A)
(p = 0.07)
4.0
3.50
3.25
3.0
(μV)
-200
0
200
400
600
800
Time (ms)
Placebo
Theanine
* (p < 0.05)
2.50
(B)
Theanine
Placebo
Difference:
Theanine - Placebo
2.50
1.25
0
-1.25
-2.50
(μV)
0.5
-0.5
(μV)

FIGURE 3


Attend Left
Attend Right
PLACEBO
THEANINE
(μV)
4.0
3.50
3.0
3.75
3.25
2.75
3.50
3.0
2.50
0
400
800
Time (ms)

CHAPTER 7

DISCUSSION

This thesis project was composed of five experiments that investigated the spatio-temporal dynamics of intersensory attention to the auditory and visual modalities.

Study one was aimed at characterizing the broadband and band-specific mechanisms during anticipatory attention to the auditory and visual modalities. By using an S1-S2 cueing paradigm we were able to isolate the preparatory attentional mechanisms uncontaminated by the sensory processing of the S2 stimulus. Using single trial and broadband ERP analysis we uncovered a collection of neurophysiological processes largely related to the deployment of attention to different sensory modalities. We found that the pre-target alpha biasing effect indexes a desynchronization mechanism when attention is deployed to the visual modality. This desynchronization effect significantly predicted d-prime values. Further, we contend that this pre-target alpha-band mechanism operates by enabling processing in visual cortical areas, which in turn facilitate discrimination of visual stimuli in the presence of auditory distracters. We also found that gamma-band activity mediated synchronization between anterior and posterior cortices during the late stages of the attentional deployment across both attention conditions. In addition, we replicated the late sustained parieto occipital positivity (LSPOP) ERP component, and found that this LSPOP component significantly predicted d-prime and RT values, independent of attention condition. This pattern of results indicates that this LSPOP might reflect a general mechanism of attentional preparation across sensory modalities. Finally, we found that the symbolic S1-cue significantly resets the phase of the ongoing delta-band oscillation during attentional deployments to both modalities. This phase redistribution was not accompanied by an increase in power, thus indicating that this effect reflects a ‘pure’ phase-resetting mechanism. Further, the data indicates that top-down signals reorganize the ongoing oscillatory-phase dynamics, perhaps as a means to set the excitatory state of a local neural ensemble in sensory-specific cortices.

Study two was conducted to investigate so-called ‘entrained’ oscillatory mechanisms and ‘early’ attentional effects in auditory cortices during an intersensory attention task. A sound was presented every 1.5 seconds (e.g. 0.667 stimulation rate) in order to induce a rhythmic and predictable pattern. Subjects were required to maintain attention to one sensory modality throughout the whole block of trials, and detect a target stimulus in that sensory modality only. We observed a systematic relationship between the oscillatory-phase of a1.33 Hz oscillation and alpha band power. In addition, we found that alpha-band power was significantly greater at the onset of the auditory stimulus when attention was apportioned to vision. This finding provides strong support for the role of alpha as an active gating mechanism in early auditory cortex. Taken together, the findings indicate that delta-band oscillatory entrainment is invoked endogenously, aligning its phase as a means for higher-frequencies to increase or decrease responsiveness to relevant or irrelevant stimuli, respectively

Study three was conducted to evaluate whether traditional attention-directing cueing paradigms are an efficient means of inducing endogenous (e.g. voluntary) attentional deployments. We devised a target detection paradigm where subjects freely choose, on a trial-by-trial basis, to which modality they will deploy their attention. . The behavioral data revealed that participants’ performance was better during the voluntary blocks, but at the expense of a slowing in reaction time. Further, the data revealed a stronger selection negativity (SN) effect over posterior cortices when participants initiated the attentional deployment. Interestingly, this SN effect was absent over anterior cortices. Taken together, the neurophysiological and behavioral data indicate that by allowing participants to voluntarily generate the attentional deployment, a reconfiguration of the attentional biasing signals is instantiated that might give rise to a more endogenous (or less automatic) attentional set.

Study Four investigated the effects of the natural pharmacological agent L-theanine while subjects were engaged in a highly demanding intersensory selective attention task. This study showed that L-theanine caused substantial effects on the brain's generation of the alpha oscillatory rhythm (8–14 Hz) during attentional deployments to the auditory and visual modalities. L-theanine consumption resulted in a substantial decrease in overall background alpha power regardless of which sensory modality attention was being apportioned to. Further, L-theanine caused a relative amplitude increase in the alpha-biasing effect in the period immediately preceding the imperative stimulus. Taken together, the data indicate that L-theanine may be having both global and local effects on the brain's attention circuitry.

Study Five was conducted to replicate the effects observed in study four, but in a visuo-spatial attention task. Similar to the previous findings, L-theanine significantly reduced the power in the tonic alpha-band activity, but had no significant effects during the attentional deployment period. This pattern of results implies that, unlike during executions of intersensory attention, during a visual-spatial attention task L-theanine plays a more general role in attentional processing, facilitating longer lasting processes responsible for sustaining attention.

While some of the findings from study 1 indicate that oscillatory-phase mechanisms in the gamma-band serve as a bridging mechanism for large-scale neural networks across anterior and posterior cortices, results from study 1 and 2 seem to indicate that high-frequency oscillations (> 7 Hz) influence neural activity through rapidly fluctuating amplitude mechanisms that either enhance or suppress the relevant or irrelevant inputs, respectively; while low-scale oscillations (< 8 Hz) operate through phase-dependent mechanisms as a means to mediate and maintain effective synchronization across and within neural networks, as well as to set the firing state of a local neural ensemble by placing it in an excitatory or inhibitory condition (see Bishop 1932; Kruglikov and Schiff 2003; Canolty et al 2007; Lakatos et al 2005; Lakatos et al 2008; Rajkai et al 2008).

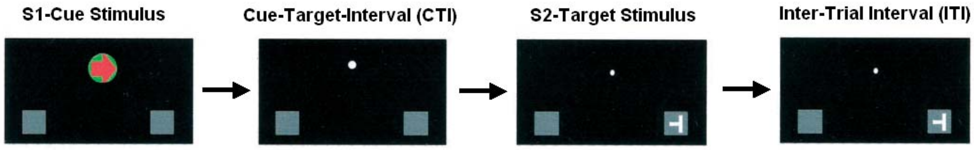
Similar to previous attention studies (see Luck 1994; Luck & Hillyard 1995; Talsma et al 2005; Foxe et al 2005b), studies 2 and 3 showed that the attentional network selectively influences sensory activity at different stages of the processing stream in both visual and auditory-related areas. Moreover, the EEG and behavioral findings from study 3 indicate that when the subject is in complete control of his/her attentional selection, greater and different manifestations of attentional effects are observed. We found that these ‘voluntary’ biasing signals tap into earlier sensory processing stages over visual-related cortices. Furthermore, we found evidence of a speed-accuracy tradeoff during blocks where subjects self-initiated and self-selected the task, which strongly indicates that these ‘voluntary’ signals give rise to a more endogenous (or less automatic) attentional set.

A potential benefit of this ‘voluntary’ paradigm pertains to attention deficits in clinical populations, especially in those that suffer from sensory processing deficits. It is contended that by implementing this ‘voluntary’ paradigm, researchers can assess attentional deficits in clinical populations free of any sensory processing confound. The rationale is that because during typical ‘cueing’ paradigms symbolic cues are presented, then these cues have to be first processed and decoded before any attentional deployment is actually made. Now consider the case where a schizophrenic patient is performing one of these cueing paradigms. Indeed, there have been many reports that consistently show patients exhibiting severe attentional deficits (see Iwanami et al 1998; Kamio et al 2001; van der Stelt et al 2006; Wood et al 2007). In addition, there have also been many reports indicating that patients have severe problems in the early stages of the sensory processing stream (cite Foxe et al 2001; Butler & Javitt 2005; Yeap et al 2006; Butler et al 2007; Leavitt et al 2007). Thus, it is entirely possible that the early sensory processing deficits in these patients may be consequently affecting their ability to make an effective attentional orientation. That is, if patients have problems with the processing of the sensory cue, which is a processing stage that most likely precedes an attentional orientation process, then these sensory processing ‘errors’ might propagate throughout the attentional deployment stages and result in an ineffective attentional biasing set. However, by implementing this ‘voluntary’ task, where the presentation of a sensory symbolic cue is obviated, researchers can directly assess attentional orientation and maintenance mechanisms in clinical patients without worrying about sensory processing confounds. Finally, studies 4 and 5 showed that the natural pharmacological agent L-Theanine significantly modulates attentional mechanisms within the alpha-band.

APPENDIX: Figures for Introduction & Discussion Chapters

Figure 1 - Examples of typical trials in a visuospatial and intersensory attention study

(A) Typical trial in a visuospatial attention study



(B) Typical trial in a intersensory attention study

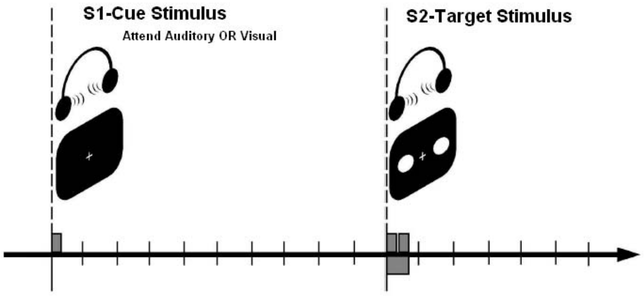


Figure 2 – Framework model of attentional deployment

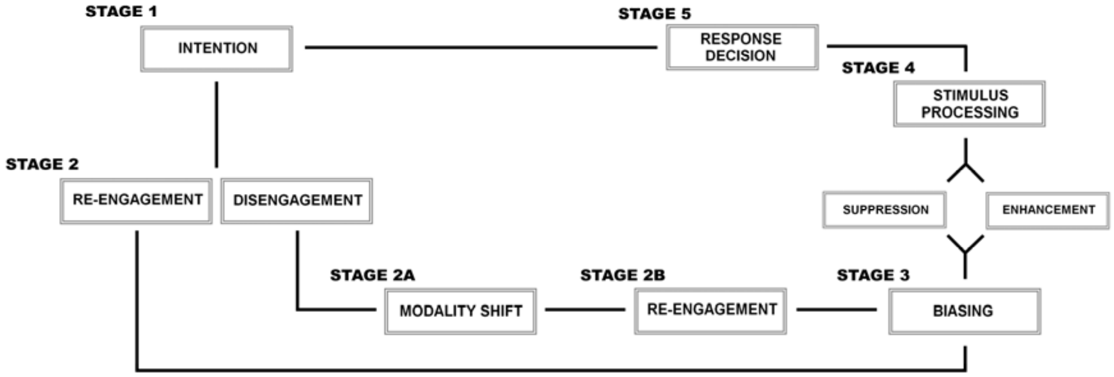


Figure 3 – Meta analysis of the ERP components during anticipatory attentional deployments in visuospatial attention

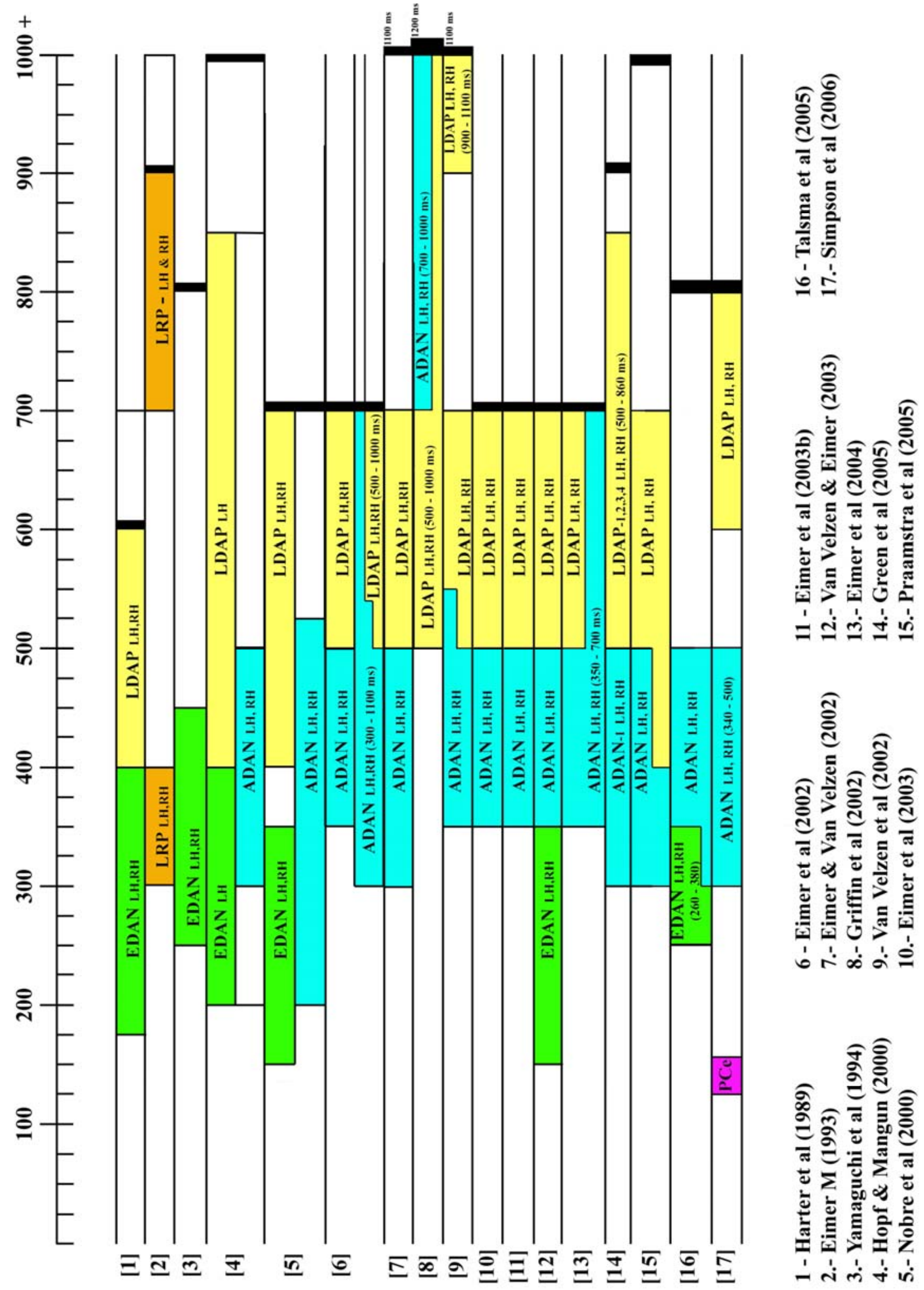
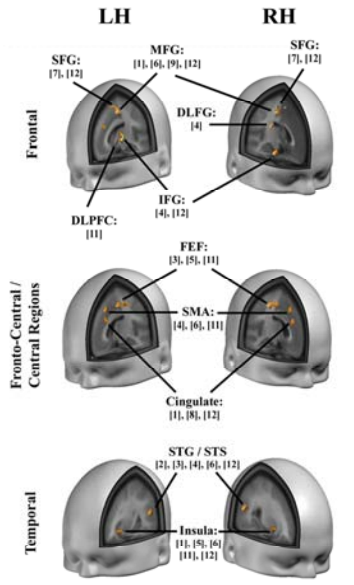
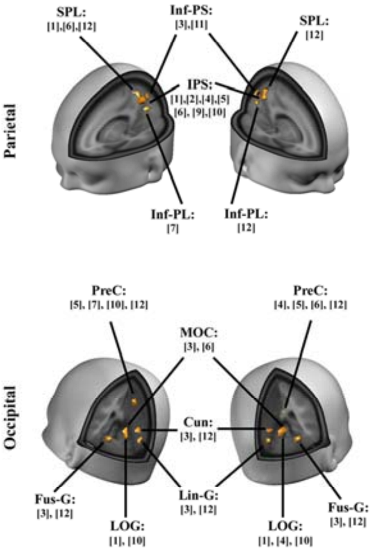


Figure 4 – Meta analysis of the fMRI activation during anticipatory attentional deployments in visuospatial attention

fMRI Activations:



	Frontal Regions	Fronto-Centro / Central Regions	Temporal Regions
[1]	L-SFG -16, 48, 36 -44, 36, 16 L-MFG -20, -4, 52 R-MFG 24, 4, 52	L-PCing -12 -44, 28 R-PCing 8, -36, 28	L-STG -60, -24, 8 R-STG 48, -12, 8 L-INS -26, 30, 0 R-INS 30, 26, -4
[2]			R-STS 51, 55, 4
[3]		L-FEF R-FEF	L-STS R-STS
[4]	L-IFG -49, 4, 30 DLFG 37, 5, 26	P-SMA 7, 11, 44	R-STG 53, -47, 18 L-INS -35, 13, 2 R-INS 37, 17, 2
[5]		L-FEF R-FEF R-DPreCG 35,-5,50	
[6]	L-MFG -26, -11, 50 R-MFG 26, -8, 50	PC-G -49, -4, 30 L-SMA -11, 0, 55	R-STG 49, -56, 10 L-INS -35, 15, 5 R-INS 34, 23, 5
[7]	L-SFG -4, 10, 50		
[8]		R-PCing 9, -39, 24	
[9]	L-MFC -23, -4, 46 R-MFC 27, 1, 46		
[10]			
[11]	L-DLPFC -41, 30, 23	L-FEF -34, -4, 41 R-FEF 34, 0, 49 L-SMA -8, 15, 49 R-SMA 11, 15, 45	L-INS -26, 30, 0 R-INS 30, 26, -4
[12]	L-SFG -7, 4, 67 R-SFG 10, 8, 67 L-MFG -27, -1, 46 R-MFG 46, 15, 33 L-M-FG -6, 11, 54 R-M-FG 9, 14, 53 L-IFG -27, 27, -8 R-IFG 36, 25, -10	L-Ant-Cing / L-Mid-Cing -6, 21, 31 / -4, -17, 29 R-Ant-Cing / R-Mid-Cing 9, 26, 31 / 7, -17, 29	L-STG -61, -37, 17 L-Ant-INS 37, 23, -1 R-Ant-INS -29, 26, 0



	Parietal Regions	Occipital Regions
[1]	L-SPL -16, -52, 56 R-SPL 20, -40, 52 L-IPS -44, -64, 32 -40, -48, 32 R-IPS 40, -68, 28 36, -48, 32	L-LOG -36, -76, 8 R-LOG 24, -84, 8
[2]	L-Ant, Pos, Ven - IPS -25, -57, 46 / -25, -67, 48 / -23, -67, 32 R-Ant, Pos, Ven - IPS 27, -59, 52 / 21, -65, 52 / 29, -71, 22	
[3]	L-InfPS R-InfPS	L-Cun R-Cun L-MOC R-MOC L-FusG R-FusG L-LinG R-LinG
[4]	L-IPS -35, -55, 44 R-IPS, R-VenIPS 33, -59, 50 / 29, -67, 26	R-PreC 15, -65, 36 R-LOG 33, -83, 4
[5]	L-AntIPS, L-PosIPS -31, -51, 46 / -29, -61, 52 R-AntIPS, R-PosIPS 39, -53, 54 / 31, 59, 52	L-PreC -1, -55, 52 R-PreC 3, -47, 52
[6]	L-SPL -23, -71, 50 -23, -68, 45 L-IPS -38, -45, 40 R-IPS 26, -56, 45	R-PreC 26, -64, 35 R-MOC 34, -83, 15 L-FusG -49, -64, -10 -41, -68, -15 L-LinG -23, -94, -10
[7]	L-InfPL -54, -50, 42	L-PreC -2, -62, 48
[9]	L-MPC -15, -58, 48 R-MPC 20, -57, 50	
[10]	L-IPS -27, -79, 16	L-PreC -7, -55, 54 L-LOC -37, -87, 4 R-LOC 27, -89, -2
[11]	L-InfPS -23, -68, 41 R-InfPS 30, -68, 45	
[12]	R-InfPL 54, -47, 48 L-SPL / PreC -11, -63, 62 R-SPL / PreC 8, -62, 55	L-PreC / SPL -11, -63, 62 R-PreC / SPL 8, -62, 55 L-Cun -9, -89, 13 R-Cun 10, -88, 14 L-LinG -13, -98, 5 R-LinG 8, -97, 4

[1] Hopfinger et al (2000)

[2] Corbetta et al (2000)

[3] Hopfinger et al (2001)

[4] Shulman et al (2002)

[5] Astafiev et al (2003)

[6] Giesbrecht et al (2006)

[7] Macaluso et al (2003)

[8] Small et al (2003)

[9] Woldorff et al (2004)

[10] Corbetta et al (2005)

[11] Wilson et al (2005)

[12] Wu et al (2007)

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