International School for Advanced Studies

Oscillatory signatures of unimodal, bimodal, and cross-modal sensory working memory

Thesis submitted for the degree of Doctor of Philosophy

Candidate:

Māris Skujevskis

Supervisor:

Prof. Mathew E. Diamond

July 2017

Cognitive Neuroscience Sector

SISSA, Via Bonomea 265, TRIESTE, ITALY

Contents

ABSTRACT

Neural oscillatory activity is an essential brain mechanism that enables and subserves a vast range of cognitive functions. Studying them non-invasively through electroencephalography (EEG) has proven to be an effective method of discovering associations between oscillations in different frequency bands and various cognitive functions. Studying the oscillatory dynamics of human working memory (WM) – a core component of human higher cognitive functioning – has been particularly fruitful, leading to insights about the mental processes, frequency bands, and brain areas involved. In addition to frequency band specificity, the application of source reconstruction methods has led to further insights by revealing specific brain areas associated with WM related processing.

In the present study, we focused on the oscillatory power dynamics during sensory working memory (SWM) in auditory and tactile modalities in the alpha band. In a delayed comparison two alternative forced choice task participants received two sequential stimuli and had to respond whether the intensity of the second stimulus was stronger than that of the first stimulus. In three related EEG experiments we examined SWM processing under unimodal (stimulation in one modality), bimodal (stimulation in both modalities simultaneously), and cross-modal (sequential stimulation of the modalities) conditions. An additional non-WM control condition allowed us to explore not only the differences between auditory and tactile WM, but also the effects of the WM task itself on the delay period oscillatory activity within each sensory modality.

Our results showed that, while the bimodal stimulation condition led to behavioral enhancement, an increased stimulus difference was necessary to maintain the same level of performance also in the cross-modal conditions. Localizing the oscillatory activity in the alpha band (8 – 12Hz) revealed a clear disinhibitory effect over the somatosensory cortex during the early and the late delay period, while the mid-delay did not show any differences in SWM between the two modalities. A similar, albeit weaker, effect was observed over the auditory cortices. A right parietal reduction of alpha power emerged

during the late delay when a tactile stimulus had to be compared cross-modally. This suggests the involvement of parietal somatosensory association cortex in the cross-modal transformation of the tactile stimulus. Lastly, the differences between cortical source distributions when contrasting unimodal and cross-modal conditions demonstrated that late delay effects do not reflect only anticipatory effects due to the upcoming modality, but also reflect the influence of the stimulus modality kept in WM.

Contrasting the bimodal condition with the unimodal ones revealed a parametric beta band effect in a right parietal area during the early delay only in the bimodal condition, which suggests that beta oscillations might play a role in multimodal integration under SWM conditions. A second effect during the early delay period was observed in the theta (4 – 7Hz) band. An early effect appeared when contrasting conditions in which the first stimuli were identical while the second stimuli differed across the conditions. This result suggests that the early delay period is already shaped by the anticipated comparison context.

The clearest differences in the contrast between WM and non-WM task were observed in theta and gamma bands. Source localizing the condition differences suggested the involvement of hippocampal and fronto-central areas in carrying out the WM task. Furthermore, sensory cortices of the respective modality conditions showed the highest levels of connectivity with the rest of the brain during the late delay, further highlighting the involvement of gamma band oscillations in SWM related processing.

Overall, this study demonstrates that the results obtained when studying SWM related processing strongly depend on the sensory modality examined and the type of WM task employed. Any observations with regard to SWM related oscillatory power dynamics should be explored in multiple contexts before drawing any generalized conclusions.

TABLE OF TERMS AND ABBREVIATIONS

WM	Working memory
SWM	Sensory working memory
WM task	The main task, requiring delayed comparison of the intensities of two sensory stimuli
Non-WM task	The control task, requiring the detection of an intensity ramp in one of two sequential stimuli
s1, s2	Stimulus 1 & 2 within each delayed comparison trial
Experiment 2, 3, 4	The 1st, 2nd, and 3rd experiment of the study (experiment 1 was not included)
Unimodal	Stimulation in which the 1st and 2nd stimulus of the trial was of the same modality and only one modality was stimulated (auditory (AA) or tactile (TT), see below)
Bimodal	Stimulation in which the 1st and 2nd stimulus consisted of stimulation in both the auditory and the tactile modality (BB, see below)
Cross-modal	Stimulation in which the 1st and 2nd stimuli were both unimodal and of opposite modalities
AA vs TT	Statistical contrast between the auditory and tactile unimodal conditions in delayed comparison task (see below for complete list of condition abbreviations)
Types of delayed comparison conditions:	
AA	1st stimulus auditory, 2nd stimulus auditory
TT	1st stimulus tactile, 2nd stimulus tactile
AT	1st stimulus auditory, 2nd stimulus tactile
TA	1st stimulus tactile, 2nd stimulus auditory
BB	1st and 2nd stimuli bimodal (auditory+tactile)
Types of ramp detection conditions (experiment 4):	
A0	1st stimulus auditory, 2nd stimulus auditory
T0	1st stimulus tactile, 2nd stimulus tactile

1. INTRODUCTION

Sensory working memory (SWM) is the maintenance of a recently experienced behaviorally relevant stimulus over short periods of time (Jensen and Mazaheri, 2010). This ability is of central importance to many higher cognitive functions such as input evaluation with respect to stored long term memories (Jeneson and Squire, 2012), mental transformation of information (Hyun and Luck, 2007), and the formation of higher level mental representations through unifying multiple sensory inputs (Nieder, 2017). As such, studying SWM and working memory in general, goes to the core of understanding human higher cognitive functioning.

1.1. Sensory working memory: areas involved and the role of attention

Successful performance of a working memory (WM) task critically depends on a number of cortical areas and the ability to prioritize the most relevant inputs and neural communication channels, while suppressing the activity in task-irrelevant areas (Klimesch et al. 2007). In this regard, top-down attention has been shown to constitute an integral part of coordinating cognitive processes during a WM delay period (Marchetti, 2014). However, it has also been shown that the role of attention during the WM delay is not constant – only the periods associated with stimulus anticipation, encoding and manipulation critically depend on attention, while the middle of the delay period associated with WM maintenance is thought to be less shaped by attentional effects (Fougnie, 2008). Nevertheless, the distinction between attention and WM is multilayered and the discussion on the way in which the two processes can be dissociated is ongoing (McCabe et al., 2010; Gazzaley and Nobre, 2012). No clear consensus has been reached and a number of researchers have challenged the notion of attention and WM forming two different cortical or cognitive systems (Oberauer and Hein, 2012; Kiyonaga and Egner, 2013).

Despite being seemingly conceptually distinct, attention and SWM-related processes show a strong cortical overlap in that prefrontal, posterior parietal, as well as sensory modality specific areas have all been implicated in both cognitive functions

(Pasternak and Greenlee, 2005; Jensen et al., 2007). For instance, the PFC carries a stimulus representation during the WM delay (Romo et al., 1999), yet it also plays a central role in modulating posterior areas during the WM maintenance period (Zanto et al., 2011). Likewise, studies show that primary sensory areas can be involved in WM maintenance (Harris et al., 2001) as well as get modulated due to top-down attention (Mima et al., 1998). Thus, in terms of simple topographical delineations, it is hard to draw a clear distinction between the two processes as they manifest themselves in SWM tasks.

This also highlights the fact that as of now no scientific consensus has been reached as to the cortical locus of SWM representations. Different studies have been able to find neurophysiological signatures in different cortical areas (Li et al., 2014; D’Esposito and Postle, 2015; Riley and Constantinidis, 2016). For instance, both the prefrontal areas as well as exclusively sensory cortices have been identified in MEG/EEG studies as the areas carrying WM information during the delay period (Spitzer and Blankenburg, 2010; Haegens et al., 2009). These observations suggest that certain aspects of a study, such as the recording modality, the hypothesis addressed, or the complexity of the stimulus can potentially lead to different patterns getting revealed in the neurophysiological signal and can thus influence the conclusions with regard to the role of a particular cortical area in SWM (Quak et al., 2015).

1.2. Neural oscillations: frequency bands and functions

While differences in cortical source topographies as revealed by broadband (ERP/ERF) or low frequency signals (the BOLD response) might provide a limited insight as to the exact underlying SWM delay function, studying frequency-resolved neural oscillations in the form of event related synchronization and desynchronization (ERS and ERD, respectively) has revealed an additional dimension of the neurophysiological signal through which the study of function is more informative (Silva, 2013). At the neuronal level, ERS/ERD happens when neurons in a particular brain area exhibit synchronous activity at a particular frequency range, which leads to a large scale summation of postsynaptic potentials (David and Friston, 2003). It must be noted, however, that the physiological mechanisms giving rise to neural oscillations have not been fully understood – they might arise due to both a higher degree of spike synchronization as well as an overall higher level of neural activity (Nauhaus et al., 2009; Denker et al., 2011). Nevertheless, the regular voltage fluctuations in a particular frequency range – measured through electrodes placed on the human scalp – has enabled researchers to draw conclusions as to the underlying cortical engagement and associate the oscillatory activity (figure 1.1) to particular cognitive functions.

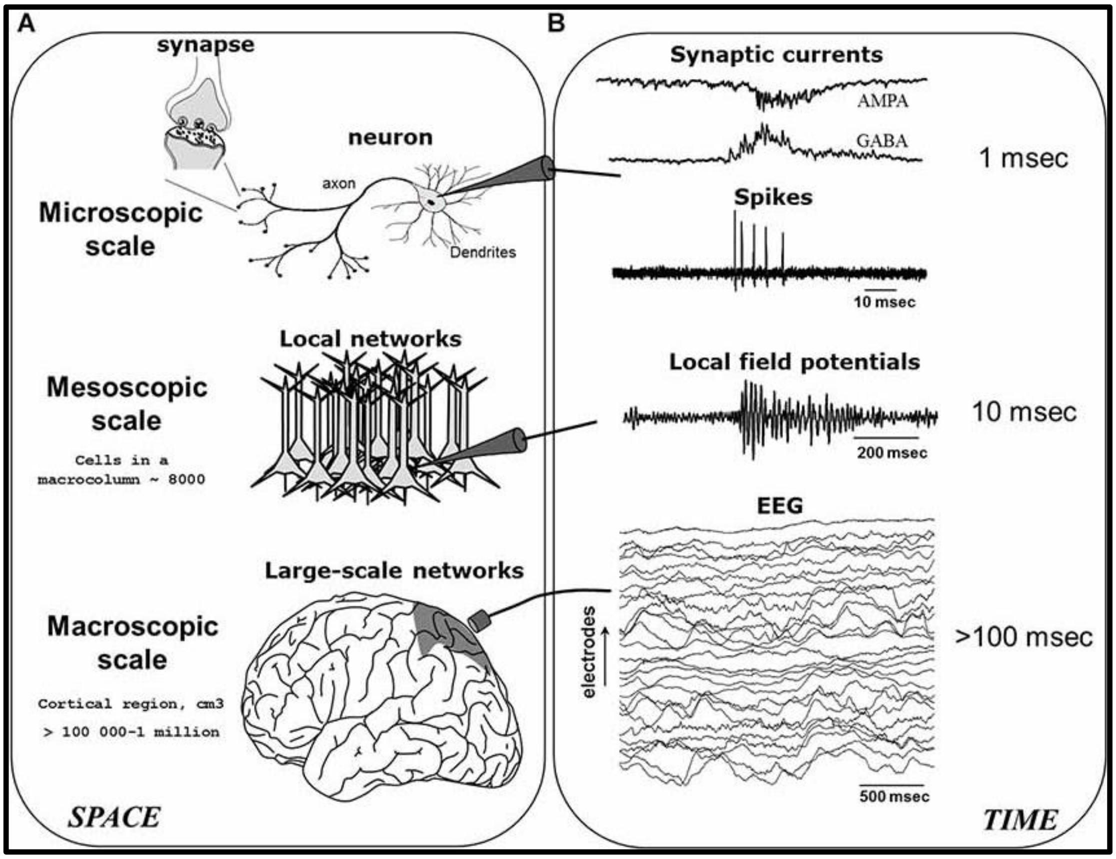

Figure 1.1. Unlike invasive recording methods, EEG records neural oscillations at a macroscopic scale reflecting the synchronous activity of hundreds of thousands of cells (Ros et al., 2014).

The synchronization of neural activity at different frequencies has been associated with different a set of broad functional categories. With regard to SWM, theta band (4 – 7Hz), especially over the frontal midline electrodes, has been linked to top-down cognitive control mechanisms (Cavanagh and Frank, 2014), but the evidence is inconclusive. For instance, a TMS-EEG WM study has recently demonstrated that the directionality between frontal and sensory areas runs in the top-down and not in the bottom-up direction as has been hypothesized by previous studies (Miyauchi et al., 2016). Furthermore, scalp recorded theta has been associated with both cortical and hippocampal generators, the latter of which is also implicated in SWM functions (Leszczynski et al., 2015).

The function of alpha oscillations (8-12Hz) has been best captured by the 'gating by inhibition' hypothesis (Jensen, 2010). This hypothesis posits that the oscillatory activity in the alpha band reflects pulsed inhibition of task-irrelevant areas – a process which, as the name suggests, simultaneously reflects the 'opening' and 'closing' of processing gates between different brain areas. These dynamics are most likely orchestrated via top-down attention (Shaw, 2003). The same process has also been conceptualized through the notions of suppression and selection, which stands in close relation with the essential functions of attention (Klimesch, 2012). Furthermore, oscillations in the alpha frequency band are the most prominent frequency band in the cortical oscillatory spectrum suggesting that the 'gating by inhibition' hypothesis captures a central principle of neural processing. Therefore, the involvement of a specific brain area in a given SWM task can be effectively studied through ERS/ERD in the alpha frequency band (Pfurtscheller, 2001). It has been effectively applied to studying the engagement and disengagement of sensory cortices (figure 1.2.).

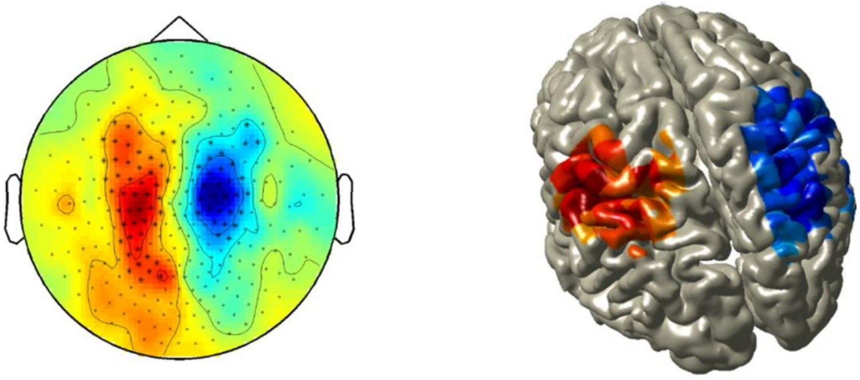

Figure 1.2. Anticipation of a tactile stimulus results into lateralized alpha power distribution over the somatosensory cortices: attention left to attention right contrast

depicted at sensor and source level from an MEG tactile discrimination experiment, with red indicating a relative increase of alpha power (Haegens et al., 2011).

Beta frequency band, defined variously as the oscillatory activity in the 13 – 30 Hz range, is regarded as subserving a number of neural processes, and, consequently, no broad hypothesis has managed to capture the principles underlying the cognitive functions associated with activity in this frequency band (Engel and Fries, 2010). While beta power modulations are most readily observed during tasks involving a sensorimotor component (Kilavik et al., 2013); their role in SWM related processing is less clear (Fell and Axmacher, 2011). Recently, beta bursts have been identified in invasive recordings in the monkey brain reflecting a default WM network state during periods of non-stimulation (Lundqvist et al., 2016). Lastly, there are some indications that beta band activity in a right prefrontal area could also play a role in stimulus maintenance during the WM period independently of the input stimulus modality (Spitzer and Blankenburg, 2012).

Gamma band (30 – 100Hz) power increase during SWM tasks has been most readily associated with stimulus maintenance (but also attention) during the SWM delay (Jensen et al., 2007; Dé et al., 2014). For instance, it has been observed to vary with the number of items held in WM during the delay period (Roux et al., 2012). More recently a simultaneous MEG/EEG study has suggested that gamma activity codes for specific stimulus features and thus reflects the contents of SWM (Honkanen, 2015). The cortical sources of oscillations in this frequency band have been identified both in sensory and frontal with stimulus feature maintenance as the claimed underlying function in both cases (Heagens et al., 2010; Roux et al. 2012).

1.3. Cross-modal and multimodal WM

While SWM is often tested in a single modality, sensory inputs in real life situations hardly ever exist in isolation. This necessitates that they be integrated or related to each other in order to achieve a more informative representation of the external world. Some studies have attempted to characterize both multi- and-cross sensory integration in the context of SWM. Invasive recordings in the Macaque monkey brain have recently identified correlates of cross-modal working memory in the pre-supplementary motor area (Vergara et al., 2016). These neurons were reported to use the same neural code independent of the sensory modality. Since the identified area belongs to the prefrontal cortex, the result adds to the ongoing discussion of the role of sensory and prefrontal areas in SWM also in the case of cross modal SWM. With regard to multimodal SWM, an additional step of concurrent information integration between modalities comes into play. Here, both beta and gamma band coherence between sensory and multimodal brain areas have been reported as a potential relevant neural mechanism (Maier et al., 2008; Kayser and Logothetis, 2009). For instance, Senkowski et al., (2006) identified oscillatory activity in the beta in an auditory-visual task as playing a role in stimulus binding and behavioral enhancement. This study, however did not attempt to localize the neural generators of this activity.

1.4. The present study

Taking advantage of the well-established hypothesis of ‘gating by inhibition’ in the alpha band, the present study was designed to investigate the involvement of sensory cortices in unimodal, bimodal, and cross-modal SWM; in addition, the same hypothesis was used to assess the involvement of extrasensory areas in cross-modal WM tasks. Secondly, since beta band has been implicated in both SWM representations as well as multimodal integration, the study explored the role of beta oscillations in multisensory integration during the WM delay period. Third, by comparing a SWM task and a non-SWM equivalent, WM effects in the gamma band were assessed. The time windows of significant differential activity between the various experimental conditions examined were subjected to source reconstruction in order to draw more specific conclusions as to the role of the prefrontal, sensory, and parietal engagement in the aforementioned SWM tasks. The overall experimental design did not allow the drawing of a distinction between attention and SWM. Instead, knowing the tight link between the two processes, both alpha and gamma power differences were treated as reflecting SWM related processing, interpreting their functional meaning in the context of related SWM studies whenever possible.

2. METHODS

2.1. Participants

Each of the three experiments had a different set of 16 participants. They gave informed consent and performed the experiments for a monetary reward. The mean ages and the proportion of males were 23.2 (SD = 4.2) and 9, 24.1 (SD = 4.4) and 8, 24.5 (SD = 4) and 7, for experiments 2, 3, and 4, respectively. All participants were right-handed and self-reported normal/corrected-to-normal vision, hearing, and somatosensory perception. The study was approved by the SISSA Ethics Committee.

2.2. Apparatus

The complete software and hardware setup consisted of the following: a LabView custom written code for connecting to and coordinating (via “National Instruments” card NI-6353) the following hardware components: two amplifiers connected to the tactile stimulus generator (“Bruel & Kjear”, type 4808) and the auditory stimulus generator (“Etymotic ER-2” pneumatic earphones), respectively; a custom made LED panel for giving visual trial instructions to the participant; two foot pedals for response collection; the operation of the LED panel and the collection of response times was done through a microcontroller board (Arduino Uno) using custom written code.

2.3. Apparatus layout

The participants were seated in a dimly lit room on an adjustable height chair in front of a 1.05 x 1.05 meter table (figure 2.1.). The tactile stimulation motor was placed on one side of the table (in Experiment 2 one motor on either side) with the vibratory probe pointing outwards, away from the table. On the edge of the table the subject rested his/her arm on a cushion so as to keep it comfortably relaxed throughout the experiment.

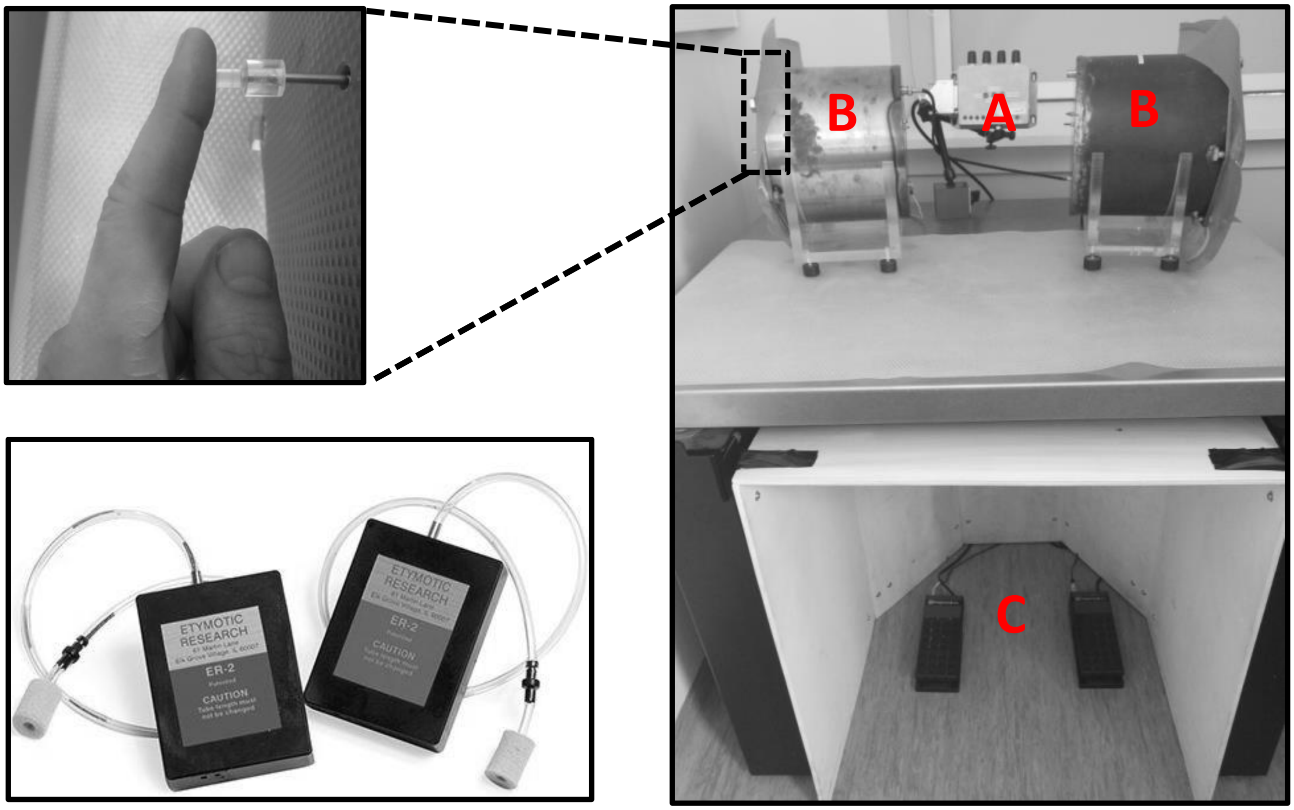

Figure 2.1. Left top: probe delivering vibrations to fingertip; left bottom: pneumatic earphones for auditory stimulus delivery. Right: Layout of the setup: (a) LED panel, (b) stimulation motors (in experiments 2 and 3 only the left one used), (c) response pedals.

Personal adjustments were made so that the tip of the left hand's (both hands' in Experiment 1) index finger would comfortably reach and touch the vibratory probe – a smooth, rounded tip made of acrylic glass. The earphones were inserted into participants' ears using disposable, sound isolating ear tips. The sound was delivered to the left ear (both ears in Experiment 2). In experiments 2 and 3 both ear tips were inserted into the participants' in order to block the sound coming from the vibration motor. On the floor below the table the participant rested his/her feet on both pedals throughout the experiment, completely covering each pedal from heel to toe with their feet. While in the resting position, the pedals' surface was positioned horizontally relative to the floor. In order to generate a response, the participant pushed the heel of one pedal downwards, thus departing from the horizontal position. Immediate response feedback was given on the LED panel, after which the participant returned the pedal to the horizontal position in preparation for the next trial. The LED panel (17 x 11 cm) was positioned at a distance of 65 cm from the participant and height and angle-adjusted to enable comfortable viewing and focusing on the central LED light throughout the experiment.

2.4. Trial design

In all experiments, the participants were given visual trial instructions on the LED panel, received two sequentially presented tactile and/or auditory stimulations on index finger(s) and/or via earphones, respectively, and responded via a left/right pedal press at the end of every trial (Figure 2.2). Participants' task was to indicate whether the second stimulus had been more intense than the first stimulus via a two alternative forced choice (2 AFC) response by pressing the left or the right pedal (counter-balanced across participants). Prior to the start of the experiment every participant performed brief training sessions to familiarize themselves with all the modality and intensity combinations used in the subsequent experiment.

All the experiments followed one pattern of trial sequence. They differed from each other only in terms of the design (block/interleaved), modality/task combinations (unimodal, bimodal, cross-modal, ramp detection), and the variations in the duration and stimulus intensity levels (see Session and Task Design below for details).

In experiment 2 the trial consisted of the following sequence of events. The central LED turned red in order to indicate the start of the trial. Throughout the trial the participant was asked to focus on this LED light. After a pre-stimulation interval of 1.5s the first 500ms stimulus was played, followed by an inter-stimulus interval of 3s. After the inter-stimulus interval the second 500ms stimulus was played, followed by the post-stimulation interval of variable duration. At the end of a variable (0.5-0.9s) post-stimulus interval the red LED turned off indicating the start of the response period. As soon as the participant had indicated his/her response by pressing one of the pedals, the central LED gave feedback – a green blink for a correct response, an orange blink for an incorrect response. Once the response had been collected a yellow secondary LED turned on to indicate the onset of a variable duration inter-trial interval during which the participants could blink and prepare for the next trial. At the end of the inter-trial interval the yellow LED turned off and the red LED turned on again, signaling the start of a new trial.

For experiments 3 and 4, three changes were made, which had the overall effect of making the trial shorter (figure 2.2., bottom row) – the pre-delay and the inter-stimulus delay were both made 0.5sec shorted, and there was no post-stimulus delay. Instead, the participant could respond as soon as the second stimulation period had ended.

Lastly, experiment 4, though having an identical trial design to experiment 3, employed an additional task. The participant had to detect ramping intensity values within each of the two stimuli, and report via a pedal press whether a ramping stimulus had been present in the trial or not. The ramp was always upward sloping.

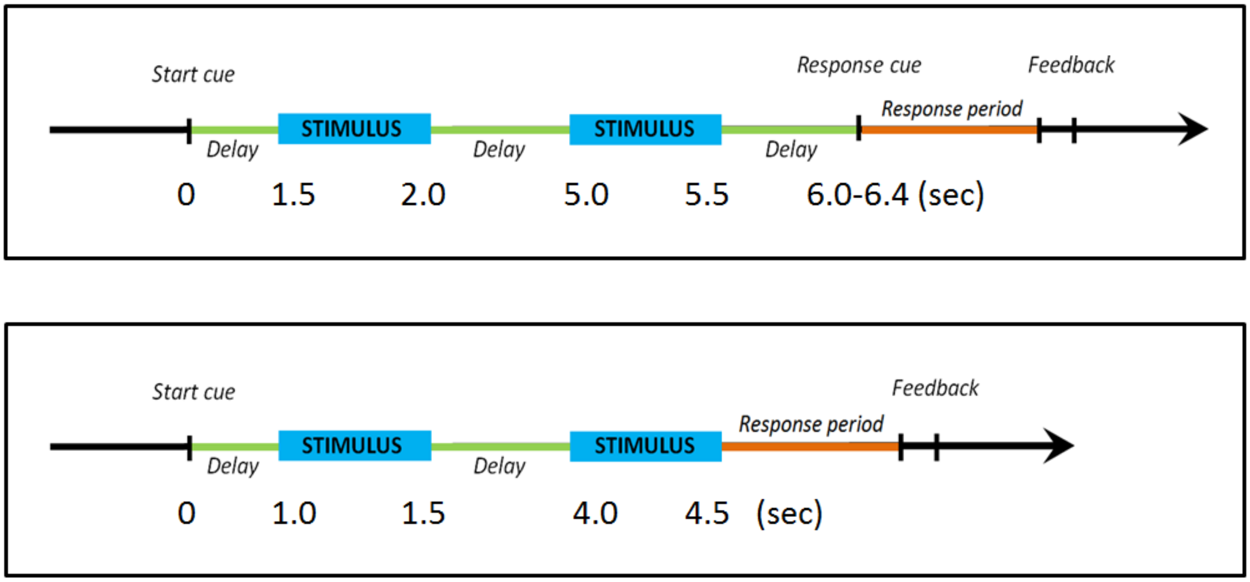

Figure 2.2. Top row: experiment 2 trial timeline; bottom row: experiment 3 & 4 trial timeline.

2.5. Session and task design

2.5.1. Experiment 2

Three different conditions were presented in pseudo-randomized blocks of 40 trials each. In auditory and tactile blocks, both the first and the second stimuli of every trial were auditory and tactile, respectively. In the bimodal block, both the first and the second stimulus were a simultaneous tactile-and-auditory stimulation. There were five different levels of first stimulus intensity and the second stimulus was equally probable to be either more or less intense. In the bimodal block, the stimulation intensities were always congruent between the two modalities (e.g., the most/least intense auditory stimulus was always accompanied by the most/least intense tactile stimulus). Both the tactile and the auditory stimulation were bilateral.

2.5.2. Experiment 3

Four different conditions were presented in twelve pseudo-randomized blocks of 64 trials each. Only tactile or auditory (no bimodal stimuli) were presented in this experiment. Every block followed one of two possible rules and before every new block the participant was informed about the rule of the upcoming 64 trials. The "unimodal" rule meant that an upcoming block would contain trials in which the second stimulus was of the same modality as the first stimulus. The "cross-modal" rule, on the other hand, meant that the upcoming block would contain trials in which the second stimulus was of the opposite modality as compared to the first stimulus. Thus, while the first stimulus modality was unpredictable in all conditions (auditory and tactile stimulus equally likely), the modality of the second stimulus was 100% predictable in both blocks.

2.5.3. Experiment 4

Two different conditions were presented in twelve pseudo-randomized blocks of 64 trials each. Only unimodal tactile or auditory trials (no cross-modal trials) were presented in this experiment. Every block followed one of two possible rules and before every new block the participant was informed about the rule of the upcoming 64 trials. The intensity comparison rule meant that in an upcoming block the subject would have to compare the intensity of the second stimulus to the intensity of the first (identically to Experiment 2 and Experiment 3). The ramp detection rule, on the other hand, required the subject to ignore the intensity differences (which were still present), but instead to detect a subtle increase in intensity in either of the two stimuli of every trial. To this end, the stimuli for the "ramp detection" blocks were slightly modified. The intensity of any stimulus could be ramped up during its presentation, while a non-ramped stimulus maintained a constant average intensity level. The subject’s task was to detect the presence of a ramped stimulus and respond with a “yes” pedal-press at the end of the trial whenever a ramped stimulus was presented, regardless of its ordinal position in the trial. If no ramped stimulus was detected, the subject pressed “no”, identically to the 2AFC response paradigm of the previous experiments. Of the 64 trials in a “ramp detection” block, ten had a ramp in the first stimulus, 18 in the second stimulus, while the remaining trials contained regular, non-ramped stimuli. The ramped/non-ramped trial counts were balanced across the two modalities. The trials with a ramp in the first stimulus were excluded from further analysis. Identically to Experiment 3, while the first stimulus modality was always unpredictable (auditory and tactile stimulus equally likely), the modality of the second stimulus was always 100% predictable from the modality of the first stimulus, regardless of the block rule.

2.6. Stimulus set

In all experiments, regardless of the intensity of the first stimulus, the second stimulus was equally likely to be one intensity level higher, or one intensity level lower. There were a total of five first stimulus intensity levels in experiment 2, while in experiments 3 and 4 there were four stimulus intensity levels (figure 2.3.). For the cross-modal comparison task in experiment 3 the second stimulus intensity difference was increased so as to achieve similar levels of accuracy across the two tasks (at equal stimulus intensity differences the cross-modal task led to comparatively poorer performance). The first stimulus intensities remained identical regardless of the WM task type. In figure 2.3. each square represents one possible stimulus pair, such that the intensity of the first stimulus is represented by the value on the x axis, while the y axis marks the intensity of the second stimulus. When depicted in this manner, all the squares on the upper diagonal represent stimulus pairs in which the second stimulus was stronger than the first stimulus, while the opposite is the case for the squares on the lower diagonal.

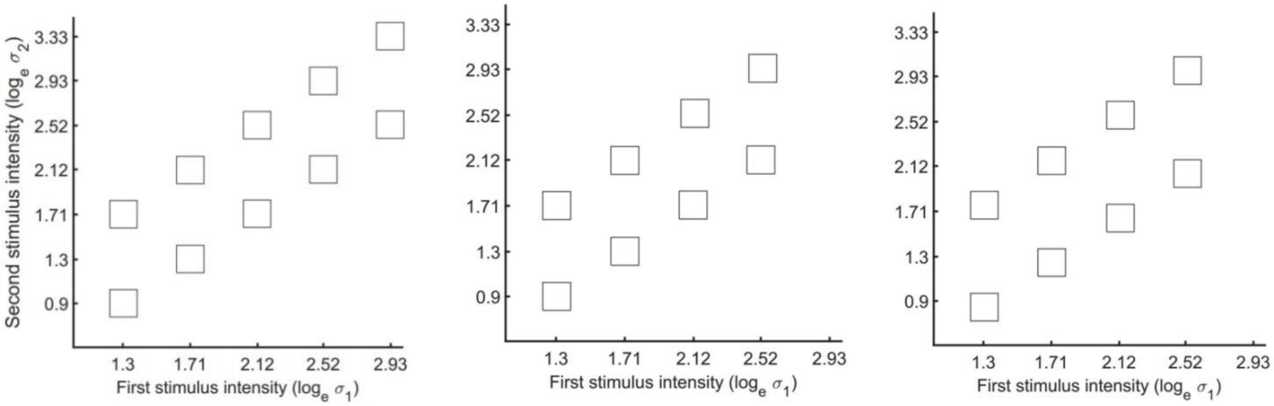

Figure 2.3. The stimuli pairs used in the experiments. From the left: experiment 2, experiment 3 & 4, and experiment 3 cross-modal task stimuli pairs.

The step size between two stimuli (stimulus difference index or SDI) defined the task difficulty and was kept constant throughout all the experiments and between all stimulus pairs. It was calcualted accroding the the following formula:

$$SDI = \frac{\sigma 2 - \sigma 1}{\sigma 2 + \sigma 1}$$

where σ1 and σ2 represented the standard deviation of the first and the second stimulus, respectively. The value of SDI was 0.2 for all experiments and conditions except for the cross-modal comparisons in experiment 3 where it was 0.25 to equalize performance levels between the unimodal and cross-modal conditions. More precisely, while the first stimulus intensities remained identical across the unimodal and the cross-modal conditions, the difficulty of the cross-modal task was reduced by increasing the intensity difference between the first and the second stimulus.

2.7. Stimulus design

The tactile stimulus was generated by randomly selecting velocity values from a normal distribution, which were then concatenated into a stimulus vector, and low-pass filtered at 150Hz to correspond the the technical specifications of the motor (figure 2.4, top row). The first step in the generation of the auditory stimulus was identical to that of tactile stimulus creation. The stimulus vector was then convolved with 1-2kHz band-pass filtered white noise in order to bring the stimulus into human hearing range (figure 2.4., bottom row).

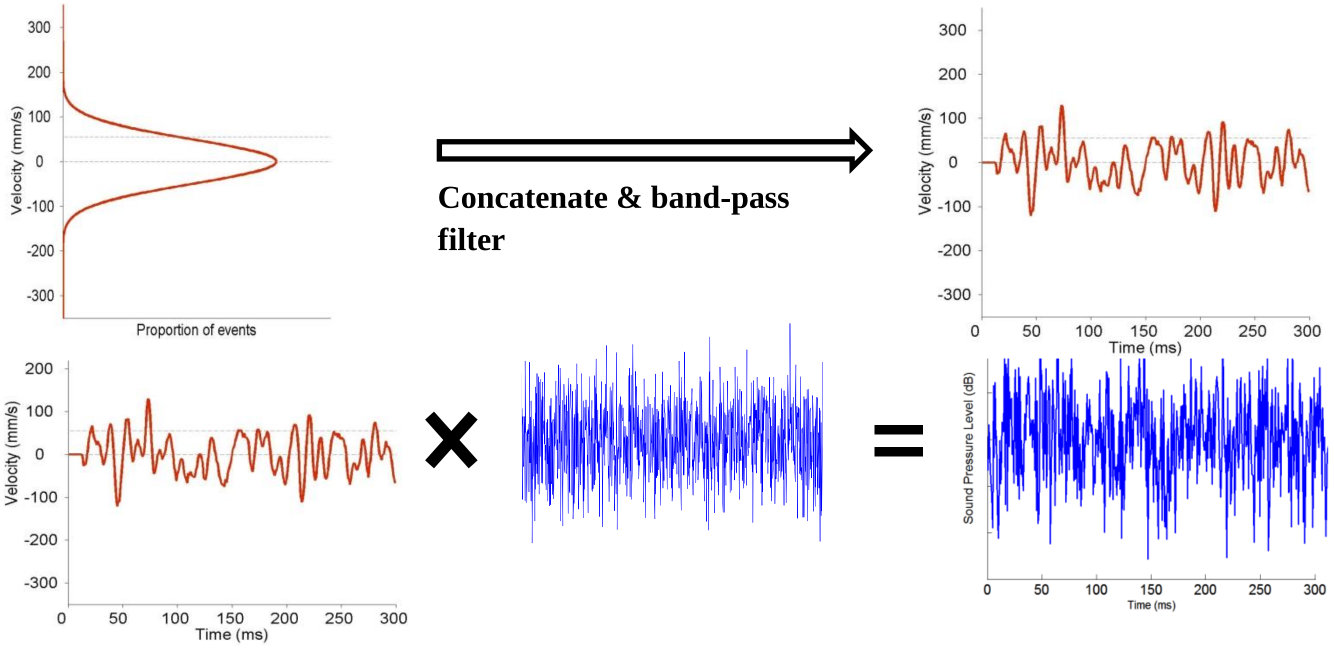

Figure 2.4. The generation of the stimuli used in all the experiments. Top row from the left to right – tactile stimulus generation: a normal velocity distribution from which stimulus values are picked, concatenated and 110Hz low-pass filtered to achieve the final tactile stimulus vector, which were then translated into voltage values driving the vibration motor probe. Bottom row from the left to right – auditory stimulus generation: an initial step identical to tactile stimulus generation was followed by convolution step with a 1-2kHz band-pass filtered white noise.

Stimulus intensity was varied by varying the standard deviation of the underlying velocity distribution from which stimulus vector values were picked. Thus, in a trial where a low intensity stimulus would be followed by a higher intensity stimulus (Figure 2.5.), the standard deviation underlying the first stimulus was smaller, leading to a higher proportion of low velocity the values, while the subsequent stimulus velocity values would be drawn from a distribution with a relatively larger standard deviation leading to a higher proportion of high velocity values. When sent as voltage values to the vibration motor or the membrane of the earphones, the lower values would translate into smaller displacements of the respective actuator, and would be perceived by the participant as a lower intensity stimulus.

.

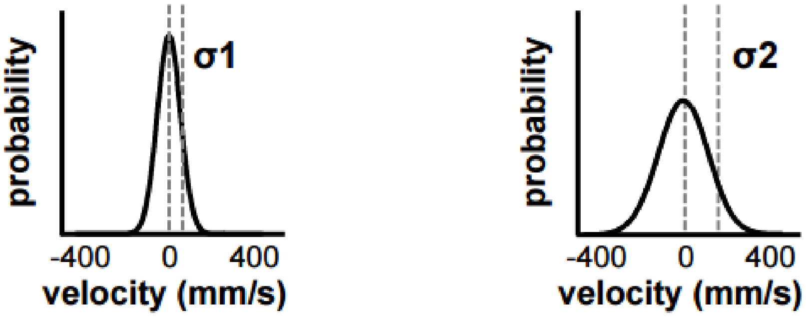

Figure 2.5. The velocity probability distributions underlying the first and the second stimulus of an example trial. A smaller standard deviation leads to the stimulus containing lower velocity values, thus leading to a lower intensity stimulus.

Lastly, in experiment 4 the downward intensity ramp was added by multiplying element wise the non-sloped tactile or auditory stimulus vector with the ramp vector, which contained linearly decreasing coefficients from 0.7 to 1.3.

2.8. EEG recording and preprocessing

EEG data were recorded at a sampling frequency of 2 kHz using the Biosemi ActiveTwo recording system with 128 electrodes that were positioned on the scalp using the Boisemi 128 electrode head cap. The signal was then down-sampled to 256Hz, average-referenced, segmented into trial epochs and 0.1 – 45 Hz bandpass filtered, followed by a visual inspection of every trial. Trials exhibiting high amplitude artifacts and channels with persistent, non-stereotyped artifacts were excluded from further processing. All incorrect trials were also excluded from further analysis. After this step the data were subjected to independent component analysis for artifact detection and removal. Component of every participant were inspected, and the ones showing typical eye blink, heartbeat, or high frequency muscle artifacts were excluded from the data. The "ADJUST" toolbox (Mognon et al., 2010) was used to aid the process of artefactual IC identification. After this step, the remaining ICs were projected back into the electrode space and every trial was examined again to evaluate the success of the ICA-based artifact removal procedure. While eye-blink artifacts were generally identified and removed, a number of trials still containing non-stereotyped artifacts had to be removed from further analysis manually. On average, 7.6% (minimum – maximum range of 2.1% - 10.7%) of the trials were rejected. The data were then average-referenced again and processed further depending on the type of analysis. For the ERP analysis the pre-processed signal was bandpass-filtered between 0.1 and 40Hz using a Butterworth filter, while for the frequency domain analysis a specific bandpass filter was used for each of the EEG frequency bands: 4 – 7Hz for theta, 8 – 12Hz for alpha, 15-25Hz for beta, and 26 – 40 Hz for gamma.

2.9. General analysis considerations

Analysis focused on contrasting the delay period activity between different conditions in order to bring about sensory WM differences between two conditions. During preliminary investigations, it was noted that source localization effects relative to the early trial baseline (derived from the average across the three conditions) provided no consistent insights in terms of the sources identified during the delay period. This is most likely due to the fact that a large number of factors differ between the baseline and the inter-stimulus interval, such as the level of attention, WM related processing, and keeping track of the passage of time, to name but a few.

This observation, in combination with the fact that the choice of a baseline itself can introduce differences in the result observed (Gross, 2014), made it clear that contrasting different conditions is a more sensitive approach to exploring the WM delay period oscillatory activity. Furthermore, while the delay period offered a relatively controlled environment in that the participant was required to keep an active representation of the first stimulus while anticipating the second stimulus, the baseline period, strictly speaking, does not have any task associated with it and thus can lead to a greater variability in the signal observed, which can be negatively affect subsequent analysis of the delay period activity and lead to lower interpretability of the results observed.

The approach of contrasting two conditions is not without its faults either in that the changes observed cannot be strictly attributed to just one of the conditions. Nevertheless, since the contrasted periods differ only along one dimension, which in the present experiment means the modality of the stimulation, the attribution of the differences observed is conceptually straight forward – any significant result highlights the ways in which tactile WM differs from auditory WM in a given frequency band at a particular time period during the inter-stimulus delay. More specific claims can then be made based on the cortical topography of the differences as well as the variations observed when different condition pairs are contrasted.

2.10. Analysis software

All of the analyses were carried out in the Matlab computing environment (8.0 R2012b & 8.6 R2015b) using the Fieldtrip toolbox (Oostenveld et al., 2011) functions for data processing, statistical testing, and visualization unless noted otherwise in the text.

2.11. Quantifying the contraction bias

A behavioral effect observed in sensory delayed comparison tasks called a contraction bias (for a description of this phenomenon see the behavioral results section) can be quantified by estimating the change in accuracy across stimulation intensity levels for either the s1 > s2 trials, the s1 < s2 trials, or both. In order to do this, for each subset of trials (i.e., s1 > s2, and s1 < s2) a slope was fitted to the accuracy data across the five first stimulus intensity levels. This was done for each condition (i.e., auditory, tactile, and bimodal) for each participant and the slope coefficients were entered into a statistical test of slope differences:

$$\boldsymbol{Z} = \frac{\boldsymbol{b}_1 - \boldsymbol{b}_2}{\sqrt{\boldsymbol{SEb}_1{}^2 + \boldsymbol{SEb}_2{}^2}}$$

where b_1 and b_2 represent the mean slope for each condition, and SEb_1 and SEb_2 represent the standard error of the mean for the respective group. The Z value was then converted into a p-value via a look-up table to determine the significance of the test.

2.12. Evoked response potentials

For the analysis of the evoked response potentials (ERPs), the signal was band pass 0.1 – 35Hz band-pass filtered, segmented into individual trials and then averaged for each condition to obtain the grand average waveform.

2. 13. Time-frequency analysis

For time-frequency analysis, the frequency bands established in the EEG literature were used, with 4 – 7 Hz for theta band, 8 – 12Hz for alpha band, 15 – 25 Hz for beta frequency band, and 26 – 40Hz for gamma frequency band (Teplan, 2002). A multitaper method (Percival and Walden, 1993) was used in combination with a smoothing parameter to cover the respective frequency band of interest. An adaptive sliding time window of four cycles per frequency was used with a step size of 50ms. Higher frequencies bands were not analyzed. Lastly, for visualization purposes, time-frequency plots were log transformed since this normalizes the power distribution and makes the differences more salient (Yuvaraj et al., 2014).

2.14. Source localization and statistical analysis

Neural sources were localized using the DICS (dynamic imaging of coherent sources) beamformer (Gross et al., 2001). The approach uses an adaptive spatial filtering technique, in which a regular grid in the source space is constructed and the source strength at each grid point is calculated. Fourier spectra were calculated using a fast Fourier transform of a given frequency in combination with multitapers to achieve the desired spectral smoothing (e.g., 10Hz +/- 2Hz to obtain the 8 – 12 Hz alpha band signal). A realistic head model of the scalp, skull, and the brain was constructed based on the Fieldtrip MRI template, and the leadfields were calculated for the within-brain grid points at a 10mm resolution. Using the data of the contrasted conditions, a common filter was constructed for each participant, which was then used to reconstruct the source distribution. The resultant source distributions were subjected to cluster based permutation testing to determine significant source level differences between the conditions and time windows of interest.

2.15. Parametric correlation analysis

An analysis was performed on the correlation between stimulus strength and beta frequency band induced signal amplitude during the delay period in all three modality conditions. In order to examine induced, i.e. non-phase locked responses, the mean event-related potential (ERP) associated with each condition was subtracted from every trial before single trial time frequency analysis was performed. In order to minimize the variability across trials, time- frequency data were convolved using a Gaussian smoothing kernel of 3 Hz × 200ms. These preprocessing steps replicated the approach taken in several other studies (Kilner et al., 2005; Ludwig et al., 2016). After this step individual trial time-frequency data were averaged for each first stimulus intensity level. Pearson correlation coefficient was calculated between first stimulus intensity and the brain response at the sensor level in the beta band (15-25Hz). The correlation coefficients were entered into the cluster based permutation test to determine at the group level during what delay period window the correlation measure was significantly different between the conditions, as well as significantly different from zero.

2.16. Cluster based permutation testing

Cluster based permutation testing is particularly well suited to electrophysiological data due to the high number of multivariate (spatio-temporal) observations in which the activity from the same source is measured at multiple locations . This approach was used for all statistical significance tests unless noted otherwise in the text. The test involved two steps. At the first level, every time-electrode sample was compared between two conditions (condition specific averages between two conditions) at the group level through a t-test. Based on a chosen threshold value, all spatio-temporally neighboring samples that exceed it are included in a cluster. For each cluster the sum of the constituent samples’ t-values is calculated and the largest cluster is used as the test statistic. During the second step, the conditions specific averages are randomly repartitioned and the t-value recalculated as described above (the Monte Carlo method). One thousand permutations were used to establish the empirical probability distribution against which the original t-value. The proportion of permutations that resulted in a larger cluster level sum of t-values was effectively the p-value for determining the significance of the difference between two conditions. It is important to note that this test establishes whether the contrasted spatio-temporal windows differ from each other; in other words, it is not legitimate to claim that it is the largest spatio-temporal cluster detected that is significantly different between the two conditions. Nevertheless, it is a legitimate approach to interpret the observed clusters based on the knowledge of the neurophysiological processes that are presumed to take place during a given period of interest.

2.17. Connectivity

In experiment 4, node centrality – a connectivity based metric – was assessed across conditions. To this end, first the source level time series were reconstructed by the use of LCMV beamformer across 82 nodes based on Brodmann areas, which covered the entire brain surface. The source level time series were then transformed into time-frequency representations. This was done for each frequency band separately and the weighted phase lag index (wPLI; Vinck et al., 2011) was used to estimate the degree of synchrony between the cortical nodes in an all-to-all fashion (81 per node). In order to establish statistical significance of node centrality differences, two conditions of interest were contrasted through cluster based permutation testing. This statistical test was appropriate because even at the source level volume conduction effects are still evident (Schoffelen and Gross, 2009) and therefore neighboring nodes show correlated connectivity patterns.

2.18. Experimental design considerations

In experiment 2, block design was chosen for its higher signal to noise ratio (SNR), since any effects observed should be enhanced by repeated stimulation of the same type. If the results observed would be clear and interpretable, the subsequent experiments would be designed with interleaved trials in order to avoid the potential pitfalls associated with block designs, such as not having a neutral pre-trial baseline. Thus, in experiments 3 and 4 the trials of the same task type but different modalities were interleaved within block, while tasks remained blocked.

Bilateral stimulation was chosen to equalize low-level cortical activation patterns across the two modalities. Since it is known that the auditory pathways cross relatively early in the neural pathway and the signal reaches both primary auditory areas regardless of the side of stimulation (Javitt and Sweet, 2015), stimulation of both the left and the right ear and index finger was chosen in order to make both modality stimuli explicitly bilateral. For experiments 3 and 4, however, stimulation was changed to unilateral since in experiment 2 the source localization procedure failed to produce two distinct sources in either hemisphere. Providing a single sensory input as well as dropping the bimodal stimulation condition would solve the issue of having to localize multiple concurrent sensory inputs under conditions of low spatial resolution.

3. EXPERIMENT 2

3.1. Introduction

Experiment 2 was designed to explore the dynamics of alpha band (8 – 12Hz) ERS/ERD in the unimodal and the bimodal conditions. It served to primarily set the stage for the subsequent experiments. This is because the human EEG research paradigm had never been tested in the laboratory in this project was carried out. Therefore, it was first necessary to examine the general dynamics of the oscillatory delay activity in order to determine whether they matched our predictions of sensory engagement in the alpha band.

Alpha band ERS/ERD has been primarily linked to and interpreted through the "gating through inhibition" hypothesis, which posits that optimal task performance will correlate with alpha power in task-irrelevant areas (Jensen et al., 2010). While several studies have shown clear effects over sensory cortices during the WM maintenance period (Haegens et al., 2009), it remains less clear to what extent alpha band ERS/ERD can be observed in other cortical areas and thus reveal areas modulated by different WM tasks or WM task demands. One of the purposes of this experiment was to explore through contrasting different sensory modality conditions whether further sources beyond sensory cortices can be identified and given a functional meaning in the context of a SWM task. Secondly, the experiment addressed the question of whether any parametric effects relating first stimulus intensity to the oscillatory power can be identified during the delay period in the beta (15-25Hz) frequency range. Beta band parametric modulation has been attributed to the maintenance of WM contents during the delay period, but also to multimodal integration (Engel et al., 2012). In experiment 2, the two lines of evidence combined to address the question of whether there a parametric bimodal WM effect observed in the beta frequency band.

3.2. Behavioral results

In this experiment three SWM conditions were tested in interleaved blocks: tactile, auditory, and bimodal. There were no cross-modal conditions in this experiment. All participants performed the task with an accuracy of at least 80% during all blocks of the experiment. The average accuracy in the auditory, tactile, and bimodal conditions were 86.8 % (SEM 1.56), 86.1 % (SEM 1.51), and 89.4 % (SEM 2.02), respectively (figure 3.1.). The reactions times for the three conditions were 395ms (SEM 25), 399ms (SEM 20), and 407ms (SEM 32), respectively. Since a post-stimulation delay was imposed after the second stimulus, no reaction times were neither expected, nor observed between the conditions. A minor increase in accuracy was observed in the bimodal condition but it was not significantly different from the two unimodal conditions.

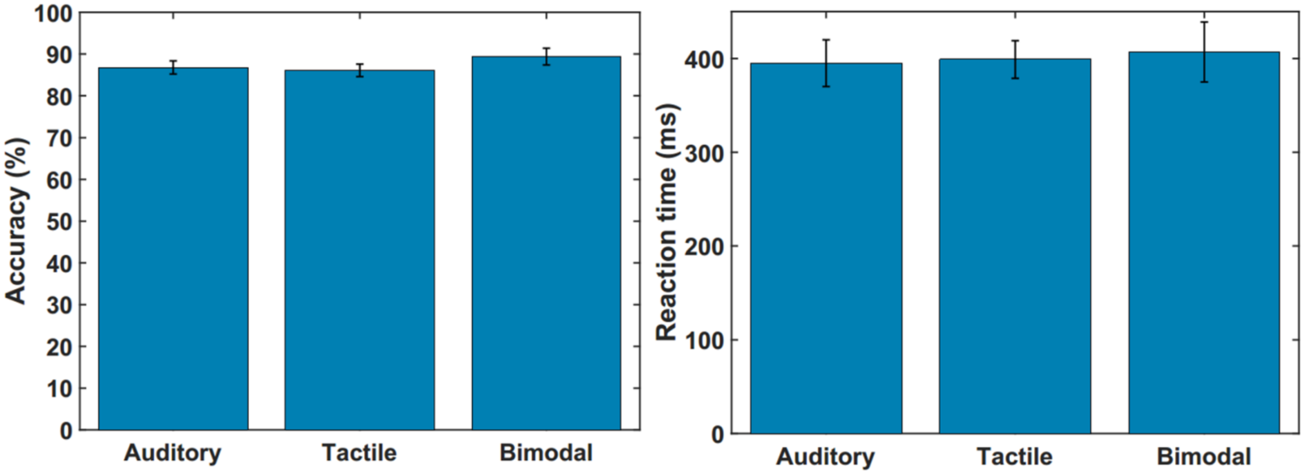

Figure 3.1.The accuracies (left) and reaction times (right) in the three conditions of experiment 2 (error bars represent +/- 1 SEM).

3.3. Differences in contraction bias strength reveal multisensory WM enhancement

In order to have a more solid basis for the interpretation of the EEG results when contrasting the bimodal condition to the unimodal ones it was important to determine whether there was any enhancement in performance due to bimodal stimulation also at the behavioral level. When subdivided into different stimulus pairs (figure 3.2.), the response accuracy patterns could be evaluated for the presence of the bias (Fasihi et al., 2014), which could be seen as a measure of the strength of the WM representation. The contraction bias hypothesis proposes that the WM representation of the first stimulus will drift towards an average stimulus intensity based on the recent stimulation history. Based on this supposition, this “drift” would bias high intensity stimuli to be remembered as being weaker, while the opposite would happen to low intensity stimuli. Upon the presentation of the second stimulus, the drift would have an opposite effect on the intensity comparison, depending on whether the second stimulus intensity is higher or lower than that of the first stimulus. For instance, a high intensity first stimulus would be remembered as being weaker than it actually was, thus making a comparison to a weaker stimulus harder. A high intensity stimulus followed by an even higher intensity stimulus would have the exactly opposite effect, in that the “drift” towards the mean would render the intensity difference between the two stimuli subjectively more salient. When represented graphically, this effect can be observed as a monotonous increase/decrease of accuracies along the diagonal with increasing/decreasing second stimulus values.

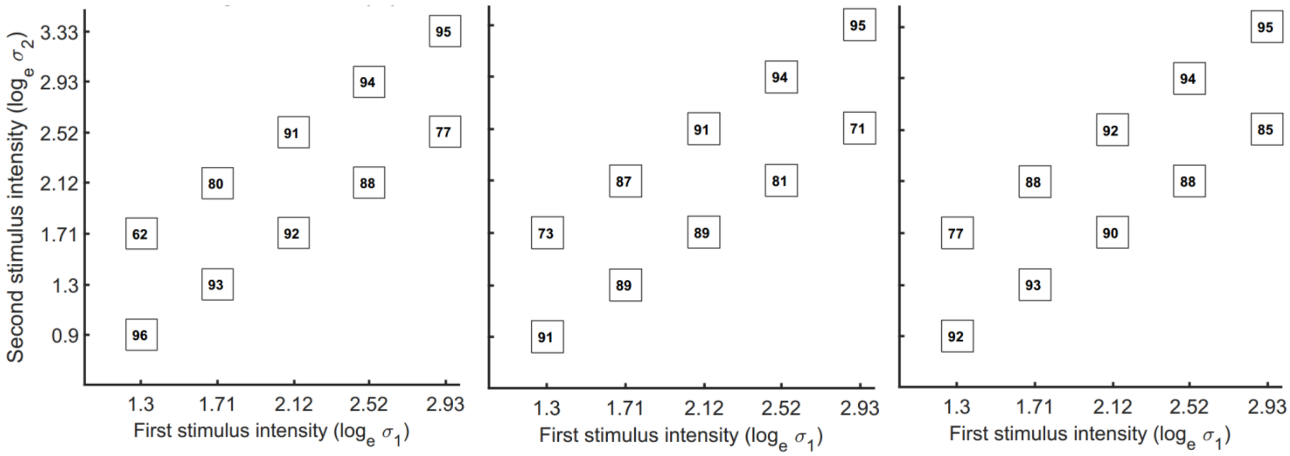

Figure 3.2. Response accuracies for all stimulus pairs in all conditions. From the left: auditory, tactile, and bimodal condition. Every square represents one possible stimulus pair, with first stimulus intensity marked on the x axis, the second stimulus accuracy marked on the y axis, and the accuracy for the stimulus pair (in %) plotted inside the square.

While absolute accuracy differences between conditions indicated no benefits, the strength of the contraction bias revealed that in the bimodal condition this effect was significantly reduced. One way of quantifying the contraction bias is by estimating the slope of the accuracy increase or decrease (for s2 > s1, and s1 > s2 diagonals, respectively) across the intensity values for each of the three conditions. At the group level these slope coefficients were compared across the three conditions and the results showed that all three conditions had slopes that were significantly different from zero, thus indicating the presence of a contraction bias. Most importantly, however, the slope in the bimodal condition was significantly shallower than in either of the unimodal conditions (figure 3.3.; $p < 0.05$, Bonferroni corrected). This suggests that the bimodal WM representation was less subject to memory degradation over the delay period, despite the fact that at the level of overall accuracies no significant difference was detected across the conditions. Thus, the enhancement of bimodal stimulation for WM was clearly demonstrated and any EEG effect specific to the bimodal condition during the delay period could potentially be associated with this behavioral effect.

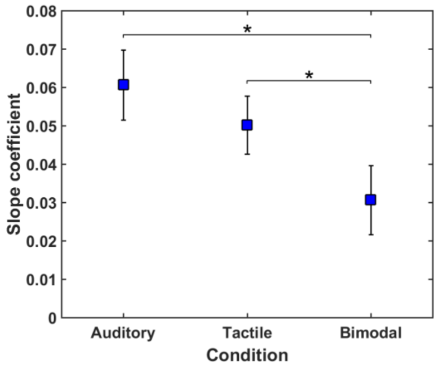

Figure 3.3. Quantifying the contraction bias. The accuracy slope coefficients across all the s1 > s2 and the s2 > s1 stimulus pairs were estimated separately and then evaluated at the group level. The auditory condition and the tactile conditions showed the steepest slopes (suggesting a stronger contraction bias) and were significantly steeper than the slope of the bimodal condition.

3.4. Evoked responses

Since experiment 2 was the first time in the context of the laboratory that a SWM experiment was run using EEG as the recording modality, the results section starts with several observations with regard to the ERP dynamics, which served as preliminary and precautionary checks. This served the purpose of establishing that the overall recording and analysis methodology reflects task related activity and is sensitive to experimental manipulations. It is the followed by analyses in the time-frequency domain.

The strongest evoked response potentials (ERPs) were observed over the fronto-central electrodes during the first stimulation period in all three conditions. The evoked responses (ERPs) showed a clear negative peak at 100ms (N100) post stimulus onset, as well as a positive peak at 200ms (P200). Further late stimulation low amplitude peaks could be distinguished with increasingly lower amplitudes and shorter periods. Only the P200 was clearly modulated by the stimulus amplitude in a parametric fashion (figure 3.4.) , while in the earlier and the later peaks this pattern was less pronounced. This was the case across all three conditions.

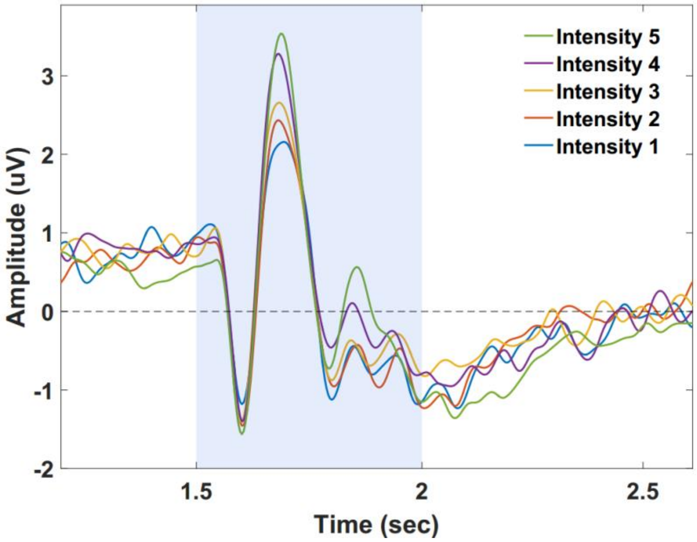

Figure 3.4. Auditory condition ERPs during the first stimulation period. A similar pattern of increasing ERP amplitudes with increasing stimulus intensity values was observed across all three conditions.

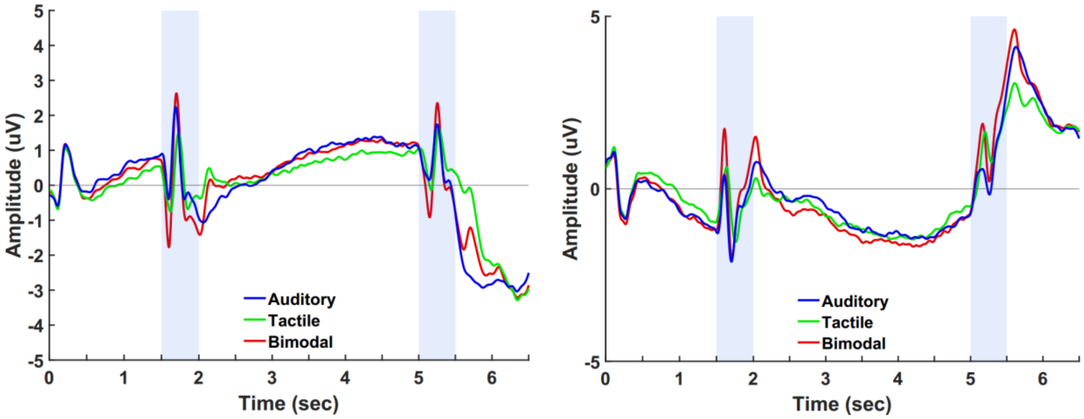

Figure 3.5. Grand average condition ERPs. From the left: fronto-central electrodes (FCz) and centro-posterior (POz) electrodes.

At a coarse scale, the ERPs of the three conditions showed a similar pattern across the entire trial period and varied similarly from electrode site to electrode site (figure 3.5.). As a preliminary signal assessment, a number of statistical tests were conducted comparing the delay period ERPs between the conditions. Differences were observed in the time periods just after (2 – 2.7 sec) and just prior to stimulation (4.6 – 5 sec). With the exception of fronto-central (FCz and surrounding electrodes) activity in the 250ms following the first stimulus offset, no other electrodes sites could distinguish between the three conditions during the delay period. These results served as a preliminary characterization of the EEG signal only, and were not examined further due to the aim of this study being the investigation of oscillatory activity during the WM period.

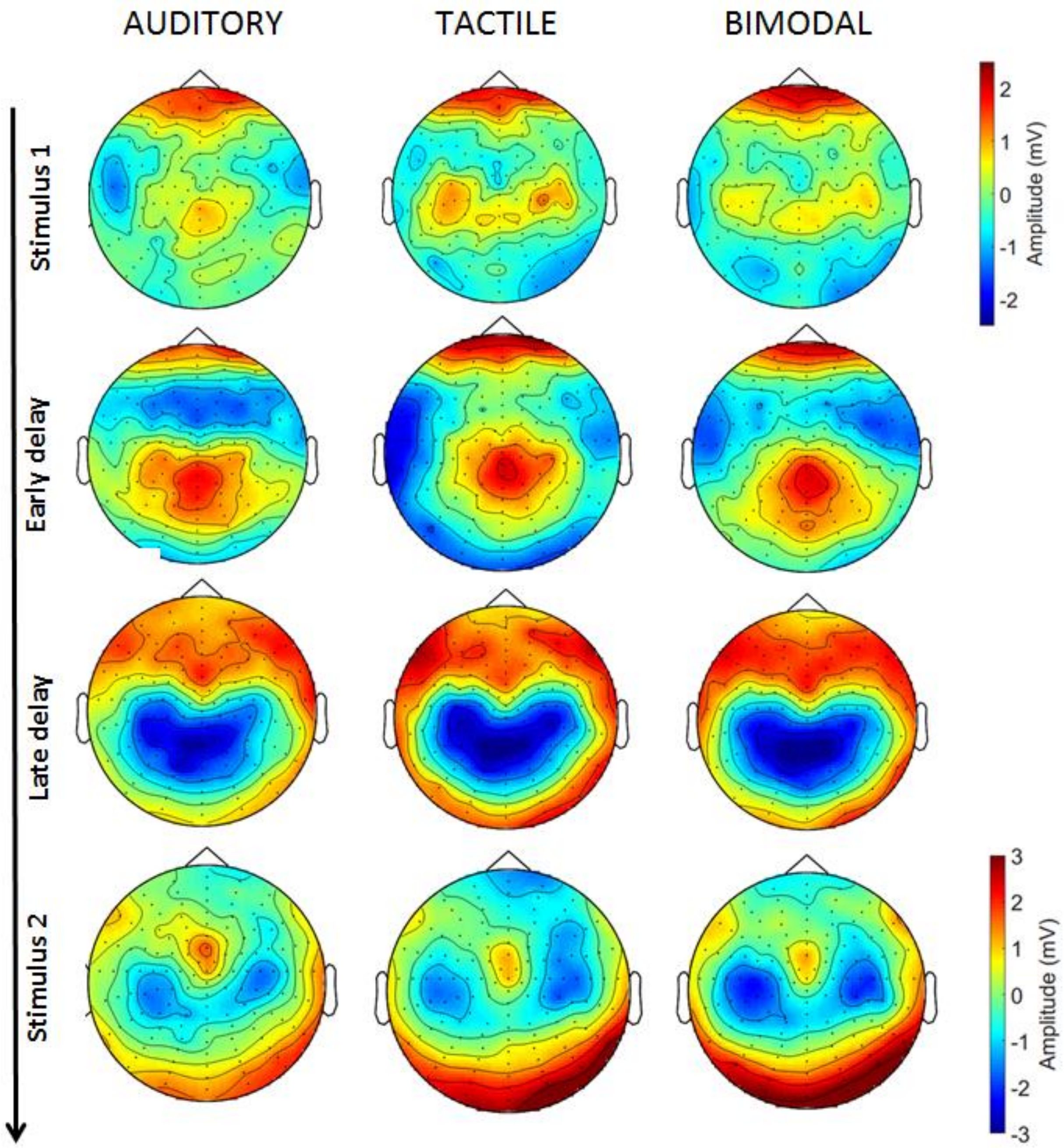

Figure 3.6. Time line of scalp voltage evolution in the three conditions. Stimulus 1: Auditory condition at 50ms, the rest at 100ms; early delay: 0-250ms post first stimulus offset; late delay: 250-0ms before second stimulus onset; stimulus2: 50-150ms into the second stimulation period.

3.5. Preliminary observations in the time-frequency domain

Several general observations were made with respect to power distribution topographies during the trial to further ascertain that the dataset shows some key characteristics in line with what has been already reported in the literature. All three conditions showed a general increase of power in the alpha frequency band across the entire scalp area recorded starting from the late baseline period till the onset of the second stimulation period. This effect was expected as most studies with tasks involving sustained, top-down coordination of attention report a similar pattern of alpha power dynamics (Shaw et al., 2003). In the present experiment a difference between the conditions was observed at the end of the first stimulation period, such that the conditions containing tactile stimulation (i.e. the tactile and the bimodal condition) showed a visible reduction of power, most notably in the alpha frequency band (figure 3.7.).

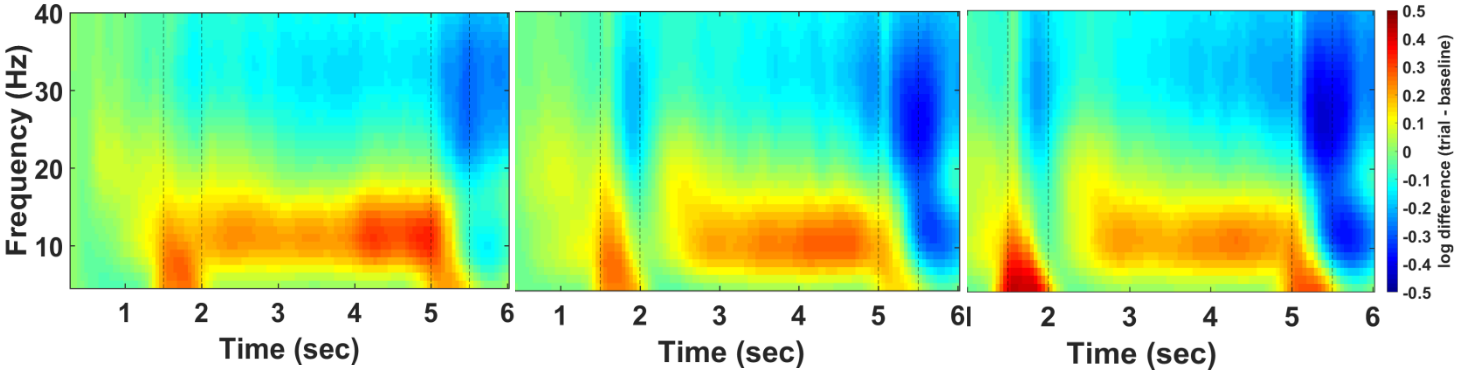

Figure 3.7. Time-frequency representation of the grand average baseline (0.4 – 0.6s) relative ERS/ERD during the trial averaged over 5 centro-frontal electrodes. From the left: auditory, tactile, and bimodal condition. The dashed lines at 1.5 & 2.0 and 5.0 & 5.5 sec indicate the onset and offset of the first and the second stimulation period, respectively.

As can be seen in the figure above, there were several baseline-relative changes and the effects, in particular in the alpha band, lasted throughout the delay period. On the other hand, contrasting conditions with each other (figure 3.8.) produces a more limited set of effects that are more specific in time. As an initial observation it is important to note that the differences between the

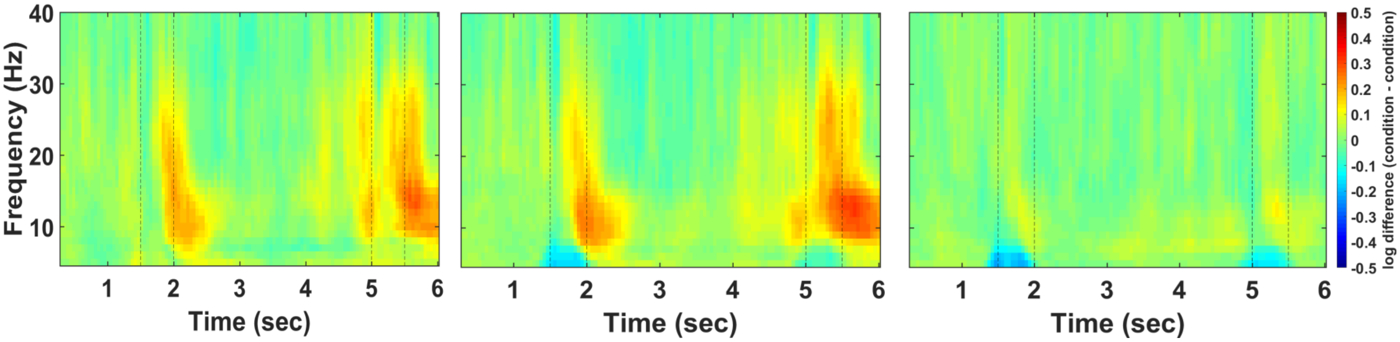

Figure 3.8. Time-frequency representation of the grand average absolute power differences between condition pairs. From the left: auditory – tactile; auditory – bimodal; tactile – bimodal condition. The signal was averaged over 5 centro-frontal electrodes. The dashed lines at 1.5 & 2.0 and 5.0 & 5.5 sec indicate the onset and offset of the first and the second stimulation period, respectively.

tactile and the bimodal condition are minimal, while both the auditory to tactile and the auditory to bimodal contrasts. This, again, suggests that the difference is most likely dominated by the signal caused by tactile stimulation.

3.6. Sensor and source level differences in the alpha band

3.6.1. Auditory (AA) vs tactile (TT) condition

At the sensor level, statistically significant differences were observed during both the early and the late delay period, but not during the middle of the delay (Figure 3.9; for illustrative purposes also the first and the second stimulation period differences are shown). Here, a topography characteristic of differential activity in the somatosensory emerged. It was the clearest during the first stimulation period, while during the subsequent stages more pronounced asymmetries emerged suggesting the involvement of cognitive processes beyond those evoked by the exogenous stimulation.

-

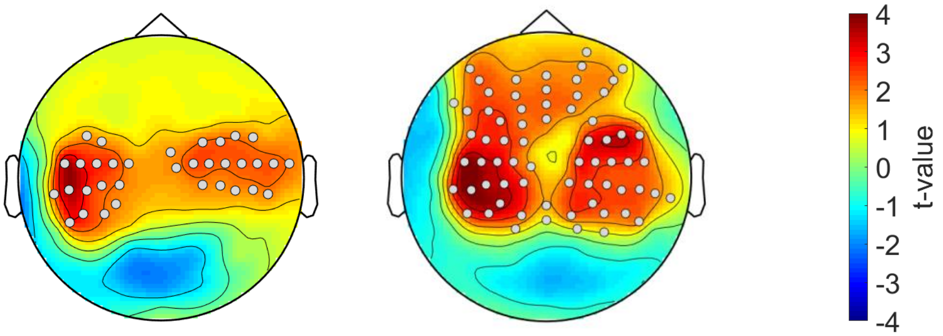

Figure 3.9. AA vs TT statistical difference topography during the two stimulation periods. From the left: first stimulus (1.5 -2.0 sec); second stimulus (5.0 - 5.5sec). Positive values (red colored) indicate reduced power in the tactile condition relative to the auditory condition. Highlighted with white circles are electrodes that formed a cluster during the time period in which the conditions were statistically significantly different from each other.

The clusters highlighted the scalp areas to which both the auditory and the somatosensory cortex signal would be expected to project to most strongly (Simson et al., 1977; Eimer and Forster, 2003). There were more widespread differences observed during the second stimulation period, in particular over the frontal sensors.

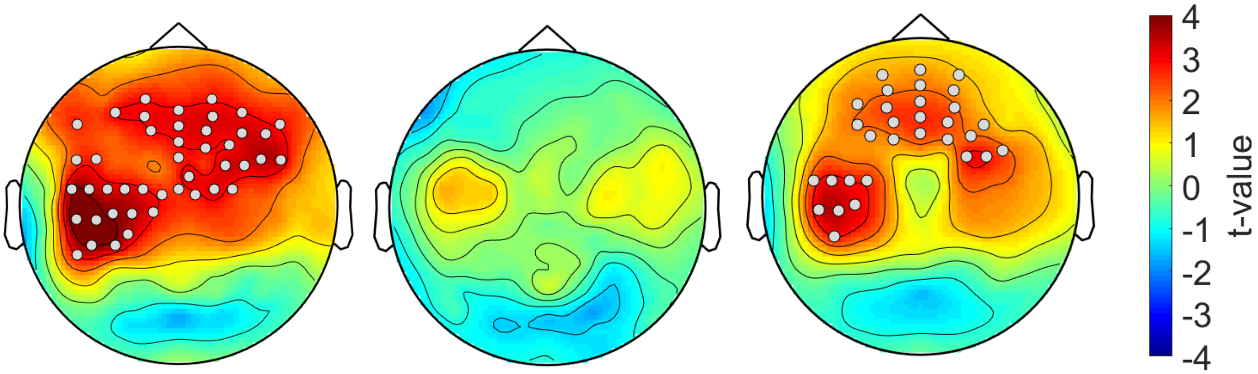

Figure 3.10. AA vs TT statistical difference topography. From the left: early delay (2.0 - 2.6 sec), mid-delay (3.25-3.75sec – no significant difference), late delay (4.4 -5.0 sec). Positive values (red colored) indicate reduced power in the tactile condition relative to the auditory condition. Highlighted with white circles are electrodes that formed a cluster during the time period in which the conditions were statistically significantly different from each other.

An evolution of condition differences was observed during the delay period (figure 3.10) – the late delay topography had shifted relative to the early delay,, but, most importantly, both were interrupted by a non-significant mid-delay period, in line with the notion of the reactivation of WM related processes prior to the onset of a comparison stimulus (Romo et al., 1999).

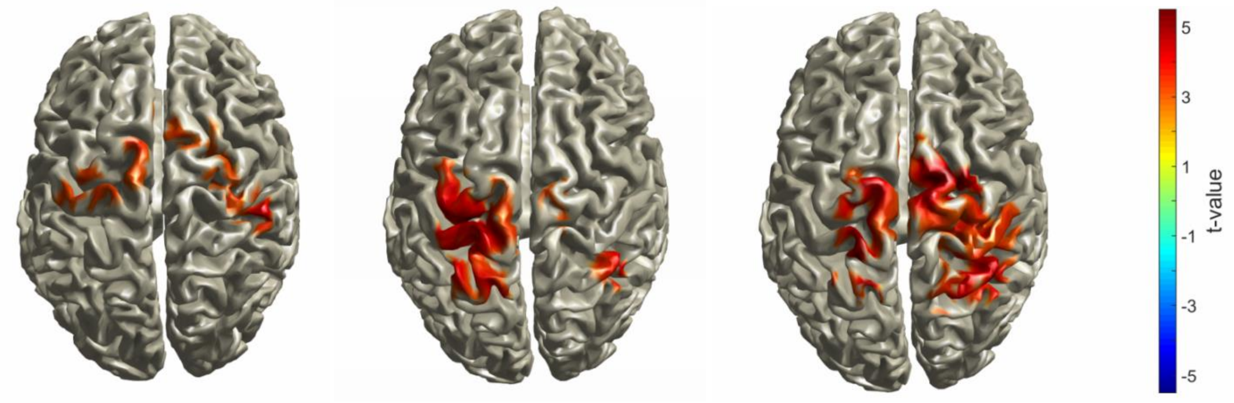

Figure 3.11. Source level differences between the auditory and the tactile condition in the alpha band. From the left: early baseline (1.0 – 1.5 sec); early delay (2.0 – 2.8); late delay (3.7 – 5.0 sec). Positive values (red colored) indicate reduced power in the tactile condition relative to the auditory condition.

Statistical testing at the source level highlighted a central posterior area spread mostly across the somatosensory cortex, and to a degree, also parietal areas (figure 3.11.). There were no separate clusters observed in each hemisphere. Instead, the clusters stretched across the hemispheres, connecting both sides of the somatosensory cortex. Lastly, there seemed to be an evolution of source differences across the three time periods, with the late delay period showing the largest differences, also spreading into the posterior areas.

While the difference was clearly observed over the somatosensory areas, no similar effect was seen over the auditory cortices. The possible causes and solutions to this asymmetry of results are addressed in the discussion section.

3.6.2. Auditory (AA) vs bimodal (BB) condition

During both stimulation periods the two conditions were statistically different from each other. During the first stimulation a cluster electrodes highlighted the scalp areas to which sensory cortices in question are assumed to project most strongly, though with a bias toward the left hemisphere. Unlike the AA vs TT contrast, here no separate clusters emerged; instead there was one cluster stretching across a central band of electrodes, possibly due to the merging of the signal from the four sources simultaneous sources at the sensor level. The second stimulation period showed a clear asymmetry in that a central cluster emerged only in the left hemisphere, while another cluster was positioned over the right frontal electrodes (figure 3.12.).

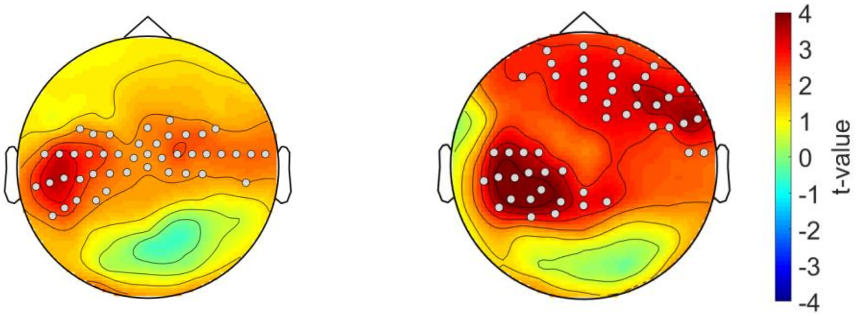

Figure 3.12. AA vs BB statistical difference topography during the two stimulation periods. From the left: first stimulus (1.5 -2.0 sec); second stimulus (5.0 - 5.5sec). Positive values (red colored) indicate reduced power in the bimodal condition relative to the auditory condition.

Delay period activity showed a similar temporal pattern to the AA vs TT contrast in that the mid-delay period (3.7 – 4.2s) did not show any statistically significant differences between the two conditions, while the early and the late delay period showed a partly similar topography with the most notable difference being the emergence of a fronto-central highlight during the late delay period (figure 3.13.).

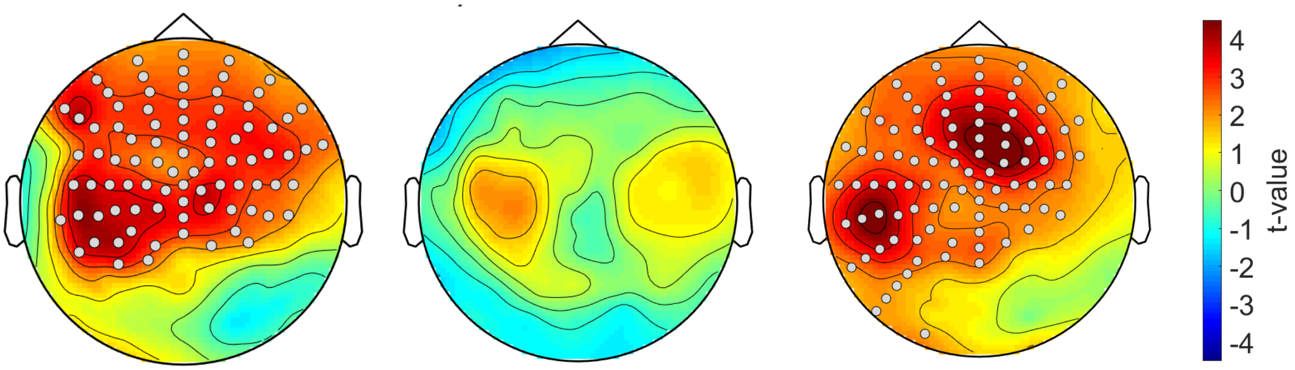

Figure 3.13. AA vs BB statistical difference topography during the delay period. From the left: early delay (2.0 -2.7s), mid-delay (3.25-3.75s – no significant difference), late delay (4.2 – 5.0 s). Positive values (red colored) indicate reduced power in the bimodal condition relative to the auditory condition.

Source reconstruction revealed a symmetric activation of both sensory cortices both during the early (2.0-2.7s) and the late (4.1 – 5s) delay period (figure 3.14.), which, similarly to the AA vs TT contrast also extended into the posterior areas to a degree. Interestingly, unlike in the AA vs TT contrast, a frontal difference was observed. During the early delay period the cluster extended towards and also included the prefrontal cortex (PFC).

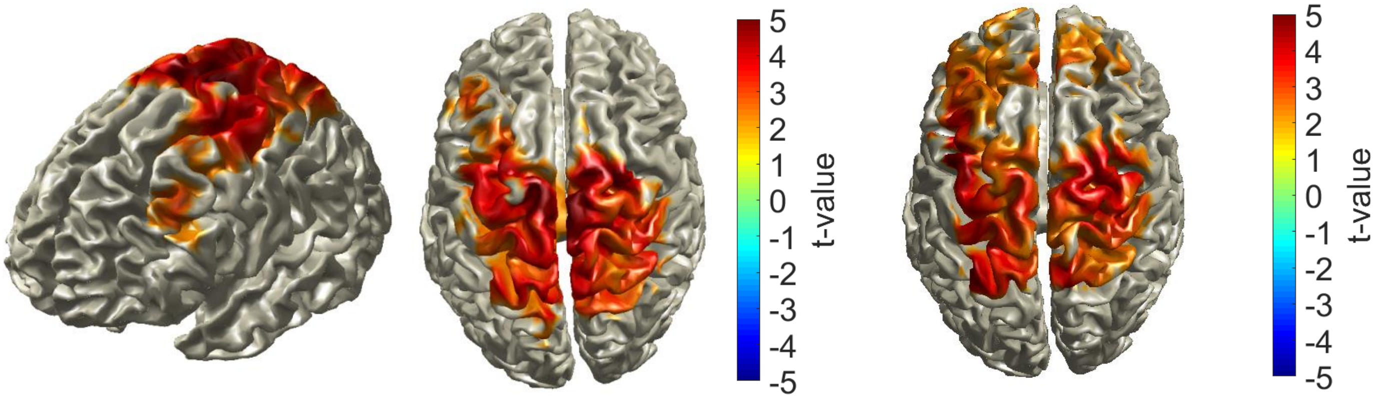

Figure 3.14. Source level differences between the auditory and the bimodal condition in the alpha band during the delay period. From the left: early delay (2.0-2.7sec) front-left and top view; late delay (4.1-5.0sec). Positive values (red colored) indicate reduced power in the bimodal condition relative to the auditory condition.

3.6.3. Tactile (TT) vs bimodal (BB) condition

Similarly to the previous two contrasts, central bilateral topographical features could be discerned, especially during the second stimulation period. The topography of the clusters, however, differed markedly from the previous two contrasts. A central cluster stretching along the fronto–posterior axis was observed during the first stimulation period while the second stimulation period cluster was limited to a right temporal area (figure 3.15).

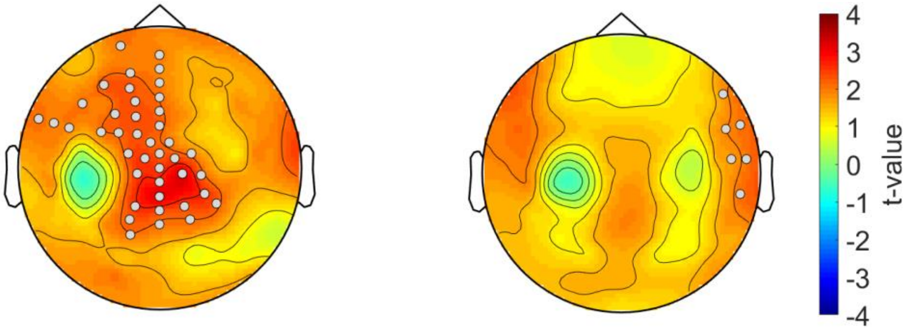

Figure 3.15. TT vs BB statistical difference topography during the two stimulation periods. From the left: first stimulus (1.5 -2.0 sec); second stimulus (5.0 - 5.5sec). Positive values (red colored) indicate reduced power in the bimodal condition relative to the tactile condition.

Interestingly, no delay period differences were observed between the tactile and the bimodal condition. Furthermore, the scalp topography was not reminiscent of the one observed in the first two contrasts (AA vs TT, and AA vs BB). Since there were no periods of statistical difference the scalp topographies are plotted for visual reference only (figure 3.16).

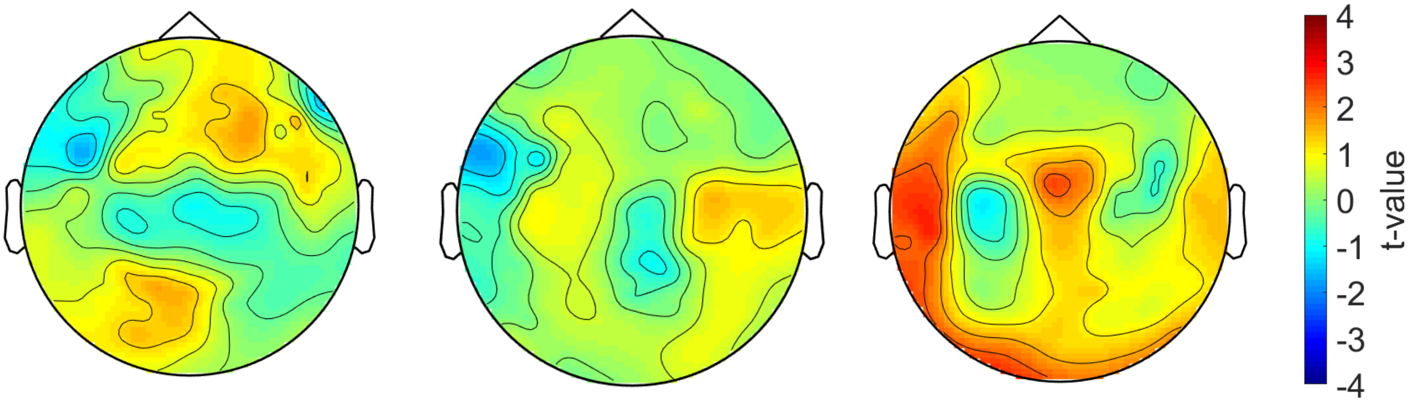

Figure 3.16. TT vs BB statistical difference topography during the delay period. From the left: early delay (2.0 -2.5 sec), mid-delay (3.25-3.75sec), late delay (4.5 – 5.0 sec). Positive values (red colored) indicate reduced power in the bimodal condition relative to the tactile condition.

Since it was observed that the reconstructed sources of the delay period in the previous two conditions largely resembled the stimulation period source differences, here stimulus periods were used to assess the differences between the conditions. During the early phase of the trial differential activity in and around the auditory cortices was observed in both hemispheres.

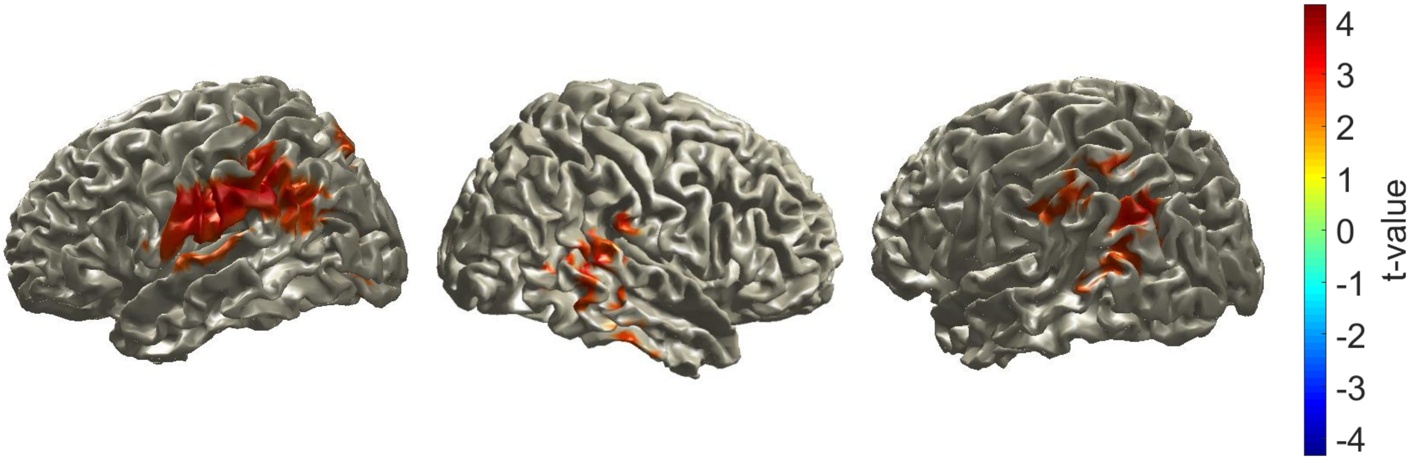

Figure 3.17. Source level differences between the tactile and the bimodal condition in the alpha band. From the left: first stimulation period – left hemisphere view; first stimulation period – right hemisphere view; second stimulation period – rear-left view. Positive values (red colored) indicate reduced power in the bimodal condition relative to the tactile condition.

Second stimulation period activity, in contrast, was source localized to an area around the left intraparietal sulcus (IPS). This cluster, however, did not reach a level of significance ($p < 0.1$; figure 3.17).

3.7. Absolute changes in alpha power in the auditory and tactile conditions

In order to assess alpha power dynamics in the two conditions, first the common voxels were identified across the three significantly different periods (late baseline, early delay, and late delay). Here, the LCMV beamformer was used to reconstruct the amplitude time series of the 8-12Hz bandpass filtered signal in the common voxels in the somatosensory cortex (figure 3.18.).

Follow-up t-tests within each condition between the early baseline and the three time periods of interest revealed that in the auditory condition all had increased significantly above the baseline value (all Bonferroni adjusted p-values < 0.001), while in the tactile condition only the late baseline and the late delay period showed a significant albeit weaker increase over the baseline (both Bonferroni adjusted p-values < 0.02). This suggests that there was active inhibition of the somatosensory cortex taking place during

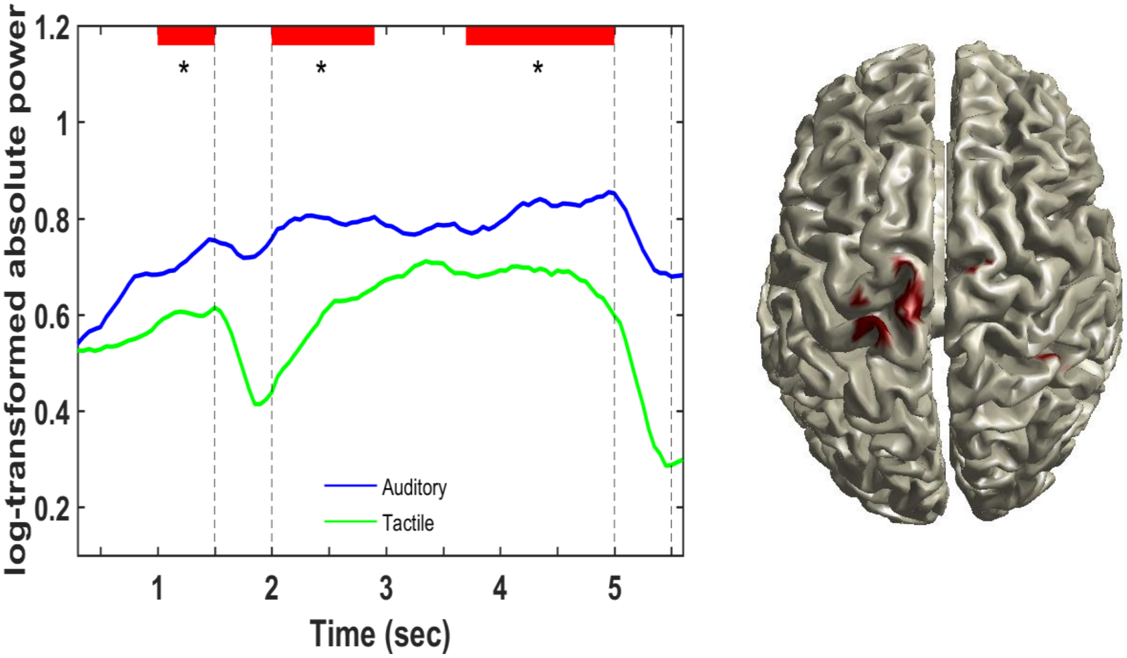

Figure 3.18. The amplitude of the alpha band signal in the somatosensory area voxels that were common to all three significantly different windows (marked with red bars at the top of the graph). The dashed lines indicate the onset and the offset of the first stimulation periods.

the auditory trials and that despite the block design clearly separating the two conditions in time. In order to determine whether this effect was indeed a specific contextual effect potentially brought about by the participants' exposure to the tactile stimuli during half of the time of the experiment, a further test of specificity was carried out. Reconstructing the auditory condition early delay sources with respect to the pre-trial baseline revealed that this effect was not specific to the somatosensory cortex (figure 3.19.). Instead, wide portions of the posterior cortex were also activated, in line with observations in other delayed comparison WM studies, in which directed internal attention is required (Khader et al., 2010; Benedek et al., 2014).

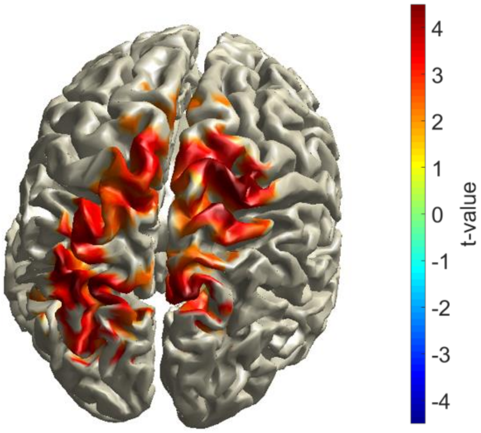

Figure 3.19. Voxels with a significant alpha power increase over the baseline in the auditory condition highlighted in red. The effect covers central parietal areas between the somatosensory and visual areas, with the maximum effect located in the right posterior parietal cortex.

The proximity of the sensory associated areas to the somatosensory cortex does not allow for a definitive conclusion as to the absence of heightened sensory cortex inhibition during the auditory blocks. An additional experiment in which naïve participants are exposed to the auditory task only would be needed to shed further light on this phenomenon.

3.8. Early delay parametric effects in the induced beta band signal distinguish between the bimodal and the unimodal conditions

In the present experiment induced beta power over the right posterior electrodes was parametrically modulated during the late stimulation and the early delay period (1.9 – 2.7 sec) in the bimodal condition. The general power dynamics of the induced signal resembled the complete signal (i.e., without the ERP removed prior to time-frequency analysis), however, the complete signal did not produce the same statistically significant result. There was a general power increase across alpha and beta frequency bands observed throughout the delay period, while the phase locked signal associated with the onset of stimulation in the lower frequencies had been removed (see Methods).

Correlating first stimulus intensity with beta power across the entire scalp area in the alpha and beta frequency bands (15 – 25Hz) revealed a moderately strong negative correlation (< - 0.6) in and around the right parietal area. No such effect was observed in the two unimodal conditions (figure 3.20). A cluster based permutation test revealed that the correlation was significantly different from zero only in the bimodal condition ($p < 0.01$), but not in either of the unimodal conditions. A cluster emerged over the right parietal area which was spectro-temporally limited to 17 – 24Hz and the early delay period (2.0 – 2.7 sec). Since the onset of the window coincided with the edge of the time period of interest, a follow-up test was run with an extended temporal window, which also included the period of stimulation. This test revealed a 400ms earlier onset (1.6 – 2.7sec), thus showing that the effect was temporally centered around 150ms past the offset of the first stimulation period.

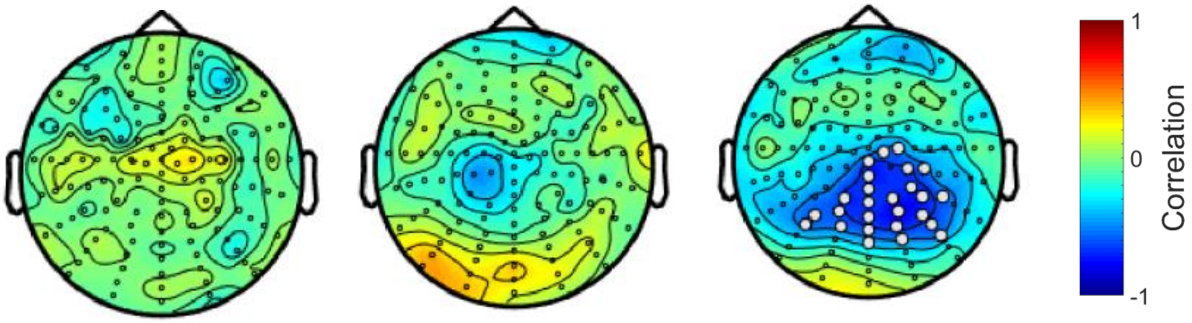

Figure 3.20. From left: auditory, tactile, and bimodal condition stimulus amplitude – beta power correlation values. Highlighted with white circles is the electrode cluster in the bimodal condition from the spectro-temporal window in which the correlation was significantly different from zero (1.6 – 2.7sec and 17 – 24Hz).

Furthermore, the correlation in the bimodal condition was significantly different between both the bimodal and the auditory condition and the bimodal and tactile conditions ($p < 0.01$, and $p = 0.02$), while no significant differences in beta power-stimulus intensity correlation were observed between the auditory and the tactile conditions.

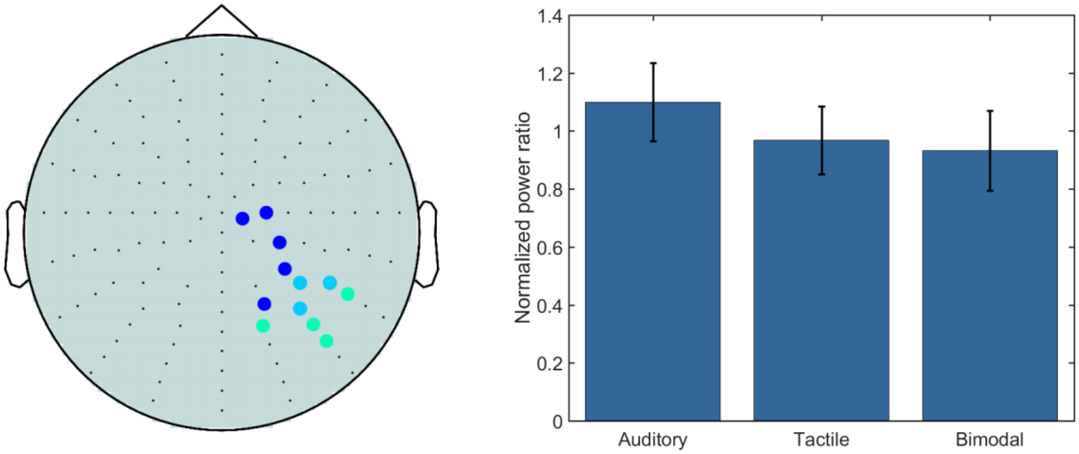

Figure 3.21. From the left: significant electrode locations in the auditory vs bimodal (dark blue), tactile vs bimodal (light green), and the significant electrodes common to both statistical tests (light blue); the average power in the electrodes common between the two statistical contrasts (AA vs BB, and TT vs BB) at the group level.

Since an increased signal to noise ratio (SNR) can lead to an improved detection of a correlational pattern, it was conceivable that all conditions showed this parametric effect, but it was detectable only in the bimodal condition exhibited the correlational effect due to the summing of the evoked responses at the scalp electrodes, which in turn led to an improved SNR. To test for this, the power from the electrodes common to both posterior clusters (i.e. from the AA vs BB, and the TT vs BB contrasts) was averaged over the spectro-temporal window, where the cluster was detected, normalized within each subject, and compared at the group level (figure 3.21). There were no significant differences observed between the conditions. This was in line with the observations of the ERP signal, which showed no consistent amplitude differences above the 12Hz in any of the conditions beyond the initial 250ms of stimulation.

Once the existence of the correlational effect was established, it was followed up by source localization of the signal in question. The lowest and the highest amplitude stimulation trials from the bimodal condition trials were contrasted (since this, based on the correlation observed, meant contrasting the trials with the highest and the lowest power) to localize the cortical source of the beta power difference in the 17-24Hz and 1.6

– 2.7s spectro-temporal window. Cluster based permutation testing revealed a cluster in the right parietal cortex.

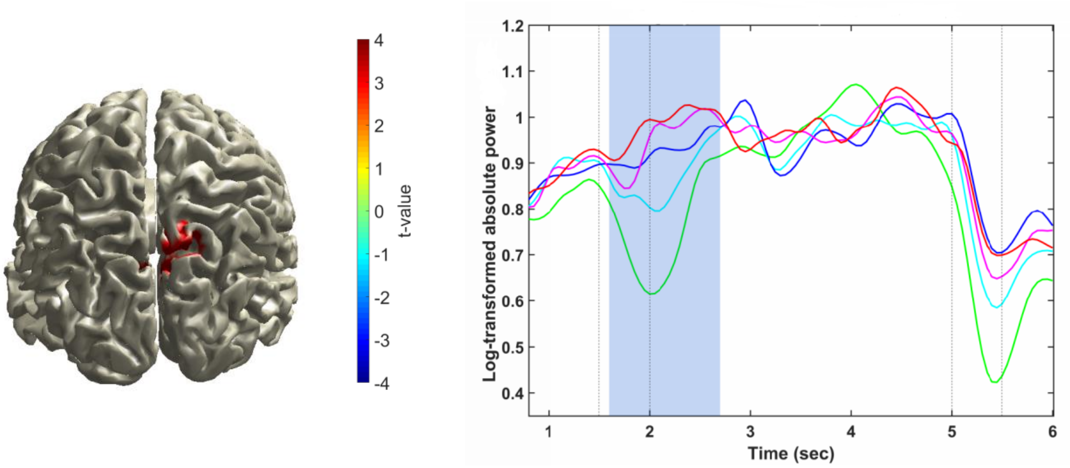

Figure 3.22. From the left: source reconstruction of the early delay window (1.6 – 2.7) in the bimodal condition showing beta power difference across the stimulation levels; source level beta power for the different intensity stimuli (highlighted in blue is the period showing a significant correlation between stimulus amplitude – and beta band power.

To characterize this effect further, the source of beta power were localized within each condition relative to the average cross-condition baseline, and the time series of the 17-24Hz signal was reconstructed for all five first stimulus intensity levels (Figure 3.22.). A clear pattern was seen during the period already previously identified as being significantly parametrically modulated by the intensity of bimodal stimulation.

Lastly, since a significant increase in the beta band power relative to the baseline was observed all throughout the delay period (see figure 3.23 for a general visualization of the effect), the sources of the early delay period overlapping with the correlation period were reconstructed for all three conditions. This revealed a widespread cluster over the parietal region, suggesting that, while the way in which beta band activity was modulated showed a clear difference between the bimodal and the unimodal conditions, the general increase of beta band power in the parietal area during the early WM delay was not specific to any of the modalities (figure 3.24.)

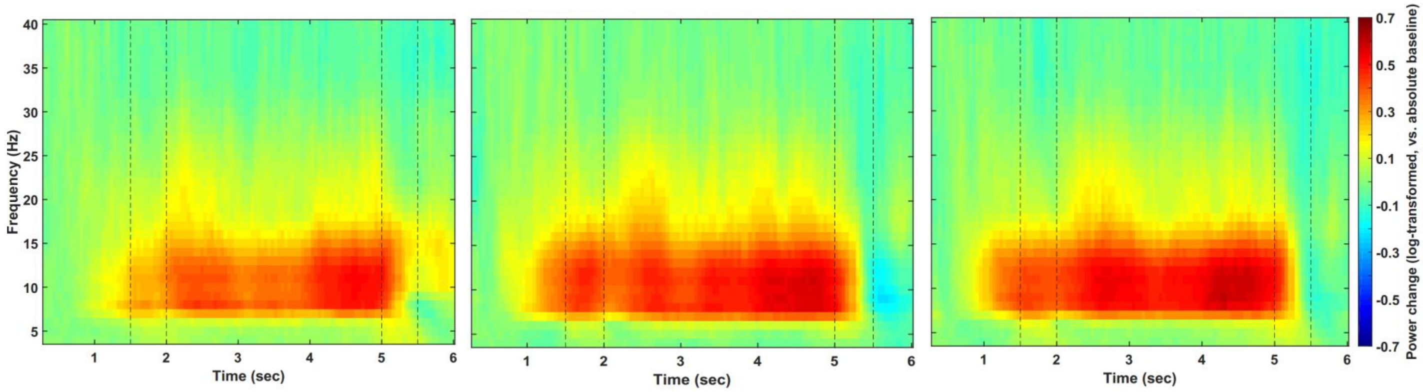

Figure 3.23. Baseline (0.4 – 0.6s) relative power change in the three right posterior electrodes that were common to both AA vs BB and TT vs BB significant correlation tests. From the left: auditory condition, tactile condition, bimodal condition.

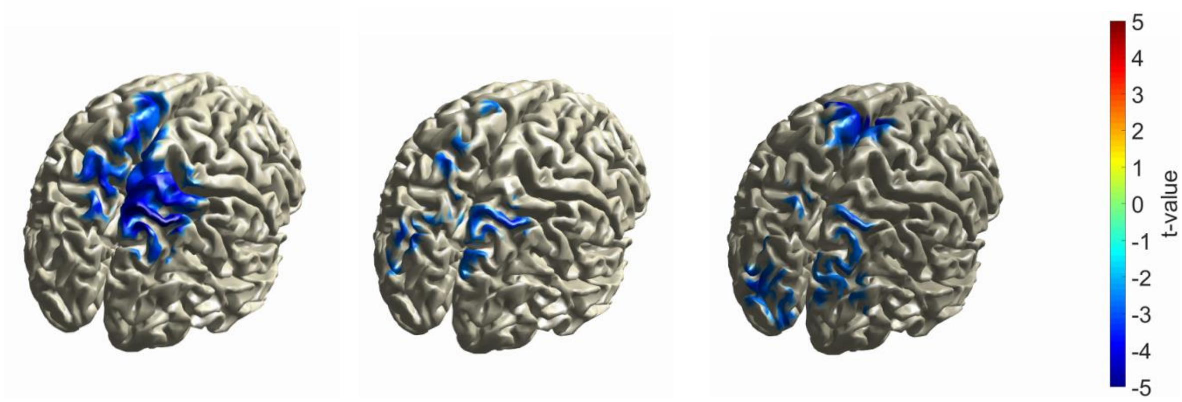

Figure 3.24. Baseline-relative beta power change in the early delay period (1.6 – 2.7 sec). From the left: auditory, tactile, and bimodal condition source plots with blue signifying beta power increase with respect to the early baseline period.

3.9. Discussion

The focus of this experiment was on evaluating the effects during the WM delay period through the prism of the hypothesis of gating by inhibition in the alpha band (Jensen et al., 2010). Besides the expected effects over the somatosensory cortices, it was also anticipated that further source level differences should emerge, highlighting additional SWM differences between the three conditions.

Clear somatosensory sources were detected when contrasting auditory and tactile conditions. While inhibition through alpha power modulation has been shown to exist also in auditory areas (Lehtelä et al., 1997; Spitzer et al., 2012), this effect was not detected in the present experiment during the delay period in the AA vs TT contrast. It is possible that due to volume conduction the stronger signal stemming from the sensory cortices masked the auditory cortex alpha power dynamics. This interpretation is further supported by the observation that in the TT vs BB contrast no significant delay period differences were observed, implying that the addition of the auditory signal did not make the combined stimulation condition sufficiently different from the tactile condition. Furthermore, in the AA vs TT contrast instead of two distinct somatosensory sources a single central cluster was observed. Since the somatosensory cortex has been shown to respond rather specifically to particular limb and even finger stimulation (Prueckl, 2015), this source reconstruction result gives additional evidence that the low spatial resolution of EEG source reconstruction is a likely cause of the absence of an auditory alpha effect. The above observations suggest that an experimental design in which the strength of the somatosensory alpha effect could be minimized might potentially lead to a better identification of the inhibitory effects in the auditory processing areas. Possible experimental design improvements will be discussed further below.

When comparing the extent and location of the EEG sources across the late baseline, early, and late delay period in the AA vs TT it stands out that over time the difference becomes more widespread, particularly in the posterior direction. There are two interpretations of this possible. On one hand this could potentially reflect the involvement of parietal somatosensory association areas being preferentially involved in somatosensory WM tasks (Ku et al., 2015). On the other hand, it is possible that the end of the delay experienced the largest alpha power differences between the two conditions in the somatosensory cortex and the reconstructed source appears larger solely due to field spread. The latter interpretation, however, does not seem to be supported by the alpha power time series reconstruction in the voxels common to all three periods of significance in the AA vs TT contrast. Nevertheless, a precise quantification of the true extent of the underlying sources is not possible with the currently available methodology. Thus, the involvement of the posterior parietal cortex in unimodal somatosensory WM, as indexed through alpha ERS/ERD remains to be explored further.

One of the goals of this experiment was to examine the differences between unimodal and bimodal conditions. In the alpha range, no unifying results were observed between AA vs BB and TT vs BB contrasts. Only the AA vs BB contrast showed an effect, which, unlike the AA vs TT, also covered the PFC. While the lack of generality across both unimodal vs bimodal comparisons leaves many interpretational possibilities open, perhaps not all has been lost. If, as suggested earlier, the delay period effects after tactile stimulation under SWM conditions mask an equivalent alpha band effect in the auditory cortex, the signal strength differences or the lack thereof should equally apply to the case of the TT vs BB contrast. Therefore, the presence of identical tactile stimulation in both conditions would mask any less prominent differences there may be due to auditory stimulation.

This left just one condition in which unimodal vs bimodal SWM could be assessed. The prefrontal topography of AA vs BB seems consistent with the idea of multimodal SWM requiring a larger involvement of executive or cognitive control resources (Miller and Cohen, 2001). The most congruent explanation would be that the reduced power over prefrontal areas implies a relatively greater activation of the PFC in order to promote communication between frontal and sensory areas during the delay period. However, while alpha ERD in more posterior areas is clearly associated with cortical activation, the role of prefrontal alpha in WM seems to be less straight forward. Different studies have shown both alpha ERS and alpha ERD in relation to increased unimodal WM task demands (Stipacek et al., 2003; Sauseng et al., 2005). Perhaps, this could be due to a possible distinction between lower alpha (8-10Hz) and upper alpha (10-12Hz), where the two sub-bands have been attributed slightly different cognitive roles (Krause et al., 2000; Fink et al., 2005). However, in the present study it was impossible to determine whether the bimodal condition was more or less cognitively demanding, since bimodal stimulation could be interpreted as both requiring additional cognitive processing in order to integrate the two stimuli, as well as a leading to reduced cognitive load due to multiple congruent inputs easing the encoding and maintenance processes.

For this reason no further analysis of alpha sub-bands was carried out. Despite the ambiguity with respect to the effect of task on prefrontal alpha power, this result shows that the prefrontal alpha band signal was sensitive to differences between unimodal and bimodal WM in areas that would be expected based on the results of similar studies exploring alpha band effects in unimodal WM.

While this was not a planned comparison, there were clear differences observed in the TT vs BB contrast between the sources of the first and the second stimulation period. While the first stimulation period showed alpha power differences around the auditory cortex, exactly as would be predicted based on the stimulation differences between the two conditions, the second stimulation period differences were located in an area around the left intraparietal sulcus (IPS). While this was not an expected result, the consistent results of the other source localization results exclude the possibility that this is an artefactual effect. Moreover, having already observed that the auditory signal in the alpha band is relatively weak during the delay period and that alpha ERS/ERD is sensitive to the exact task demands it is feasible that the reconstructed source reflects multisensory related processing in the angular gyrus. While during the first stimulation period it is critical that the stimulus be encoded in WM as accurately as possible, the WM task necessitates that a comparison be carried out during the second stimulation period. The role of the angular gyrus in multisensory integration and multimodal representation maintenance is well established (Bonici et al., 2016). For instance, it has been proposed that the angular gyrus serves a key role in retrieving multimodal memory representations such that a recognition of a multimodal input recruits the relevant already stored representations (Levy, 2012). Since the use of prior sensory knowledge in solving WM tasks has already been shown through the analysis of the contraction bias in this experiment, a preferential involvement of the angular gyrus during the late delay period in a unimodal vs bimodal WM task contrast seems plausible.

With regard to the result observed in the beta band, currently auditory-tactile integration is not well understood. Proposals as to where this might take place cover a wide range of brain areas, such as the cerebellum, premotor cortex, and superior PFC (Huang et al., 2013). Some studies have suggested that in a stimulus detection task requiring cross-modal integration an early phase-locked beta band response is enhanced when compared to unimodal stimulus detection (Senkowski et al., 2005). Cross-modal effects were also found in the beta band when auditory and tactile stimuli were presented sequentially in a pseudorandom manner (Kisley et al., 2006). In that study, higher beta band responses were observed when a preceding stimulus had come from the opposite modality. While the scientific discussion in this regard is ongoing, this experiment adds a further piece of evidence in support of the parietal cortex playing a role in bimodal integration. Whether this effect reflects the working memory consolidation activity (as reflected in the contraction bias at the behavioral level) needs to be tested through a further experiment. A unimodal comparison task under bimodal stimulation conditions in which one of the two stimuli serves as a distractor should shed further light on the role of the observed oscillatory activity in bimodal working memory tasks. Under the proposed conditions, no induced power-stimulus intensity correlation should be observed in the area of interest since not only multimodal integration would not be required, but it might also be necessary to actively inhibit such processes in order to perform the behavioral task successfully. Alternatively, if the multimodal integration is not under cognitive control of the participant, the correlation pattern observed in this experiment might still be present. The proposed experiment has already been successfully piloted behaviorally (results not reported) in order to establish the feasibility and calibrate the difficulty level of this task.

3.10. Implications for the upcoming experiments

The result in the alpha band made it difficult to draw any clear conclusions with regard to the similarities and differences of the alpha power dynamics across the two modalities tested during the WM delay. Four questions emerged from this experiment:

(1) is the late alpha difference due to the anticipation of stimulation as during the early baseline, or due to the reactivation of SWM related processing?

(2) if alpha power reduction is a general mechanism, how can this effect be detected in the auditory cortex?

(3) to what extent is alpha ERS/ERD in this WM task caused by the simple act of stimulation and to what extent is it WM task dependent?

(4) Is WM activity – as indexed by power modulations in alpha band – in the posterior parts of the cortex limited to the sensory cortices or are further SWM differences either too weak or too similar between the auditory and the tactile conditions to be detected?

These questions lead to the development of two further experimental designs. An interleaved experimental design in combination with a cross-modal WM task, it was speculated, would lead to a relatively less pronounced alpha ERD in the somatosensory cortex and therefore make the detection of auditory effects possible. If both effects can be detected to a different degree under different task and modality combinations, more precise conclusions could be reached about the processes taking place during the WM delay period.

4. EXPERIMENT 3

4.1. Introduction

As anticipated, he clearest effects in experiment 2 were observed in the alpha band. Experiment 3 retained its emphasis on this frequency band. The main focus of this experiment was on measuring the influence of both the first and the second stimulus on delay period activity. We hypothesized that contrasting unimodal and cross-modal conditions would allow us to detect and distinguish between encoding related effects and second stimulus anticipation related effects during the delay period. Secondly, contrasting unimodal and cross-modal tasks allowed us to examine the idea that the posterior parietal cortex is preferentially involved in cross-modal WM.

Several observations made in experiment 2 motivated the design and the approach to analysis of experiment 3. The results of experiment 2 had made it clear that a block design with both stimulation periods containing stimuli of the same modality led to interpretational difficulties as to the possible meaning of the delay period alpha band effects. In Experiment 3 design changes were introduced to make the transition between modalities more dynamic – a block design was replaced by an interleaved design thus making the first stimulus modality unpredictable. This would be expected to have the effect of neutralizing any possible baseline effects between conditions which, it was hoped, would reduce the relatively strong tactile anticipatory/WM signal as compared to the suspected alpha band activity due to auditory processing. Secondly, in order to determine the potential causes of early and late delay period differences, cross-modal conditions were introduced.

In experiment 3, in addition to AA and TT conditions (first and second stimulus of the same modality), participants also had to compare auditory to tactile (AT) stimuli and tactile to auditory stimuli (TA). This yielded a total of four conditions. The unimodal conditions were blocked together but interleaved randomly within the block; likewise, the cross-modal conditions were presented pseudorandomly within the cross-modal block. This had the effect of making the first stimulus modality unpredictable in both the unimodal and the cross-modal blocks. The second stimulus, on the other hand, was always predictable and depended on the block type. In unimodal blocks, the participants knew that regardless of the modality of the first stimulus, the second stimulus would be of the same modality. Similarly, while the first stimulus in the cross-modal block was unpredictable, the second stimulus would always be of the opposite modality with respect to the first stimulus modality.

In addition to making the baseline identical across all conditions with regard to the anticipated modality, it also ensured that any modality-specific WM effects would emerge only after the stimulation had begun. Furthermore, this design enabled more specific condition contrasts, in that only the first or the second stimulus could be made to differ between any two conditions. For instance, in the AA vs AT contrast, only the second stimulus differed between the two conditions, which meant that if any early delay alpha band difference were to be detected, it must necessarily reflect an effect that goes beyond differences due to stimulus modality. Since, in this particular example comparison there were differences both with regard to the task (unimodal vs cross-modal WM) and the anticipated second stimulus modality (A vs T), any effect observed would have to be interpreted with both of these possibilities in mind.

Since there were four conditions in this experiment, a total of six delay period statistical contrasts were theoretically possible (AA vs TT, AA vs AT, AA vs TA, TT vs TA, TT vs TA, and AT vs TA). It was speculated that, depending on whether and when (in early or late delay) the differences would be observed, combining observations across different contrasts could lead to a more complete picture of the interaction between task and modality effects than would be possible by observing a single contrast alone (e.g., the AA vs TA as illustrated above). To put it in other words, the analysis of the results of experiment 3 relied on a synthesis of methods, such that a number of low accuracy (due to the poor spatial resolution of EEG) source reconstruction results were analyzed in the context of multiple cross-condition contrasts and constrained by the implications inherent in the experimental design. This allowed establishing how the early and the late delay activity are shaped by both the first and the second stimulus. Additionally, cross-modal conditions allowed us to better assess the involvement of the posterior parietal cortex during the delay.

4.2. Behavioral results

All participants performed the task with an accuracy of at least 80% during all blocks of the experiment. There were no significant differences between the conditions either in terms of accuracies, or reaction times (figure 4.1.). When response accuracy and reaction times were calculated for each stimulus pair (figure 4.2.), the stimulus pairs' accuracy showed a strong negative correlation with reaction times (figure 4.3) in all four conditions (r(AA) = -0.9; r(TT) = -0.71; r(AT) = -0.93; r(TA) = 0.79). While the first stimulus intensities were kept constant in all conditions, the step size between the first and the second stimulus in the cross-modal blocks was increased in order to match the behavioral accuracy levels of the unimodal condition. For this reason it is also difficult to make any quantitative statements about the nature of the contraction bias in the cross-modal conditions as compared to the unimodal ones.

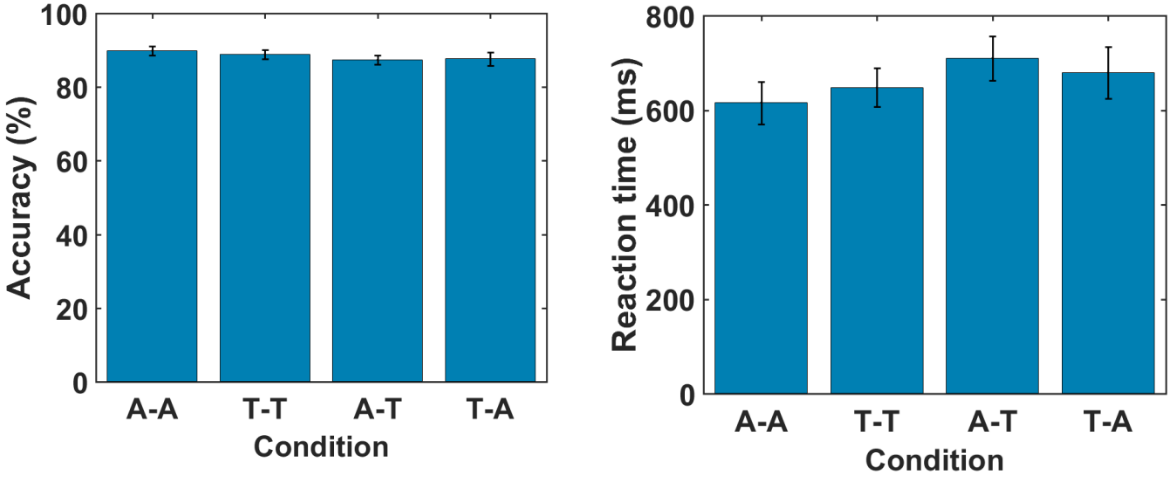

Figure 4.1. Grand average accuracies (left) and reaction times (right) for the four conditions tested in experiment 3.The average accuracy values ranged from 87.6% to 89.6%, while the average reaction times spanned between 616ms and 710ms.

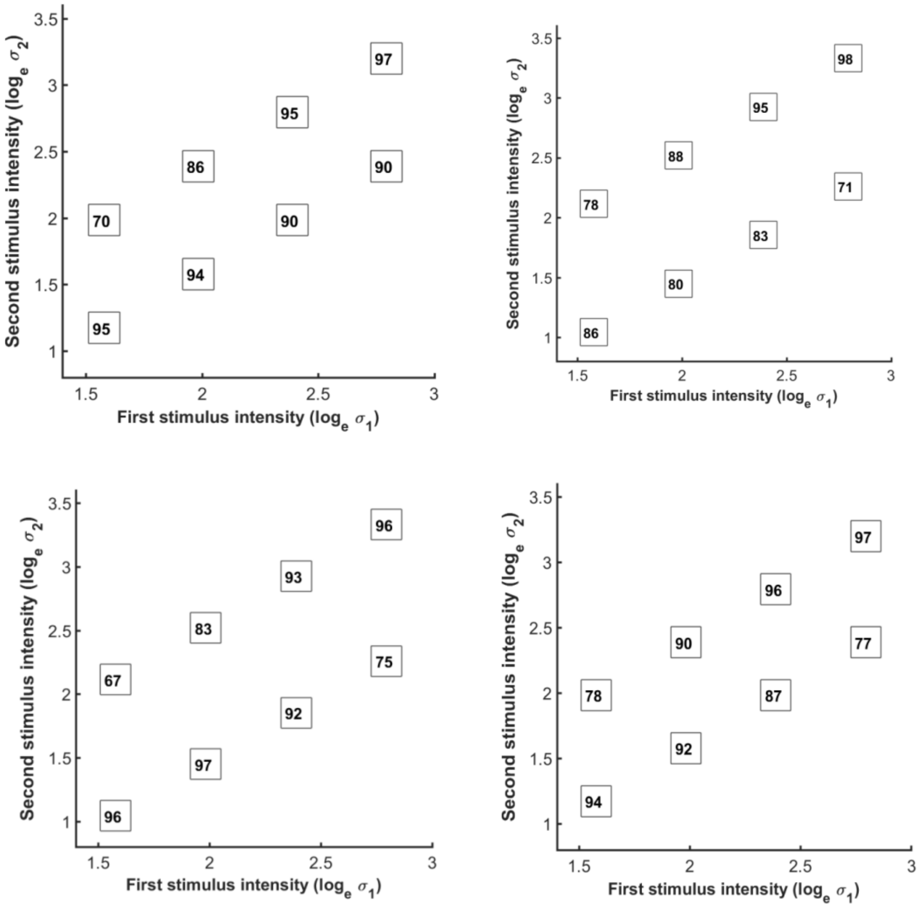

Figure 4.2. Individual stimulus pair accuracies in the four experimental conditions. Clockwise from top left: AA, TT, TA, and AT conditions. As expected, all experimental conditions showed a contraction bias across stimulation levels.

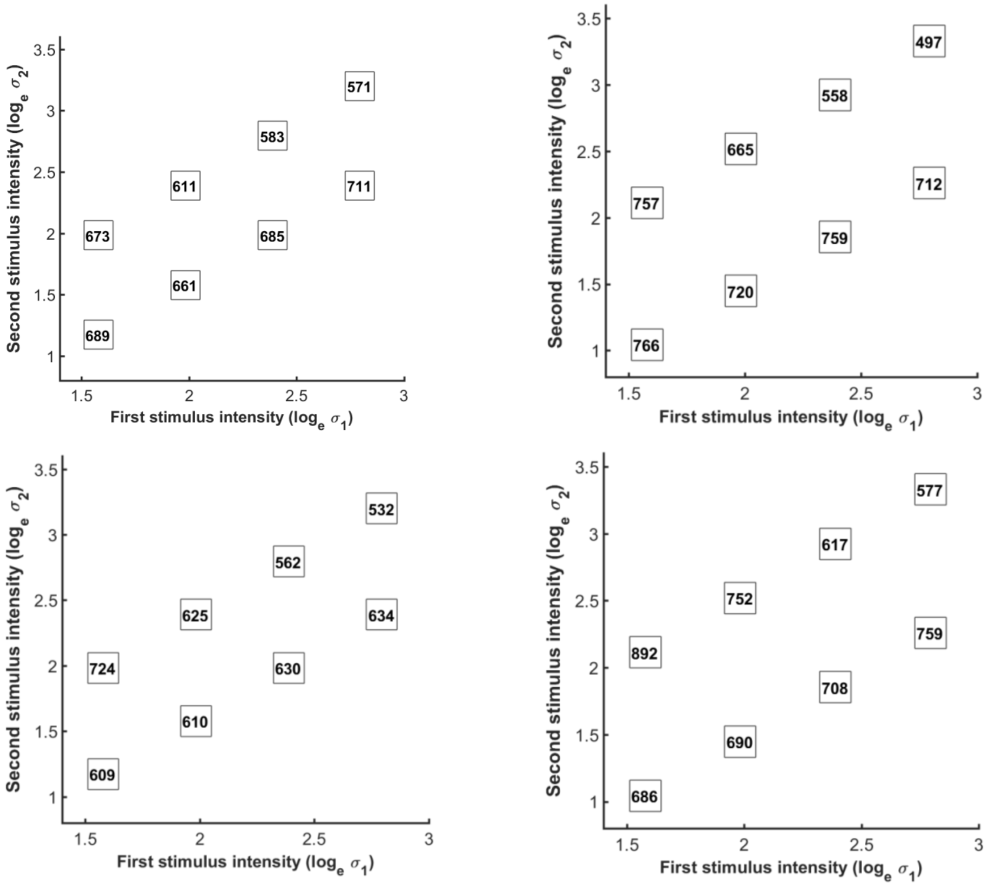

Figure 4.3. Individual stimulus pair reaction times in the four experimental conditions. Clockwise from top left: AA, TT, TA, and AT conditions. For all four conditions there was a strong negative correlation observed between response accuracy and reaction time. There was a strong correlation between

4. 3. Alpha band results summary

In order to provide a structure for organizing the early and late delay results, a summary of significant contrasts is given below (figure 4.4.). Early delay refers to a condition difference at any point during the first 500ms after to first stimulus offset, while late delay refers to an effect within the last 500ms prior to the onset of the second stimulus. These were the a priori established windows of interest; post-hoc test with more extended windows were conducted for some conditions in order to better localize the precise temporal borders of the clusters that were not contained within the first 500ms after stimulation offset. Detailed topographical results will follow this introductory section.

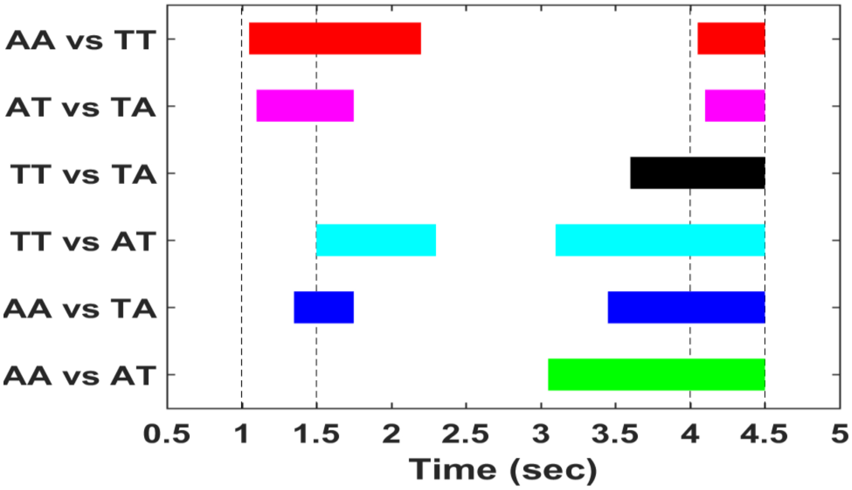

Figure 4.4. The timing of all significant sensor level contrasts: each row corresponds to one contrast, with the length and the position of the respective color bar indicating the timing of the significant difference. Please note: the response period (past 4.5s) was not analyzed.

4.3.1. Early delay effects

Early delay period differences appeared only in the contrasts in which the first stimulus modalities differed, regardless of the task type (unimodal or cross-modal WM). A question can thus be asked with regard to early delay activity alpha band activity. How does the cortical distribution of activity differ between same-task (AA vs TT, AT vs TA) and cross-task (AA vs TA, TT vs AT) contrasts? If the early delay activity arises solely due to the differences related to the first stimulus processing, the scalp and source level topographies should be identical across all four contrasts (since all entailed contrasting an A vs T post stimulation period). If, on the other hand, the anticipation of the second stimulus already has an effect on neural processing during the early delay, differences between the two types of comparisons should emerge.

With regard to the timing of the early delay sensor level clusters, two patterns were noted. First, all early delay differences subsided within the first 100 – 800ms after stimulus offset in all conditions. Secondly, while in same-task contrasts (AA vs TT, and AT vs TA) the differences emerged already during the first stimulation period (100ms after first stimulus onset in both cases), the differences in the cross-task contrasts emerged considerably later (350ms in AA vs TA, and only at stimulus offset in TT vs AT).

4.3.2. Late delay effects

Out of all the possible contrasts, only the unimodal vs cross-modal ones showed a significant alpha power difference in the late delay period. In other words, late alpha power differences emerged when and only when different WM tasks were contrasted, regardless of the second stimulus modality, while same-task contrasts (AA vs TT and AT vs TA) showed no late delay alpha band effect despite different modality stimuli being anticipated in both. Do all late delay contrasts yield the same cortical source topography? This would be the case if the late delay effect was solely driven by the task difference (i.e., unimodal vs cross-modal WM). If, on the other hand, there are task and/or stimulation modality effects present, a more complex picture should emerge, requiring a more detailed interpretation. The latter was indeed the case, as expected based on the results from experiment 2, where stimulation modality driven differences under identical task requirements had already been observed

Since the differing topographies suggested other effects beyond those due to the task type were at play, the contrasts were conceptually divided into two categories. In two of the four the late delay differences emerged even though the same modality was being anticipated (AA vs TA and TT vs AT). In the other two contrasts, two different modalities were being anticipated after an identical first stimulus (TT vs TA and AA vs AT). This grouping of the results yielded a consistent interpretation as to the likely causes of the late delay differences.

The timing of the sensor level clusters exhibited two patterns. First, two of the contrasts were not limited to the time window of interest, showing onset times of 3.1s and 3.05s (TT vs AT, and AA vs AT, respectively). The onset of the remaining two contrasts almost coincided with the window of interest (AA vs TA at 3.45s and TT vs TA at 3.6s). Secondly, all clusters extended into the second stimulation period, but, most notably, also

AA vs TA and TT vs AT in which the second stimulus was identical across the two conditions.

4.4. Early delay sensor and source level results

4.4.1. AA vs TT **contrast**

The AA vs TT contrast showed a significant difference till 700ms after first stimulus offset. While the sensor level difference during this period showed the strongest differences across a right posterior - left frontal diagonal, source reconstruction identified one large source over the right somatosensory cortex, which spread also into the right parietal area and, to a lesser degree, also to the left somatosensory cortex (figure 4.5.). The positive values imply a relative reduction of alpha power in the TT condition with respect to AA.

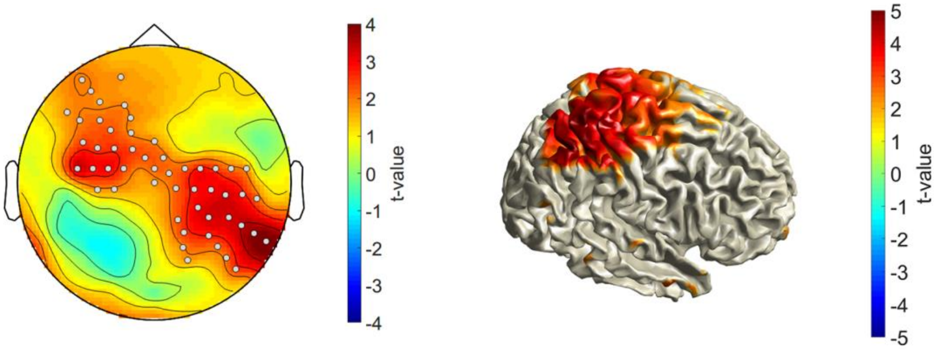

Figure 4.5. Contrast AA vs TT: early delay sensor and source level alpha band differences. This effect was observed between 1.1 and 2.2s

In the AT vs TA contrast, sensor level topography revealed a right centro-parietal cluster, and at the source level two clusters emerged (figure 4.6.). Both had a relatively short temporal span, lasting until 250ms after the first stimulus offset. The positive cluster was centered on the somatosensory cortex, while the negative cluster was identified in the right temporal lobe, conceptually suggesting an effect stemming from the auditory areas, though the exact location was more posterior.

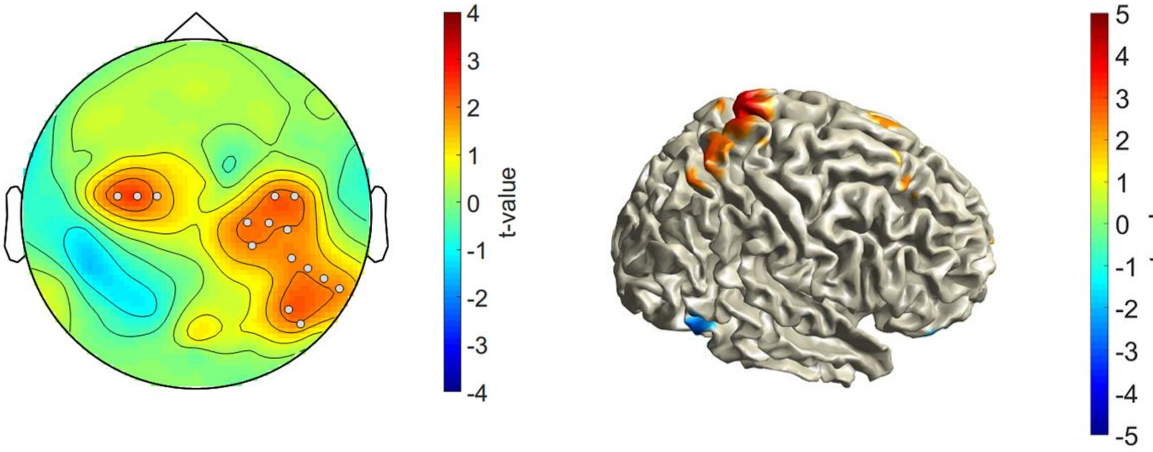

Figure 4.6. Contrast AT vs TA: early delay sensor and source level alpha band differences. This effect was observed between 1.1 and 1.75s (first stimulus duration: 1 – 1.5s).

4.4.2. AA vs TA **contrast**

The AA vs TA contrast showed a clear right lateralized sensor cluster with an apparent bilateral negativity over temporal areas. At a coarse level the scalp topography resembled the other contrasts. At the source level, both the auditory ($p < 0.1$) and the somatosensory areas were identified in the right hemisphere.

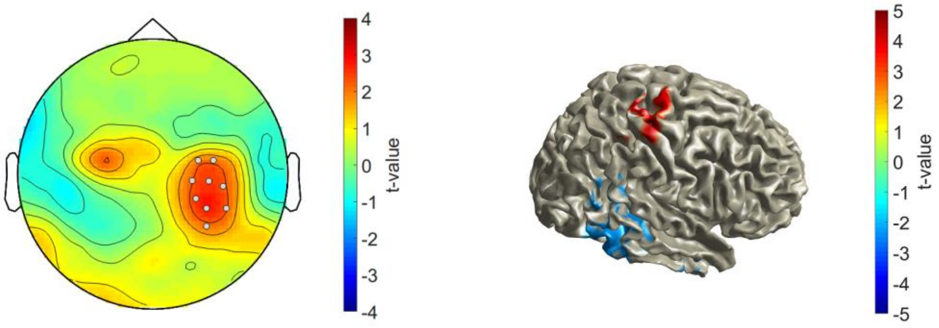

Figure 4.7. Contrast AA vs TA: early delay sensor and source level alpha band differences. This effect was observed between 1.35 and 1.75sec (first stimulus duration: 1 – 1.5s).

4.4.3. TT vs AT **contrast**

Lastly, the TT vs AT contrast showed a similar topography with a strongest effect at the sample level lying on a right posterior – left frontal diagonal (note that the colors are reversed hre, since by convention, the unimodal contrast was always placed first in any comparison pair). The cluster identified at the source level was centered on the somatosensory cortex and lasted for the first 800 ms of the delay period (figure 4.8.). Additionally, the largest positive difference was observed over an auditory area, though statistical testing did not lead to identification of a cluster over this area.

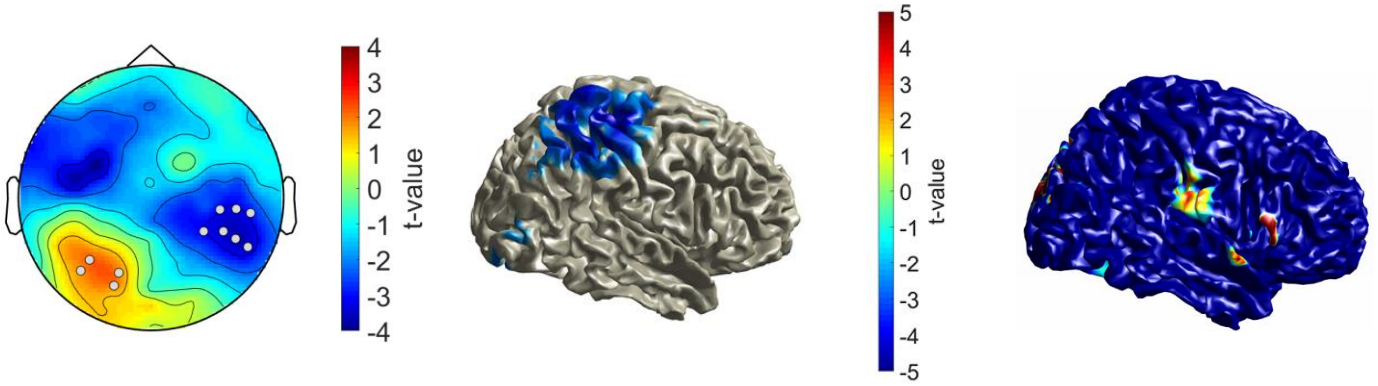

Figure 4.8. Contrast TT vs AT: early delay sensor and source level alpha band differences. This effect was observed between 1.45 and 2.3s (first stimulus duration: 1 – 1.5s). On the right: thresholded t-value map at voxel level revealed that the largest positive difference between the conditions was situated over the right primary sensory cortex.

4.5. Discussion

4.5.1. Anticipated comparison modality plays a role in early delay cross-conditions differences

Even though the four early delay contrasts all juxtaposed auditory and tactile modalities, source reconstruction revealed distinct differences between the four contrasts, thus indicating that the early delay period is not a simple reflection of fading post-stimulation effects; instead, the early delay period is most likely already affected by the anticipated comparison modality.

When comparing the contrasts in which the first stimulus differed while the second stimulus did not (AA vs TA, TT vs AT), a similar pattern could be observed. A positive cluster over the somatosensory cortex (indicating reduced power in the TT condition) was identified in the TT vs AT contrast, while the auditory areas showed elevated t-values without reaching the cluster threshold. In the AA vs TA contrast a negative cluster (indicating reduced power) was identified over and around the right auditory cortex in the AA vs TA condition, while a negative cluster was present in the somatosensory cortex.

This pattern of results shows that, as predicted, contrasts in which dynamic switching of attention from one modality to the other (i.e., a cross-modal comparison) is required during the delay period, alpha dynamics in both sensory cortices would become evident at the source level. It also reconfirms the ‘gating by inhibition hypothesis’, since all the identified sources showed reduced alpha power over a sensory cortex when the area in question was expected to be engaged in active processing, while not showing this effect at other times.

Furthermore, the observed pattern of results suggests that whenever a tactile stimulus needed to be maintained during the delay period, it was the dominant signal at the source level during the early delay and masked any differential activity in the auditory areas. This pattern of stimulation was the case both in the AA vs TT and the TT vs AT contrast. Indeed, the early delay in the TT vs AT and the AA vs TT contrast yielded the largest clusters at the source level over the somatosensory cortex while no significant cluster over the auditory cortex could be identified. If, on the other hand, the tactile modality got stimulated but the tactile input had to be compared with the opposite modality stimulus, the alpha power reduction was much less pronounced already during the early delay. This, in turn, caused the effect in the auditory areas to be detectable. This was indeed the case in both conditions with such a stimulation sequence (AA vs TA and TA vs AT).

Thus, it is possible that the upcoming modality plays and essential role already during the early phase of the delay period as illustrated by the alpha power dynamics in the somatosensory cortex. The same dynamics also seems to govern the auditory modality though the detection of this pattern is more challenging. The largest cluster over the auditory cortex was indeed observed under the conditions in which the auditory cortex received input during the first stimulus period and the auditory WM representation had to be maintained during the delay period (AA vs TA contrast). The second condition in which this pattern should be observed is AA vs TT. However, since in the other condition entering this comparison also the tactile modality was stimulated and had to be retained in WM during the delay, the auditory effect could not be effectively measured due to the strong signal from the somatosensory cortex. While the source reconstruction step is supposed to separate the signals at the source level, closely overlapping signal projections on the scalp in combination with the volume conduction still having an effect even at the source level can easily mask and blur the underlying sources (Shoffelen et al., 2009).

The timing of the appearance of clusters during the first part of the trial gives further support to the idea of the early delay period activity being affected by the anticipated comparison. More specifically, in the contrasts showing a difference already early into the first stimulation period (50-150ms in AA vs TT and AT vs TA contrasts) the second stimuli were of different modalities. In the contrasts in which differences appeared closer to the end of the second stimulus (350-450ms in TT vs AT and AA vs TA) the anticipated second stimuli were of the same modality. Importantly, these observations generalize across task types and modalities in that both unimodal and cross-modal within-task task contrasts led to the onset of an early difference, while the anticipation of the same modality second stimulus delayed the onset of the first stimulation period differences regardless of whether the anticipated stimulus was of the tactile or the auditory modality.

4.5.2 Involvement of sensory cortices in early delay WM related processing

This interpretation of the early delay source level dynamics has specific implications for the involvement of the sensory cortices in delay period working memory maintenance. As already stated, activity in the early delay did not merely reflect the differences due to recent stimulation, but was also affected by the knowledge of the upcoming stimulus. Crucially, the differences in alpha power dynamics during the early delay were expressed in the sensory cortices. This suggests that during the period immediately following the first stimulation period the sensory cortices are involved in WM related processing. For instance, when a tactile input was required to be later compared to an auditory stimulus, the involvement of the somatosensory cortex (as indexed by alpha power reduction) was more limited and of a much shorter duration (0 – 350ms post first stimulus offset). Studies have shown that primary sensory areas can be involved in working memory processing (Supèr et al., 2001; Harris et al., 2002), and that they do get modulated via top-down processes depending on WM task demands (Sauseng et al., 2005). While in the present experiment it is not possible to localize a specific primary or secondary sensory area, nor to distinguish between WM encoding, maintenance, and attentional effects, it is clear that at least one of the WM related processes shaped the early delay sensory activity based on the anticipated comparison stimulus.

4.5.3. No evidence of non-sensory cortex involvement in early delay WM related processing

Lastly, no differences beyond the sensory cortices were identified, suggesting that other WM related processes are not modality-specific and therefore could not be identified, or alternatively, that the sensory sources, due to the poor EEG spatial resolution, masked further, more subtle effects.

4.6. Late delay sensor and source level results

4.6.1. AA vs TA **contrast**

The AA vs TA contrast during the late delay period highlighted a cluster over central right electrodes, which, when source localized, identified a source level difference over the right parietal area with a slight overlap with the sensory cortex. The cluster emerged 500ms prior to the second stimulus onset and lasted till the second stimulus (3.5 – 4sec). This difference is an important result since it shows that the pre-stimulus period is not dominated exclusively by alpha ERD in the sensory cortex (since the significant cluster extended into the second stimulation period (4 – 4.5s), the sources were reconstructed and, importantly, also revealed a parietal cluster (figure 4.9.).

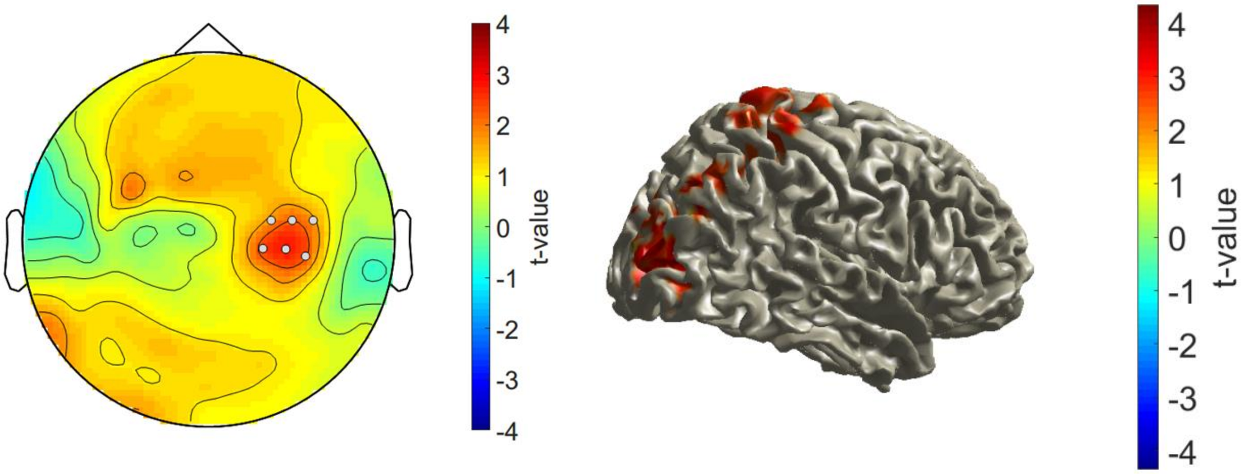

Figure 4.9. Contrast AA vs TA: late delay sensor and source level alpha band differences. This effect was observed between 3.45 and 4.5s (second stimulus duration: 4 – 4.5s).

4.6.2. TT vs AT **contrast**

In the case of the TT vs AT contrast, the cluster identified lasted from 3.1 till 4s in the late delay period. The sources, as compared to the early delay, had markedly changed. There was a clear negative cluster identified over the right auditory cortex (indicating relatively higher alpha power in the AT condition) and a small positive cluster over the right parietal cortex,indicating relatively lower alpha power in the AT condition, as compared to TT (figure 4.10.).

Similarly to AA vs TA, also in this contrast an identical stimulus was delivered during the second stimulation period, yet both the sensor and the source level differences lasted throughout the second stimulation period. When reconstructing second stimulation period source activity, similar sources were identified both in the right parietal areas and over the auditory cortex.

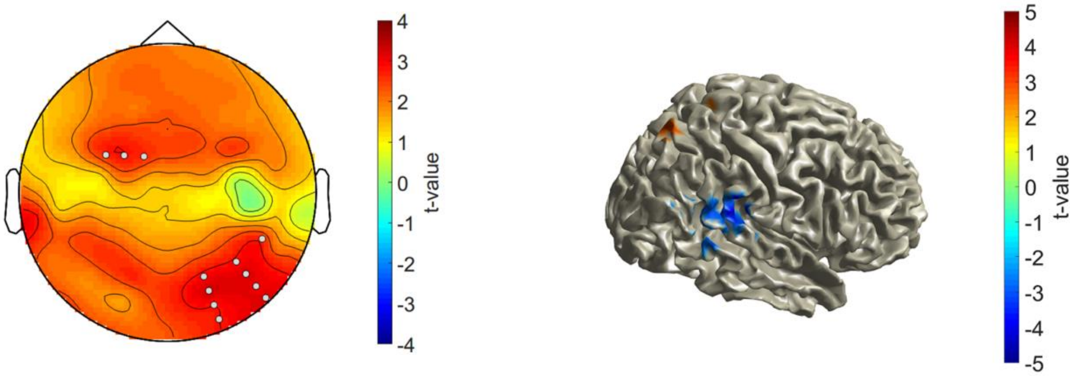

Figure 4.10. Contrast TT vs AT: late delay sensor and source level alpha band differences. This effect was observed between 3.1 and 4.5s (second stimulus duration: 4 – 4.5s).

4.6.3. TT vs TA **contrast**

Anticipation of a different stimulus after identical first stimulus period in the case of the TT vs TA contrast yielded a difference between 3.6 and 4.5s ($p < 0.1$). There were right parietal and left frontal electrode clusters identified. Source analysis identified a right posterior parietal area and a left prefrontal area (meaning relatively reduced power in the TA condition as compared to TT). The peak of the left prefrontal area corresponded to BA9, which contributes to the left dlPFC (figure 4.11.). As an additional test, also the second stimulus period activity was source reconstructed, which yielded a parietal cluster similar to the late delay source shown here, in addition to a somatosensory cortex cluster, as was expected due to differing modalities during the second stimulation period.

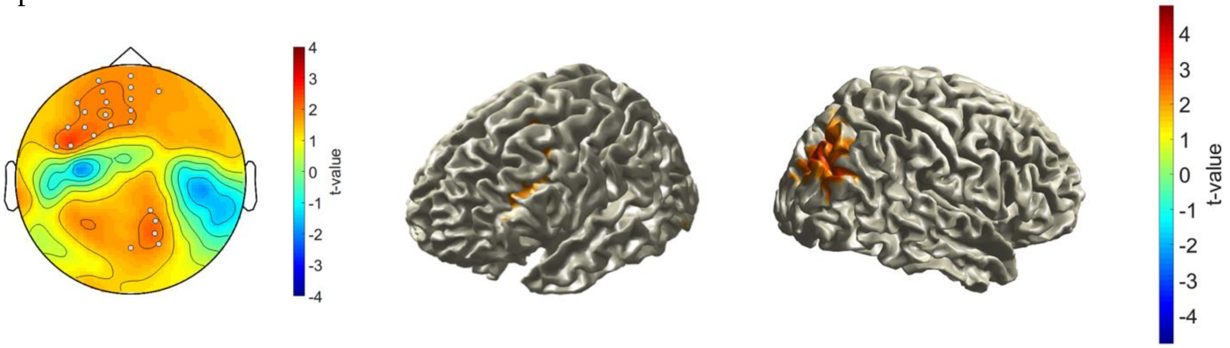

Figure 4.11. Contrast TT vs TA: late delay sensor and source level alpha band differences . This effect was observed between 3.6 and 4.5s (second stimulus: 4 – 4.5s).

4.6.4. AA vs AT **contrast**

Contrasting the other case in which a different stimulus was anticipated following an identical first stimulus (AA vs AT) highlighted a cluster between 3.05 and 4s during the delay period. Two fairly distributed sensor level clusters were identified bilaterally, while the statistical comparison at the source level identified a right somatosensory area (meaning a relative decrease in the somatosensory cortex in the AT condition as compared to the AA condition). Additionally, just in as the TT vs TA contrast, a right prefrontal source was identified in area BA9, corresponding to the left dlPFC (figure 4.12.). Lastly, an additional source reconstruction was performed on the second stimulation period. This yielded a similar (albeit larger) right somatosensory cluster, in addition to negative right auditory area cluster, as expected due to stimulation differences in the second stimulus period.

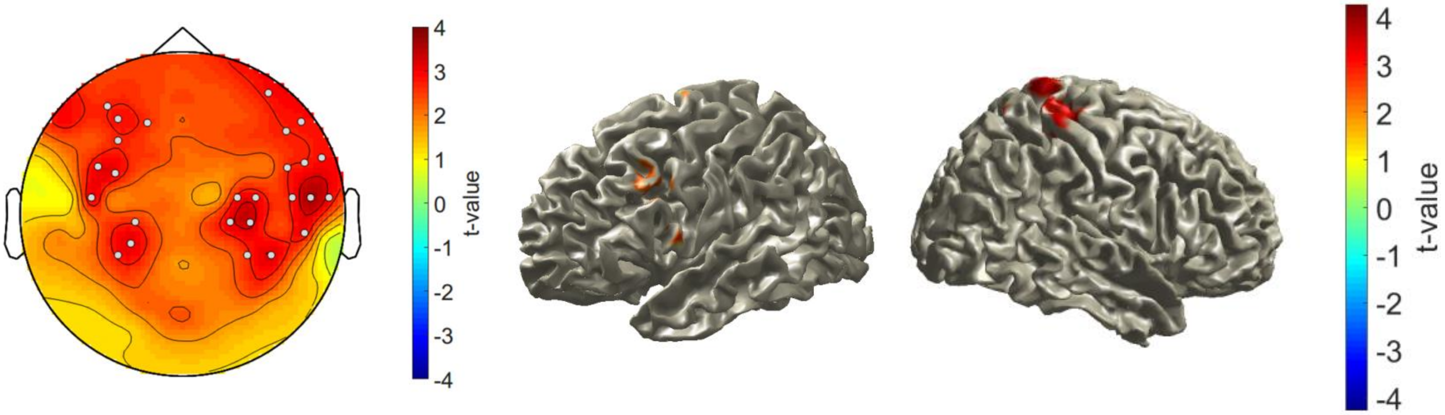

Figure 4.12. Contrast AA vs AT: late delay sensor and source level alpha band differences. This effect was observed between 3.05 and 4.5s (second stimulus duration: 4 – 4.5s).

4.7. Discussion

4.7.1. Late delay differences not due to anticipatory processes only

Despite all four late delay contrasts juxtaposing a unimodal to a cross-modal task, both the sensor and source level topographies differed across the four conditions. This suggests that the differences observed do not necessarily arise due to task differences. Since this was the case, the four contrasts were divided into two groups for further analysis according to a different criterion: the TT vs AT and the AA vs TA constitute the first group. In these contrasts a late delay difference emerged despite the same modality stimulus being anticipated (tactile in the first contrast, auditory in the second contrast). This means that the late delay effect could not have been due to the anticipation of the second stimulus. However, the sources identified were not identical between the two contrasts as would be expected if the late delay simply expressed the difference due to the first stimulation period (in both contrasts the first stimuli were of different modalities, i.e., A vs T). These two observations imply that the late delay effect is most likely due to an interaction between the difference in cortical activation from the first stimulation period and the second stimulus anticipatory processes. More specifically, the late delay source topography differences observed between the two contrasts are most likely caused by the fact that in one case a tactile stimulus is being anticipated, while in the other case the expected stimulus is of the auditory modality. This conclusion is in line with the results from the early delay, in which the influence of the second stimulation on the post stimulation period was observed. It is also in line with studies showing anticipatory effects in the alpha band in a highly sensory modality specific manner (van Ede et al., 2014).

As the second group, the TT vs TA and the AA vs AT contrasts were assessed. In these contrasts the anticipation related differences should have been identical, if only stimulus anticipation was the cause of the observed effect (in both cases auditory stimulus anticipation was compared to tactile stimulus anticipation). The implication of the pattern of results from these two contrasts is in line with the already established claim that the late delay activity was influenced by the main difference between the two contrasts, i.e., the modality of the first stimulus and the way it interacted with the anticipation caused difference.

4.7.2. Parietal involvement in tactile-to-auditory cross-modal WM processing

The hypothesis that best explains late delay parietal effects is that of differential parietal involvement whenever a tactile WM representation had to be prepared for a cross-modal comparison. This accounts for the parietal activity in AA vs TA, and TT vs TA contrasts, while in the fourth of the significant late delay contrasts (AA vs AT) there was no tactile cross-modal processing required and, in line with the prediction, there was no difference observed over the parietal areas (the positive cluster in Fig 4.13 is centered on the somatosensory cortex). The involvement of posterior parietal cortex in somatosensory multimodal integration and working memory has been well documented (Hoshiyama et al., 1997; Rawley et al., 2009).

Secondly, the positive parietal cluster in the TT vs AT contrast implies a relative increase of parietal alpha power in the TT condition, thus possibly signifying a potential disengagement of the area in the case of a unimodal tactile comparison. Alternatively, it could signal an involvement of the parietal area in the preparation of the auditory stimulus for a tactile comparison. The latter possibility, however, is unlikely likely since it would predict a parietal effect also for the AA vs AT condition, which was not observed.

These late delay observations lead to certain predictions, which could be tested on the contrasts not examined, namely, AA vs TT and AT vs TA. However, these contrasts did not show any late delay differences. Therefore the following strategy was used. As was observed in the four late delay contrasts examined above, their source topographies were consistent across the late delay and the second stimulation period. Since AA vs TT and AT vs TA did show second stimulation period differences, these periods were chosen as proxy of what might be observed also during the late delay period (though to a degree that did not reach statistical significance).

The parietal involvement hypothesis leads to two specific predictions for the AA vs TT and AT vs TA contrasts. In the case of the former, a positive somatosensory cluster should be observed (a concurrent negative auditory cluster might not be there due to the already noted difficulties of localizing the auditory areas when the contrasting condition is a tactile unimodal one). Most importantly, there should also be a negative cluster in the parietal cortex, as observed in the late delay TT vs AT contrast. This prediction is matched by the observations in the second stimulus period AA vs TT contrast (figure 4.13, left).

With regard to the latter contrast (AT vs TA), a negative cluster should be observed over the somatosensory cortex (implying relatively less alpha power in the AT condition), a positive cluster should be observed over the auditory cortex (implying relatively less alpha power in the TA condition). Crucially, there should be a positive cluster in the parietal region suggesting reduced alpha power in TA, i.e., in the condition in which a tactile stimulus had to be prepared for an auditory comparison. The source reconstruction of AT vs TA differential activity fulfills all three conditions (figure 4.13., right) note the similarity of the relatively more posterior activity location with that of the late delay AA vs TA contrast; figure 4.9.).

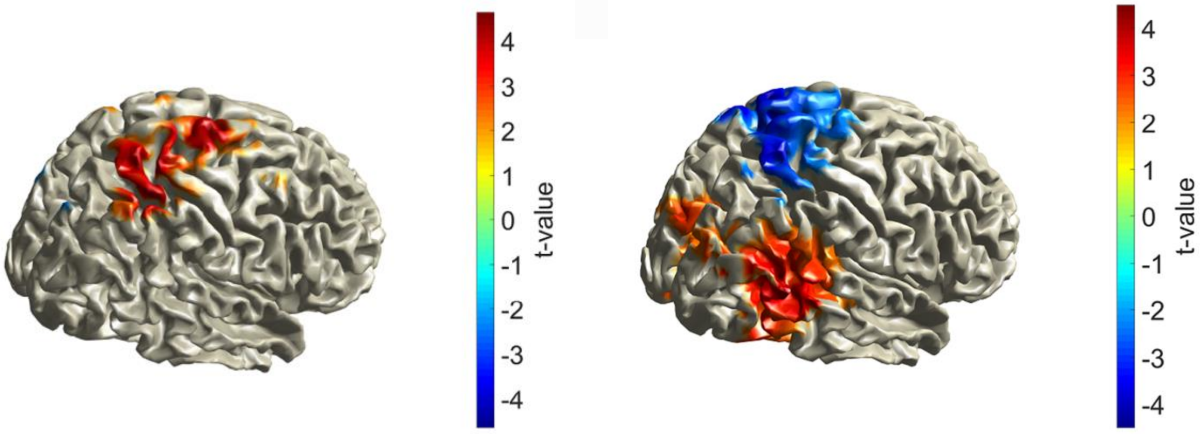

*Figure 4.13. Left:source level differences during the second stimulation period (4-4.5s) between conditions AA and TT****;*** *right: source level differences during the second stimulation period (4-4.5s) between conditions AT and TA****;***

4.7.3. The involvement of somatosensory cortex in WM related late delay processing

With regard to the somatosensory cortex, differential activity was detected in two contrasts: AA vs TA and AA vs AT, but not in TT vs AT or TT vs TA. Thus, the two contrasts in which the somatosensory cortex was not detected were those in which there had been tactile stimulation both during the first and during the second stimulation periods (TT vs AT or TT vs TA). When only an early or a late tactile stimulus was present (AA vs TA and AA vs AT), a statistically significant late delay difference was detected. It was hypothesized that this is caused by the somatosensory cortex showing a relatively strong alpha ERD both as a consequence of and in anticipation of tactile stimulation, similarly to what was already observed in experiment 2. This prediction was explored by extracting alpha power dynamics at the source level from the voxels that corresponded to the point of mean maximal activation across the two conditions displaying a clear a cluster centered on the somatosensory cortex (figure 4.14).

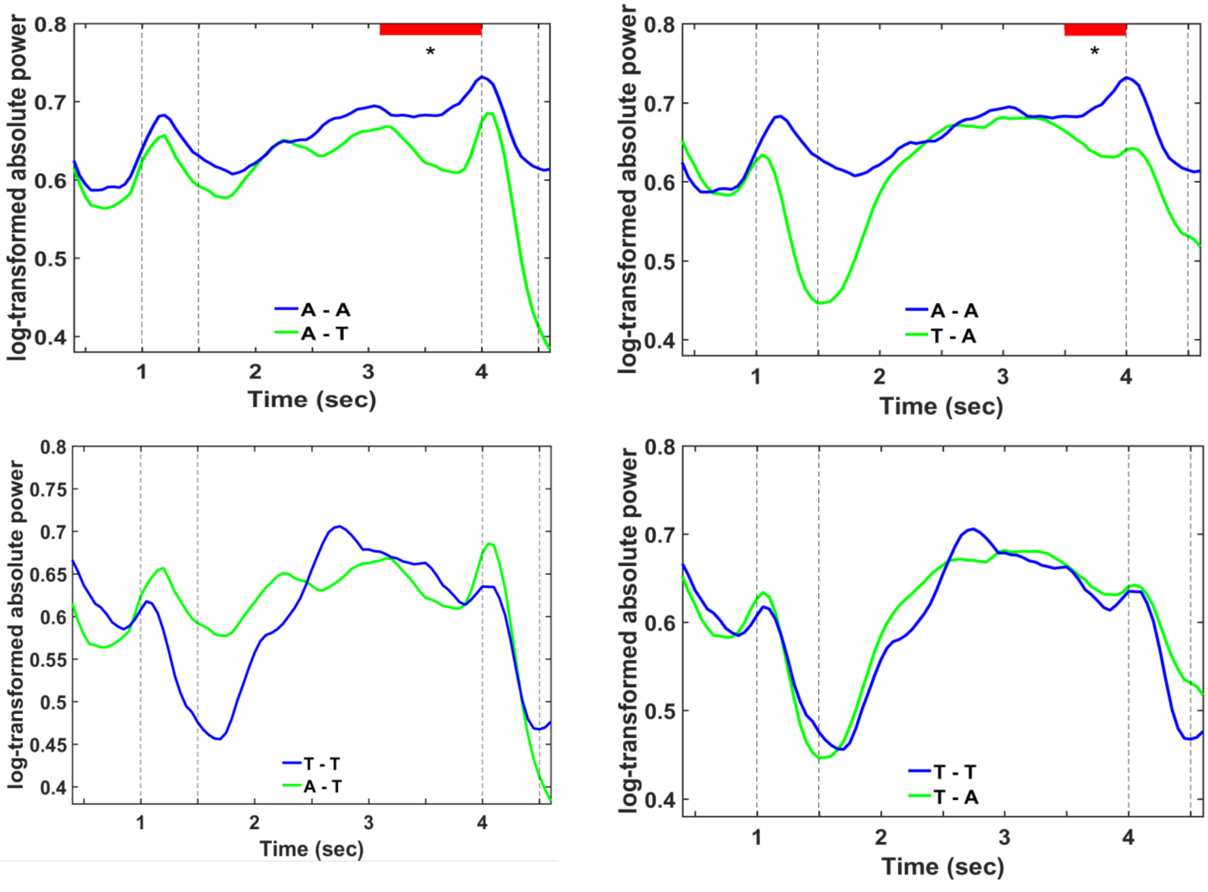

Figure 4.14. In all contrasts only the late delay sensor level significance period is labeled, the early delay differences are here meant for a visual reference only. Note that in all plots blue signifies the unimodal conditions, while green refers to the cross-modal conditions. Please see figure legends to identify each contrast.

Only the AA condition showed a significant increase with respect to the early baseline (p = 0.04, Bonferroni corrected), while the remaining conditions exhibited a more dynamic ERS/ERD depending on the sequence of tactile stimulation. It can be observed that the three conditions in which the first, the second, or both stimuli had been tactile show an ERD trend towards the late delay as compared to the mid-delay, while the auditory-only condition shows late delay ERS.

Since a mid-vs-late delay contrast was not one of the planned comparisons, it is not possible to make a statistical claim about the significance of this trend. Nevertheless, it must be noted that, as anticipated, the conditions in which one or both stimuli had been tactile, the somatosensory cortex shows a relative decrease in alpha power during the late delay. It must further noted, that this trend was specific to the somatosensory cortex in that Brodmann areas 5 and 7, (involved in somatosensory association functions) did not show a similar trend. This observation, if substantiated via further experiments, has implications for the interpretation of the role of somatosensory cortex in cross modal WM in that it suggests the involvement of somatosensory WM related processing even when a different comparison modality is being anticipated. What is more, this hypothesis is strengthened by the fact that the ‘gating by inhibition’ hypothesis would predict the exact opposite for the late delay period, i.e., an ERS over the somatosensory cortex (and other task-irrelevant areas).

4.7.4. Unclear pattern of auditory and prefrontal area involvement during delay period

Unlike the somatosensory cortex, which was identified in several contrasts, an auditory source was observed only once and therefore no pattern could be extracted from this single observation. A negative cluster in the TT vs AT implies that there was more power over the auditory cortex in the condition in which there had been early auditory stimulation. This observation, while not revealing a global pattern as in the case of the somatosensory cortex, is nevertheless an important result in that it justifies the choice of the experimental design by showing how dynamic alternations between engagement and disengagement of WM related processes can lead to the detection of auditory ERS/ERD. Further work needs to be conducted to better understand alpha dynamics in this sensory area.

With regard to the involvement of dlPFC in the present set of tasks, two of the four contrasts highlighted a cluster around the left dlPFC during the late delay period (AA vs AT and TT vs TA). The remaining two contrasts showed sensor level topographies suggestive of left frontal differential activity. However, no consistent prefrontal sources were identified across all four unimodal vs cross-modal contrasts, which leaves the potential preferential involvement of dlPFC in a cross-modal WM a rather speculative observation, which would require a more targeted further study in order to be resolved.

4.7.5. Evidence that uni- vs cross-modal WM task differences influenced delay period activity

Absence of late delay differences in the AA vs TT contrast was unexpected, which, due to no dynamic within-trial switching between modalities should lead to the greatest differences between conditions. However, this expectation was based on the result of experiment 2, in which block design could have led to a permanently biased alpha band signal due to extended single modality stimulation. In the present experiment, on the other hand, the temporal window during which modality specific WM preparatory processes could diverge from one another started only after the onset of the first stimulus. However, two pieces of evidence speak against this suggestion and offer an alternative one. First, alpha band power in the right somatosensory cortex showed a clear difference between conditions AA and TT during the late delay period (Figure 4.15; same data as in figure 4.14. above).

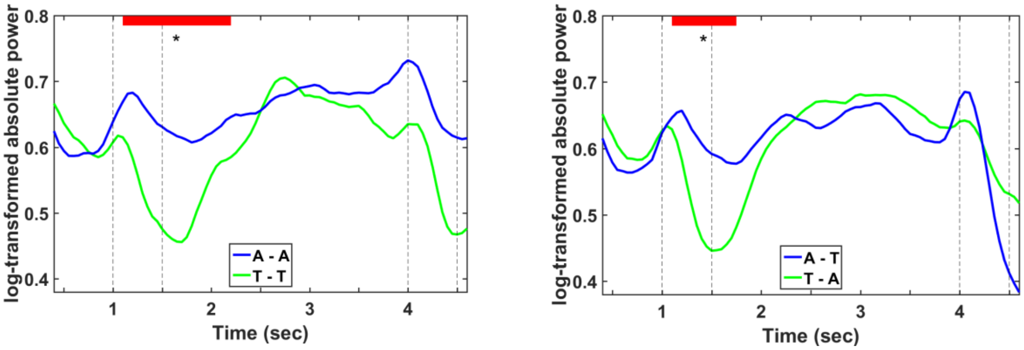

Figure 4.15. Left: contrast AA vs TT; right: contrast AT vs TA. Source level alpha power during the trial. AA vs TT contrast showed a significant difference both at the sensor and source level during and after the first stimulation period (shown by red bars with an asterisk on the x axis). There was no significant sensor level difference detected during the late delay.

The source level reconstructed absolute power difference during the late delay is comparable in magnitude to the differences observed in other (significant) contrasts. This seems to suggest that, while at a specific somatosensory ROI a significant difference between AA vs TT or AT vs TA could potentially be detected, the overall sensor level difference was not sufficiently widespread to reach significance. This leads to the second point – task differences between contrasts. As already noted, only the unimodal vs cross-modal contrasts led to late delay differences. This suggests that, while the sensory cortices might have shown sufficient differentiation also during the late delay period, an additional difference in terms of task demands had to be present for the sensor level comparison to lead to a statistically significant difference. While it is not possible to tell whether the task related differences expressed themselves through more pronounced sensory effects or through additional cortical resources getting recruited (such as left dlPFC), this still provides evidence that task demands probably did contribute to WM and/or anticipation processes during the late delay.

The effect of task differences possibly being an important factor contributing to the emergence of significant late delay differences is perhaps best illustrated through the cluster timing plot (see figure 4.4). While all the cross-task contrasts (bottom four in the cluster timing plot) showed cluster onset times between 3.05 and 3.6s into the trial, the within-task contrasts (top two rows in the cluster timing plot) yielded significant differences considerably later, i.e., only after the onset of the second stimulus.

4.7.6. Early stimulation theta effect extends alpha band results

Since studies show that theta oscillations are involved in top-down control and various memory related processes (Raghavachari et al., 2006; Herweg et al., 2016;), an attempt was made to characterize theta band patterns across conditions along the lines of alpha analysis just presented. Unlike in the alpha band, no consistent results that would generalize across modalities or task type were observed during the delay period. However, a first stimulus period/early delay effect was observed that complemented the effects observed in the alpha band. More precisely, AA vs AT and TT vs TA contrasts showed an significant difference during the first stimulation period and the first 100 ms of the early delay period. This is unlike what was observed in the alpha band and suggests a different role of theta oscillations during this period. At the sensor level, a typical frontal midline theta cluster emerged over frontal medial areas and the anterior cingulate cortex (Ishii et al., 2014) indicating relatively higher theta power in both unimodal conditions as compared to the cross-modal ones. A similar fronto-central source was identified, and, unlike all previous source reconstructions, indicated a deep cortical distribution (figure 4.16.). Theta band activity has been associated with focused attention under mentally demanding tasks (Gevins et al., 1997). However, attenuated theta activity has also been associated with stress when performing mentally challenging tasks (Gärtner et al., 2015). Since the contrast in both cases juxtaposed a unimodal and a cross-modal task, it is possible that the fronto-medial activity reflected task related difference in mental effort when encoding the first stimulus for either a within-modality or a cross-modal contrast.

Alternatively, since the contrast shows a deep cluster, it is possible that it is related to differential hippocampal activity. The strong anatomical connections between the hippocampus and the mPFC as well as the dlPFC supports this idea from an anatomical perspective (Sesack et al., 1989; Croxson et al. 2005). Several further studies have indicated a close functional relationship between the hippocampus and frontal areas through modulated theta oscillations (Benchenane et al., 2010). Most importantly, there are studies suggesting a potential role of the hippocampus in reactivating stored memory representations as well as coordinating this information with posterior cortical areas (Hsieh et al., 2014). Since the involvement of parietal cortex was observed under various task conditions in the present experiment, a proposed role of theta oscillations in coordinating this process is a potentially fruitful venue of further research.

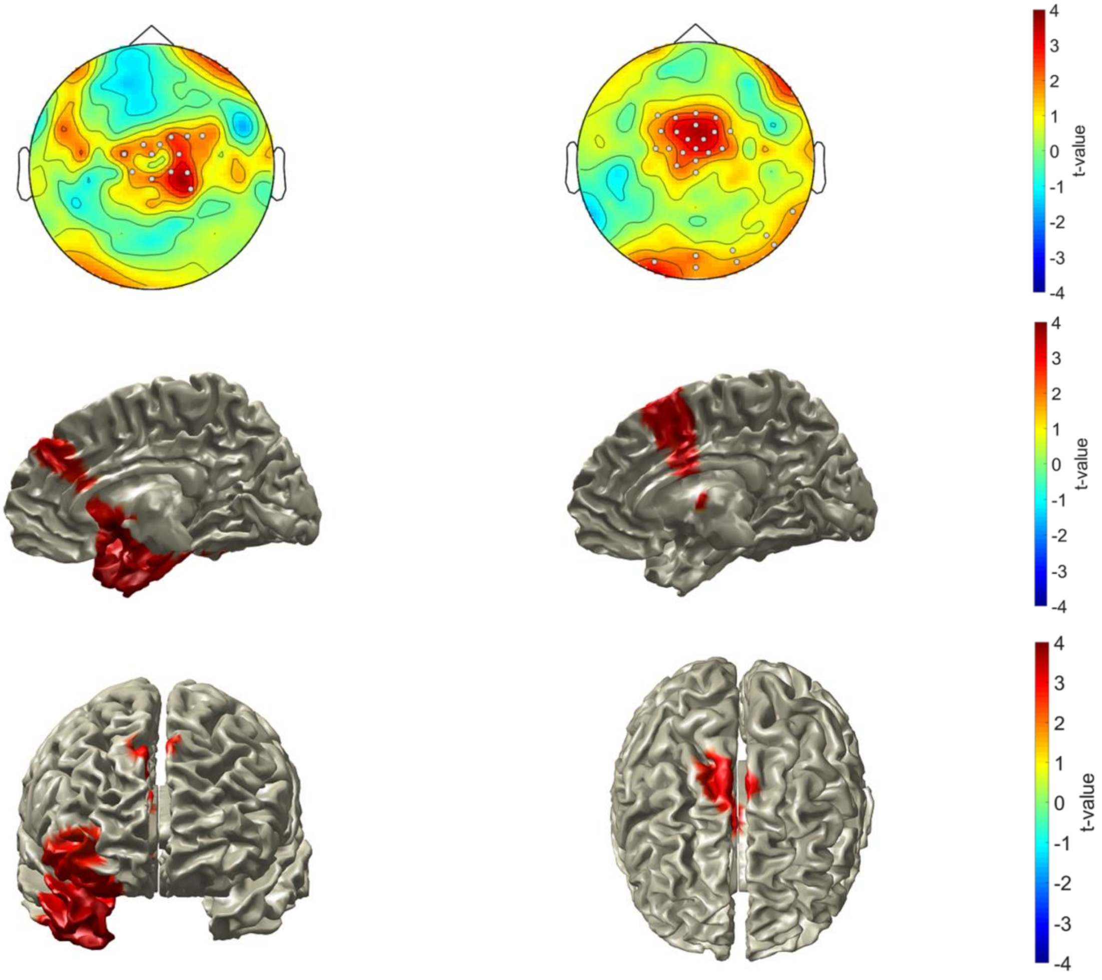

Figure 4.16. Theta band early delay source differences at sensor and source level. Left column: contrast AA vs AT sensor level difference (1.0 – 1.55s), medial view of right hemisphere, and frontal view; right column: contrast TT vs TA sensor level difference (1.0 – 1.7s, medial view of right hemisphere, and frontal top view of differential source activity.

4.8. Summary

To summarize, the present experiment suggests that the early delay effects are caused or influenced by the nature of the upcoming comparison modality and that this effect is most likely expressed through the modulation of sensory cortex activity. Secondly, late delay activity is not just a reflection of stimulus anticipation related processes; the cortical changes in the alpha band reflect an interaction between the type of WM task performed, as well as the modality of the preceding and the upcoming stimulus. Crucially, neither the early, nor late delay differences are constrained to sensory cortices, even when measured with through a low spatial resolution methodology such as EEG. Additional differential sources in the parietal and anterior parts of the cortex can be distinguished in the theta and alpha bands.

5. EXPERIMENT 4

5.1. Introduction

This experiment contrasted a WM task with a non-WM task condition under identical stimulation scenarios (for details please see General Methods section) in order to eliminate any modality anticipation or stimulation differences between experimental conditions. In experiments 2 and 3, exogenous stimulation and attentional differences related to specific modality processing were observed to dominate condition contrasts, in that mostly sensory cortices (especially the somatosensory cortex) were the main causes of differential activity between conditions. It was predicted that in this experiment a different set of sources would be detected, reflecting the differences due to WM-related processing, such as differences in stimulus encoding, stimulus maintenance, and WM-related attentional demands. The analysis focused on theta, alpha, and gamma band with a different set of questions for each of the frequency ranges. The key question of interest was whether sources expressing differential alpha band activity show any differences when contrasting auditory and tactile modalities under WM and non-WM conditions.

Theta activity is known to reflect various forms of short term memory (Vertes, 2005; Onton et al., 2005). However, it is more pronounced when there is a spatial or temporal order associated with the memorized items, such as keeping an ordered list of items in mind or estimating the passage of time (McLelland, 2016). In addition, frontal midline theta correlates positively with task difficulty related cognitive functions during the delay period (Jensen et al., 2002). Lastly, there is evidence that hippocampus, which is a source of theta oscillations, also plays a role also in SWM (Buzsaki, 2002). The above evidence suggests that theta band activity should distinguish between the two tasks. Besides testing task effects on theta, by examining the same contrast in two different modalities, the generality of theta mechanisms in SWM tasks could be assessed.

As for alpha band activity, the main focus of the experiment, contrasting the two tasks allowed us to observe whether the early delay alpha band effect was altered in the non-WM (A0 vs T0) task as compared to the AA vs TT contrast. As previously discussed, alpha band is involved in inhibition of task irrelevant areas. However, in SWM tasks the inhibition has been typically reported as “posterior” (Jensen and Mazaheri, 2010). This experiment allowed to observe whether there are inhibitory differences due to task demands once the sensory differences are controlled for.

Lastly, can gamma band enhancement be detected during the SWM delay period? While there is a relatively large body of evidence associating gamma band delay activity with working memory maintenance processes (reference et al.), few EEG studies have attempted to isolate this higher frequency WM component (Dé Roux and Uhlhaas, 2014), especially with regard to the modalities of interest in the present study. If gamma band differences do manifest themselves, two further questions can be addressed: (1) are the underlying sources located in the sensory cortices as some MEG studies have suggested (Haegens et al., 2009)? (2) do the results generalize across the two modalities in terms of timing and source topographies?

Since relative to a sensory detection task the SWM task puts higher communication demands on a number of brain regions (Peled et al., 2001), global connectivity at the source level was examined in two frequency bands associated with WM maintenance activity – theta and gamma band (Lisman and Jensen, 2013). Due to the considerable difficulties in interpreting the results of EEG connectivity analysis with any degree of specificity as to the actual underlying sources (Buzsaki and Schomburg, 2015), connectivity analysis was used to address a broad question – Are there any areas (hubs) that show a difference in connectivity strength with respect to the rest of the brain (i.e., global connectivity) in the SWM task as compared to the non-SWM task? This way, any results obtained would not depend on the accuracy of the source localization and source activity reconstruction but instead give a less specific, yet more reliable answer. The general prediction was that the SWM vs non-SWM task contrast would reveal cortical areas that are more globally connected in the SWM condition.

5.2. Behavioral results

Accuracy levels between the two tasks showed no significant differences since the ramp slopes were adjusted during the recording session to match the intensity task performance. In the intensity comparison task, the auditory and tactile condition accuracies were 91.1% and 89.8%, respectively. In the ramp detection task the corresponding accuracy levels were 91.1% and 89.5% (figure 5.1.).

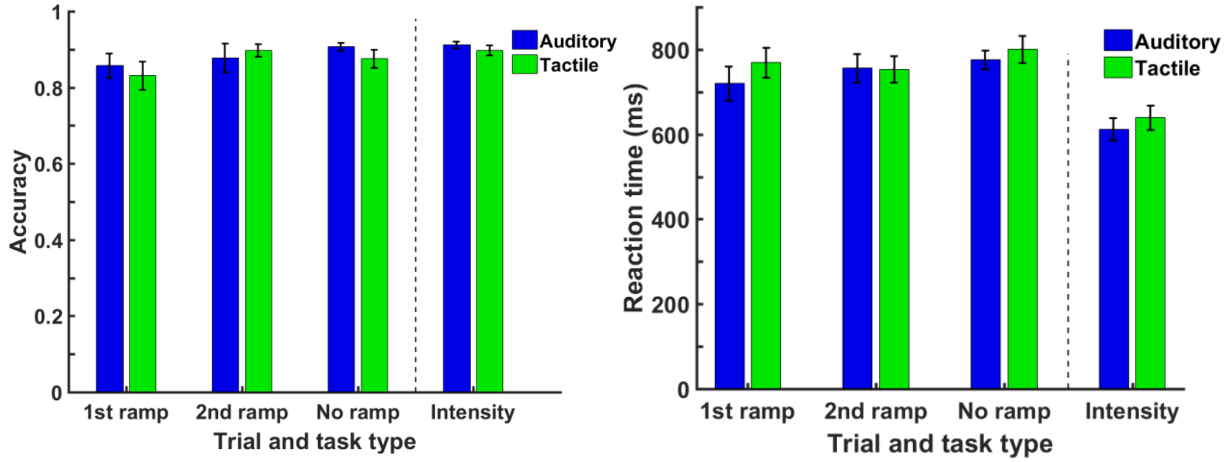

Figure 5.1. Response accuracies (left) and reaction times (right) by task trial and type: the three columns on the left refer to the ramp detection task with the three possible ramped stimulus positions separated. The fourth column on the right from the dashed line refers to the intensity comparison task. There were no significant differences between the condition, except for reaction times of the intensity task, which were significantly smaller than any of the ramp detection task conditions (error bars represent +/- 1 SEM).

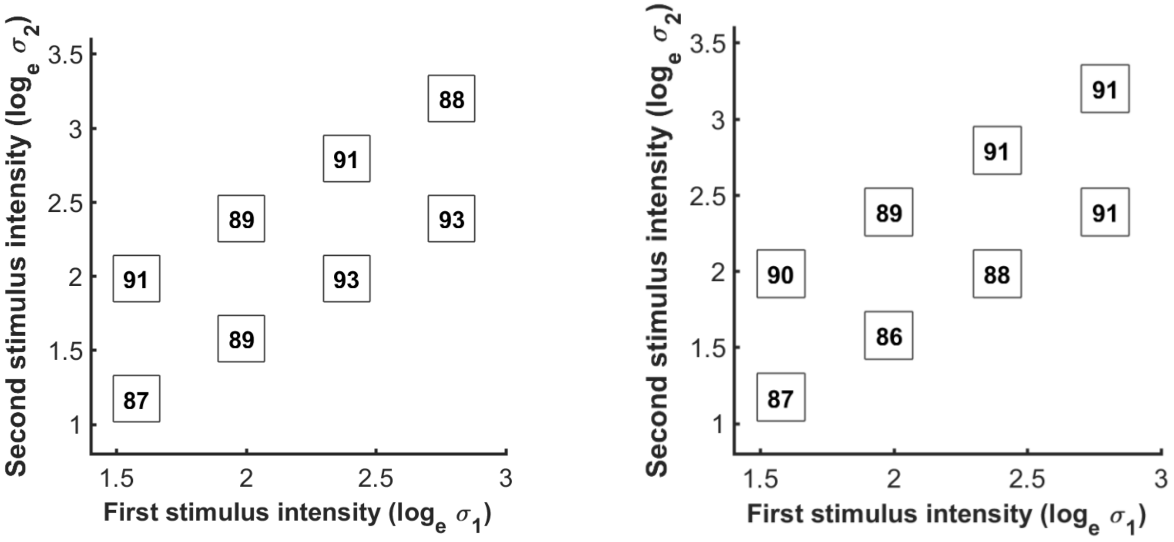

Figure 5.2.Accuracies per stimulus pair across all ramped stimulus positions in the auditory (left) and tactile (right) condition. While the intensity comparison task showed a contraction bias similar to what was observed in previous experiments, ramp detection accuracy was not affected by stimulus intensity or combinations thereof.

Reaction times differed significantly between the two conditions – in the intensity comparison task they were 611ms for the auditory condition and 640ms for the tactile condition, while in the ramp detection task the corresponding reaction times were 751ms and 774ms. Neither according to response accuracies, nor according to participants' subjective reports were the tasks of different difficulty. Therefore, the most likely cause of reaction time differences is the way in which participants attended to the second stimulus. In the intensity comparison task the average stimulus amplitude was constant throughout the stimulation period, which meant that a participant could assess the intensity value as soon as the stimulus had started. The ramp detection task, on the other hand, required the comparison between at least two intensity values, separated in time, which meant that a certain amount of time had to elapse before a ramp could be detected. While it cannot be verified through the present experiment, this interpretation suggests that the reaction time differences most likely did not reflect any differences observed in the EEG signal during the inter-stimulus delay period.

Even if the reaction times were a reflection of task difficulty, it would still most likely not be an adequate measure for capturing task difficulty during the delay period. This is because the speed of the response is more likely to reflect the differences in late trial decision-making and not the differences during the time window of interest from several seconds before, i.e., the delay period differences due to stimulus encoding, maintenance and decoding.

While it was not central to the present experiment, the individual stimulus pairs' accuracy levels were assessed for the presence of the contraction bias (figure 5.2.). As expected, despite intensity values differing identically between the two task types, no contraction bias was present, thus showing that participants performed the ramp detection task without being affected by the knowledge of the alternate task.

5.3. Sensor level statistical results and source reconstruction

Unlike the delay period differences observed in the previous experiments, the contrast between SWM and non-SWM task resulted in much more lasting differences throughout the delay period. Nevertheless, it was still the case that early and late period differences showed stronger effects and, despite the persistence of differential activity, early and late delay sensor and source level topographies did not remain identical across the delay period, especially in the in the tactile conditions. Because of these observations, and in order to retain the same analysis approach, the windows of interest were still limited to the first and the last 500ms of the delay period. For the sake of brevity, while AA and TT will continue to represent auditory and tactile unimodal conditions, respectively, the non-WM equivalent conditions will be abbreviated as A0 and T0.

5.3.1. Effects of SWM task in alpha band

Before examining within-modality task related contrasts, a comparison across modalities was carried out to evaluate the effect of alpha power on sensory cortex involvement under different task conditions. At the sensor level, the differences between the AA vs TT and the A0 vs T0 contrasts were manifest both topographically and with regard to their timing. Similarly to experiment 3, AA vs TT early delay alpha difference

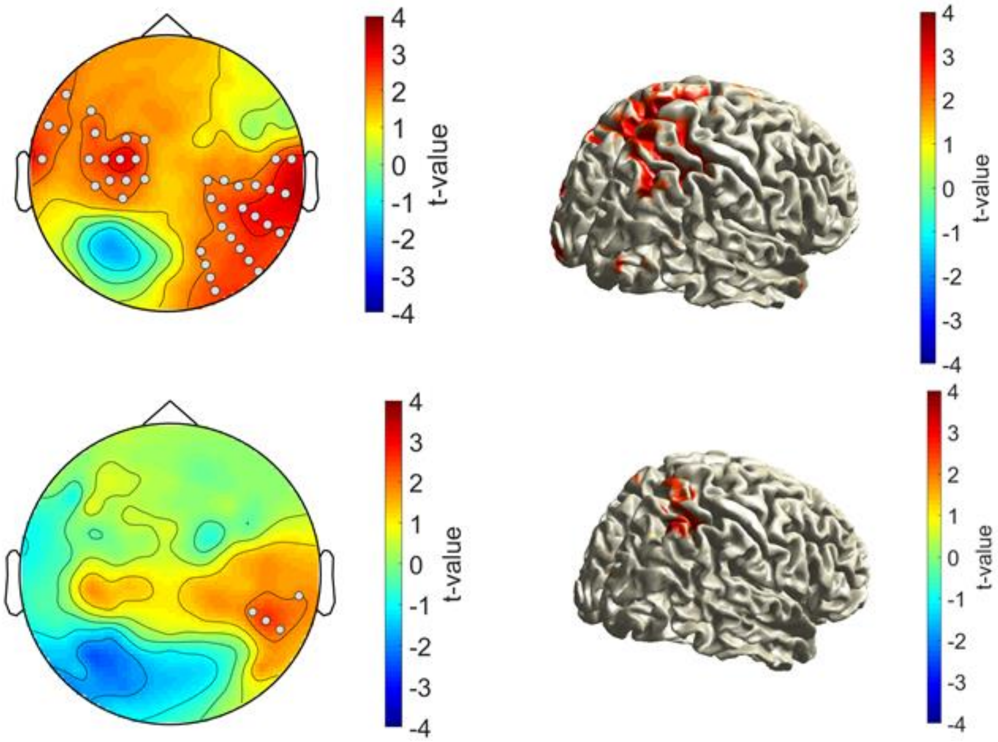

Figure 5.3. Contrasting conditions under different task demands – top row: AA vs TT sensor and source level differences (1.5 – 2.1 s); bottom row: A0 vs T0 sensor and source level differences (1.5 – 1.7s).

lasted 600ms into the delay period; A0 vs T0, on the other hand, yielded a much briefer 200ms. Furthermore, the differences between modalities were much more reduced in the A0 vs T0 condition. Source reconstruction revealed the expected source over the right somatosensory cortex, which, in the case of the A0 vs T0, was much more limited in its spatial extent (figure 5.3.).

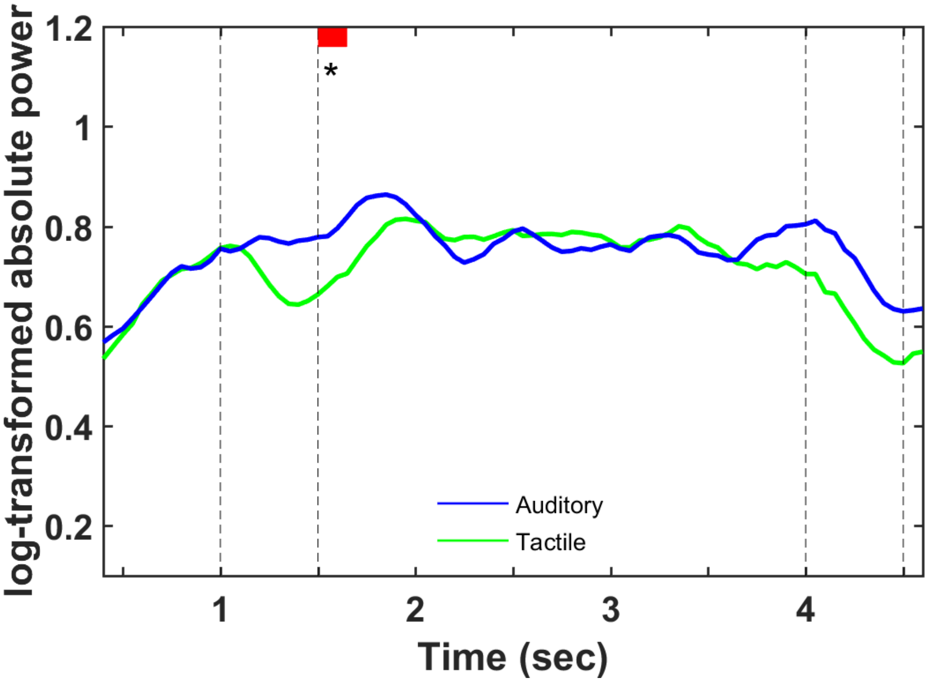

Figure 5.4. Source level power in the A0 vsT0 contrast: during the delay only the first 200ms after stimulus offset (1.5-1.7s) showed a significant difference in alpha power over the somatosensory cortex.

The cause of the reduced early delay effect in the somatosensory cortex appears to be a limited alpha power reduction in the tactile ramp detection task during the latter half of the second stimulus and early delay (figure 5.4). While both the auditory and the tactile conditions underwent a significant alpha power increase between the early and late baseline periods, the early delay decrease with respect to late baseline was not significant in the tactile condition.

5.3.2. Cross-task contrasts in theta band

AA vs A0 contrast

Early delay theta band differences were source localized to the ventrolateral PFC during the early delay and to the right temporal cortex, including auditory areas, during the late delay period (this effect was not significant: $p < 0.1$). The positive values of the identified cluster imply reduced levels of theta power in the A0 condition (figure 5.5.).

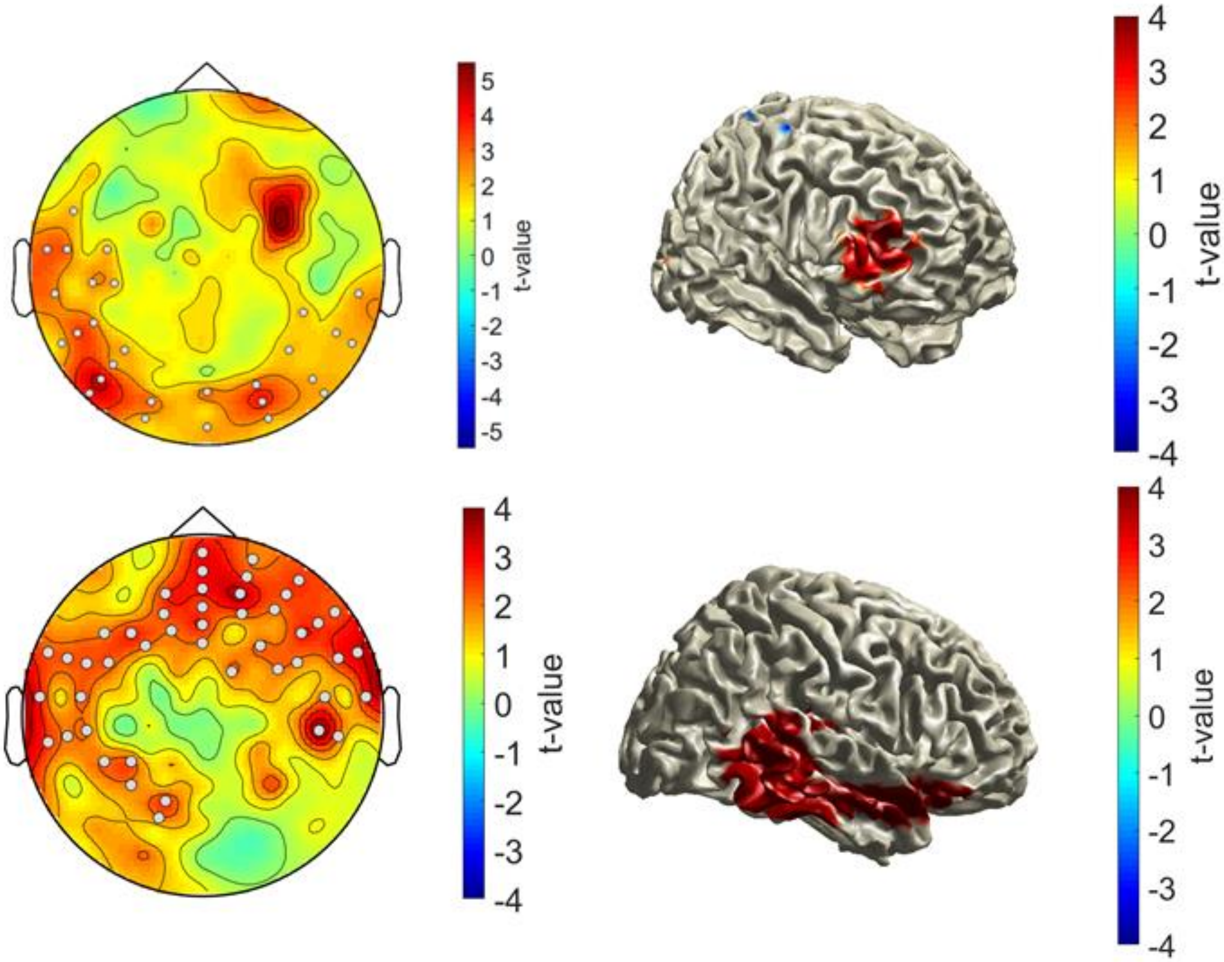

Figure 5.5. Theta band differences between SWM and ramp-detection task in the auditory modality. Top row: early delay (1.5 – 2.05s) – a cluster over ventrolateral PFC was identified; bottom row: late delay (3.45-4s) – a cluster over the right auditory areas and the temporal cortex was identified.

TT vs T0 contrast

Task contrast within the tactile modality produced a very clear bilateral source (the cluster was not split) between rostral ends of the temporal cortices, including the medial walls of temporal lobes and the hippocampal regions (figure 5.6). Positive cluster values implied a relatively higher theta power in the SWM condition during this period.

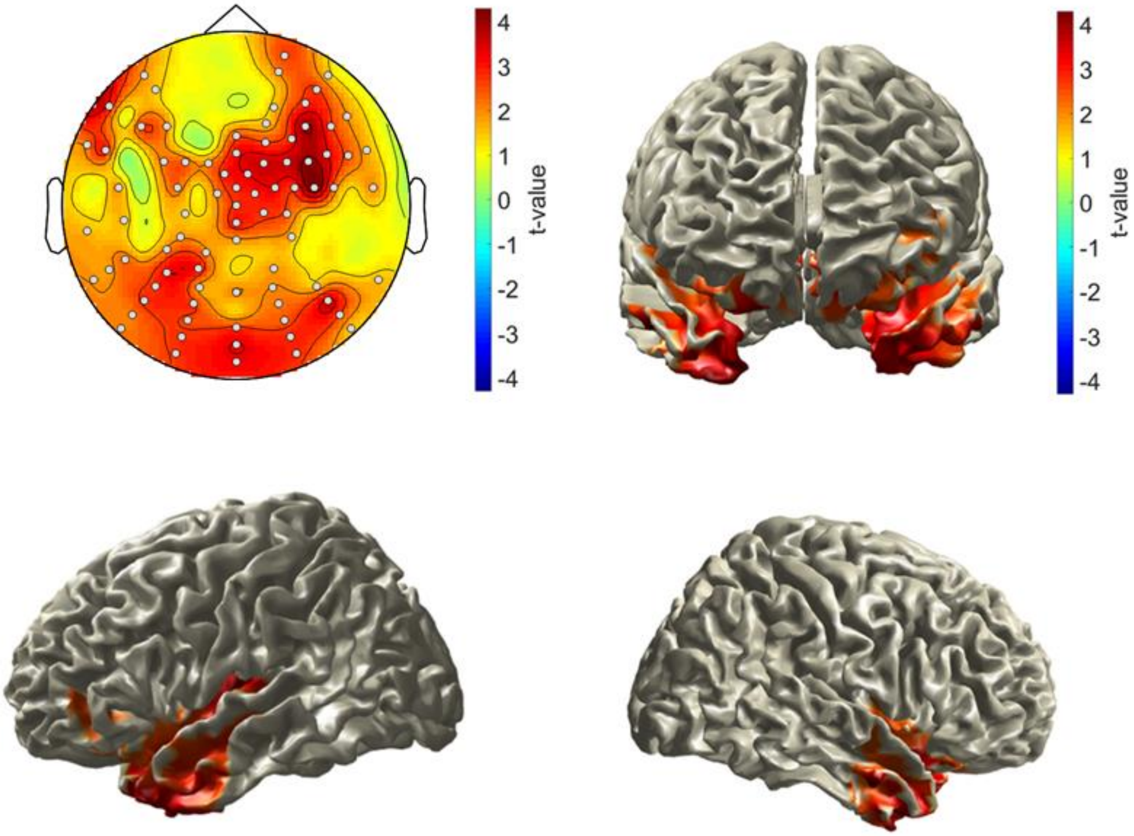

Figure 5.6. Early delay (1.5 – 1.95s) theta band differences between SWM and ramp detection task in the tactile modality. Top row: sensor level differences and frontal view of reconstructed differential source level activity. Bottom row: left and right lateral view of reconstructed differential source level activity.

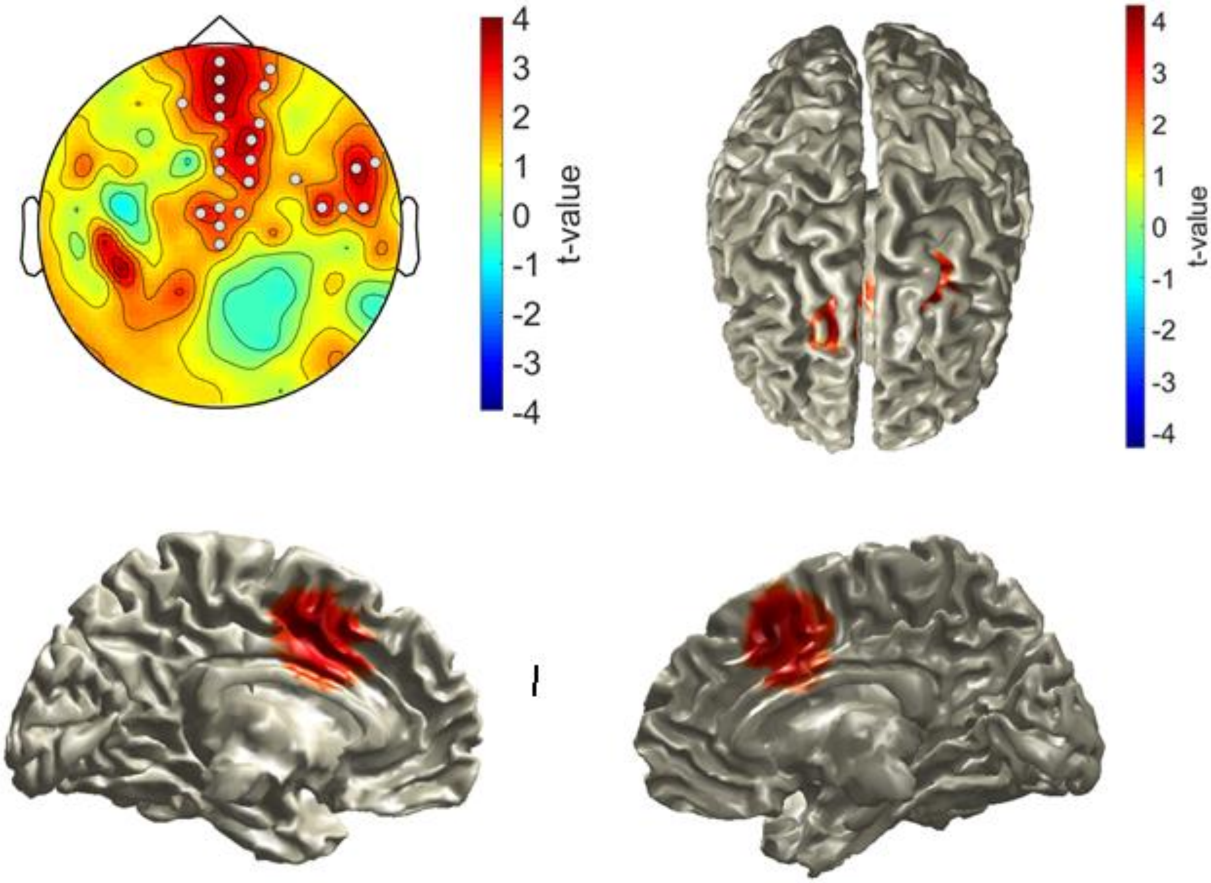

Figure 5.7. Late delay (3.55 – 4s) theta band differences between SWM and ramp detection task in the tactile modality. Top row: sensor level differences and top view of reconstructed differential source level activity. Bottom row: left and right medial view of reconstructed differential source level activity.

Late delay source reconstruction highlighted a cluster in the medial PFC bilaterally (figure 5.7.). The source was fairly focal and, somewhat unexpectedly for EEG (Malmivuo and Suikho, 2004), suggested a deeper source as the cause of the differential activity.

5.3.3. Cross-task contrasts in alpha band

AA vs A0 contrast

In the auditory modality an early delay cluster was identified over left auditory areas. During the late delay source localization highlighted a spatially stretched area over the left somatosensory, parietal, and posterior temporal cortices ($p < 0.1$; figure 5.8.).

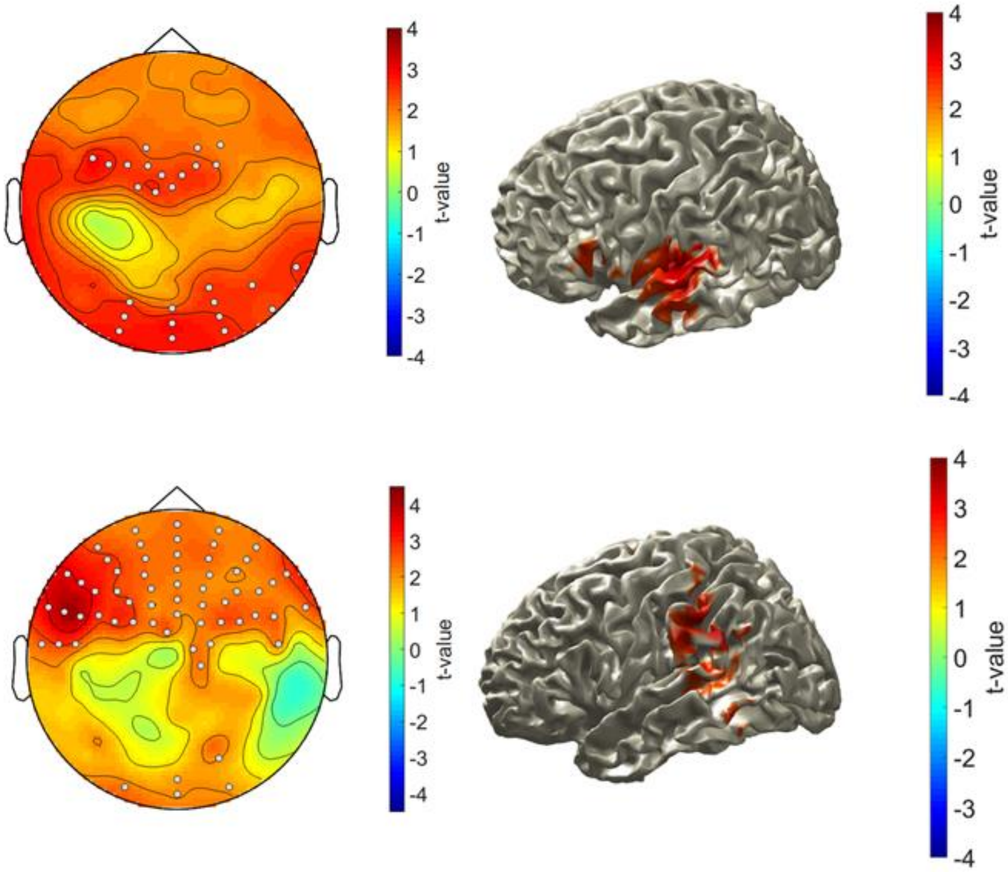

Figure 5.8. Alpha band differences between SWM and non-WM task in the auditory modality. Top row: early delay (1.5 – 2s) bottom row: late delay (3.5-4s) sensor and source level differences.

TT vs T0 contrast

Early delay source reconstruction revealed a cluster over the left auditory and secondary somatosensory cortex ($p < 0.1$) – a localization surprisingly similar to the cortical area already identified in the AA vs A0 contrast. In addition, a positive parietal cluster emerged also in the central part of the posterior parietal cortex. Late delay activity, unlike in the AA vs 0A, was markedly different from the early delay. A single positive bilateral cluster over the dlPFC was identified (figure 5.9.).

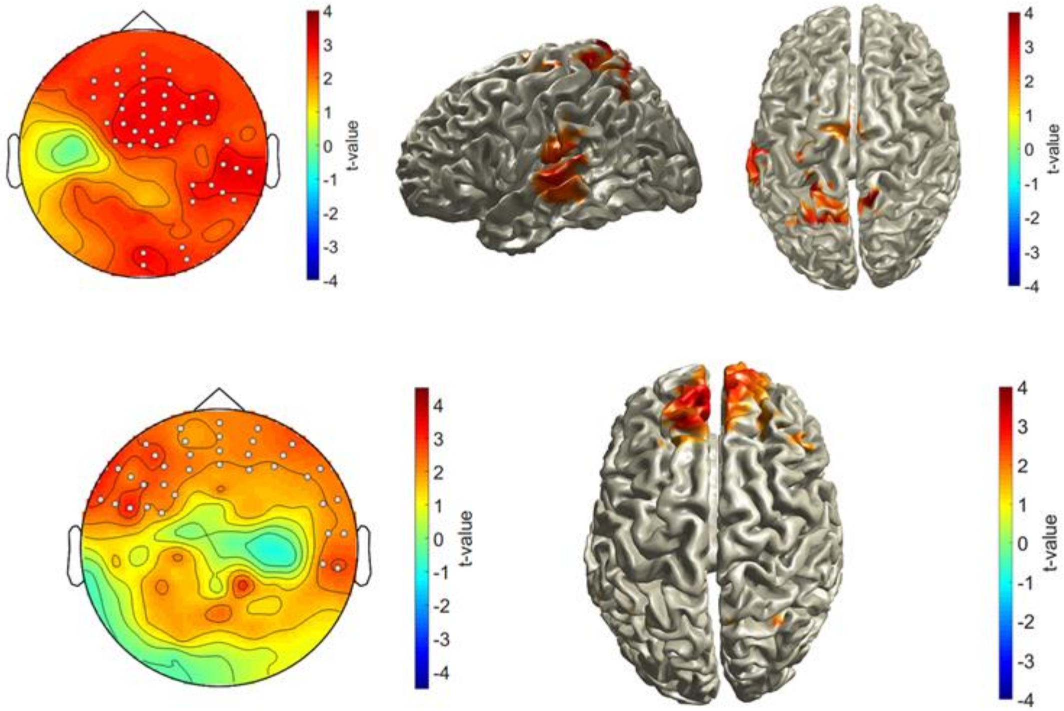

Figure 5.9. Alpha band differences between SWM and ramp-detection task in the tactile modality. Top row: early delay (1.5 – 2s), bottom row: late delay (3.5-4s) source level differences.

5.3.3. Cross-task contrasts in gamma band

AA vs A0 contrast

As with other frequency bands, cortical sources of gamma activity did not show as large a topographical difference as the TT vs T0 contrasts between early and late delay activity. Both during the early and the late delay period there were positive clusters extending over premotor areas and, to a more limited degree, also over the left PFC (figure 5.10). Again, this implied relatively more power being present in the SWM condition.

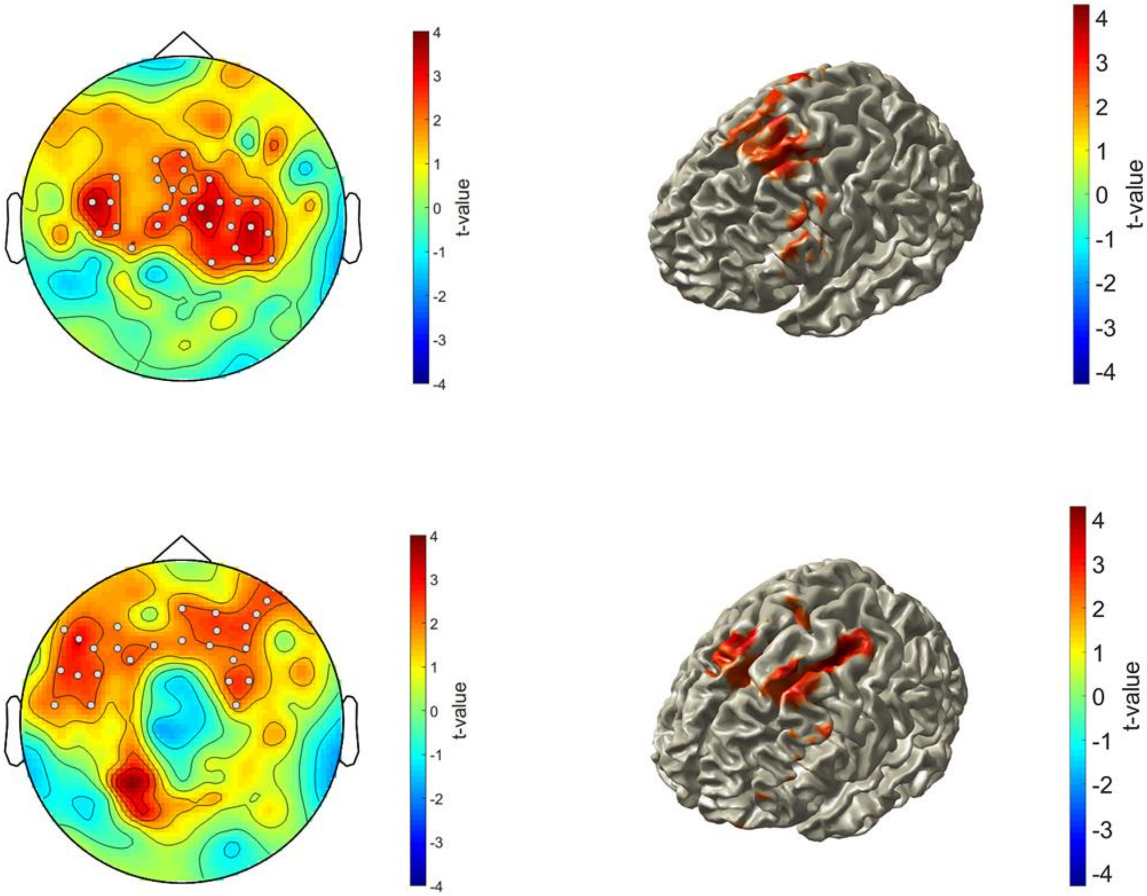

Figure 5.10. Gamma band differences between SWM and ramp-detection task in the auditory modality. Top row: early delay (1.9 – 2.6s) – a cluster covering mostly pre-motor areas was identified with a tendency to extend towards left prefrontal areas; bottom row: late delay (3 – 3.7s) – a cluster similar to early delay sources was identified.

TT vs T0 contrast

Gamma band activity in the tactile contrast showed both a relative consistency across the delay period and an overlap with the clusters identified in the gamma contrasts in the auditory modality. While during the early delay the identified cluster stretched across pre-motor areas, and the left PFC, the late delay cluster ($p < 0.1$) was limited to premotor and motor areas (figure 5.11).

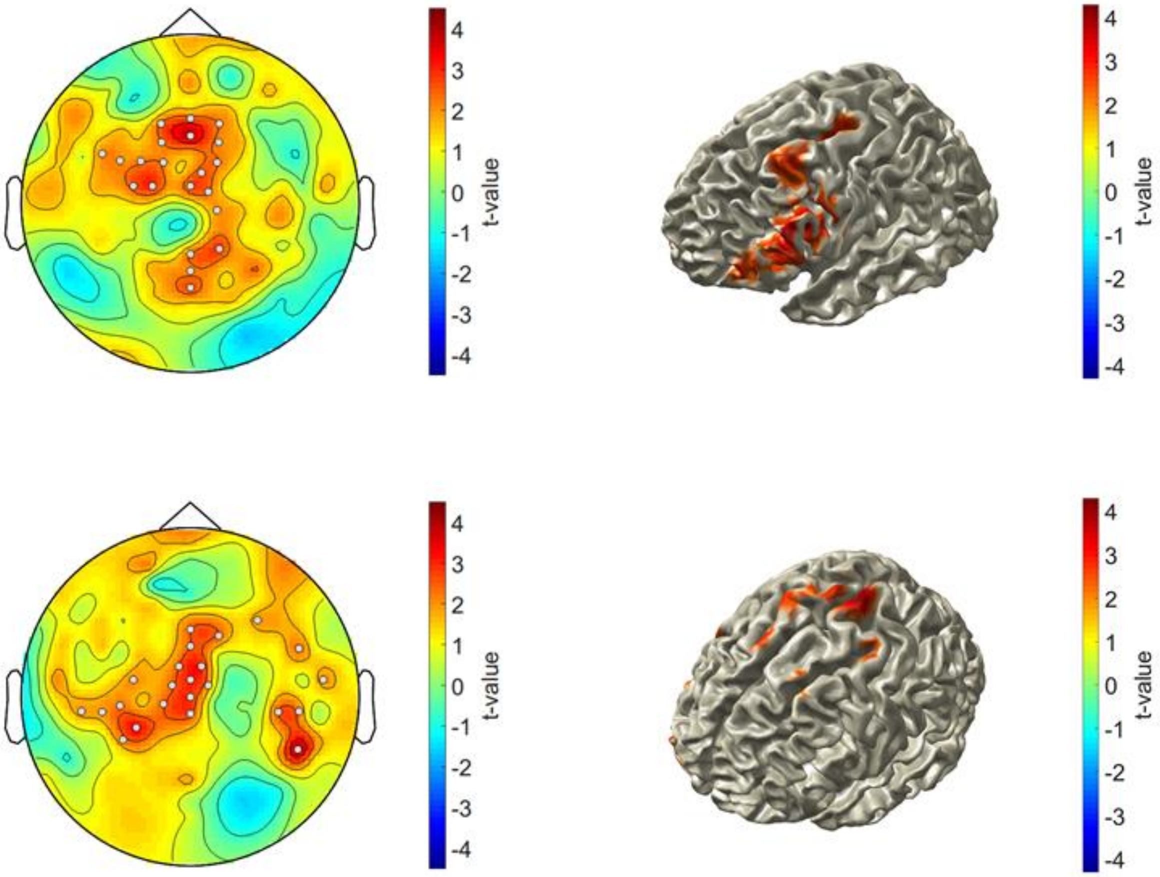

Figure 5.11. Gamma band differences between SWM and ramp-detection task in the tactile modality. Top row: early delay (1.7 – 2.1s) – a cluster covering pre-motor areas as well as lateral PFC was identified; bottom row: late delay (3 – 3.5s) – a cluster over pre-motor and motor cortices was identified.

5.4. Global connectivity

5.4.1. Early delay theta hub in tactile modality contrast

Three results were obtained when assessing global connectivity differences across brain regions in the theta band. Only the tactile contrast (TT vs T0) showed a late delay effect (figure 5.12), while no hubs with differential global connectivity were observed in the AA vs A0 contrast. The location of the hub in the tactile contrast overlapped with the left perirhinal and enthorinal cortex, areas closely associated with hippocampal – cortical interaction (David and Pierre, 2006). The areas with which the identified cluster showed the greatest connection strength differences between the conditions (green nodes) were located entirely in the posterior part of the brain.

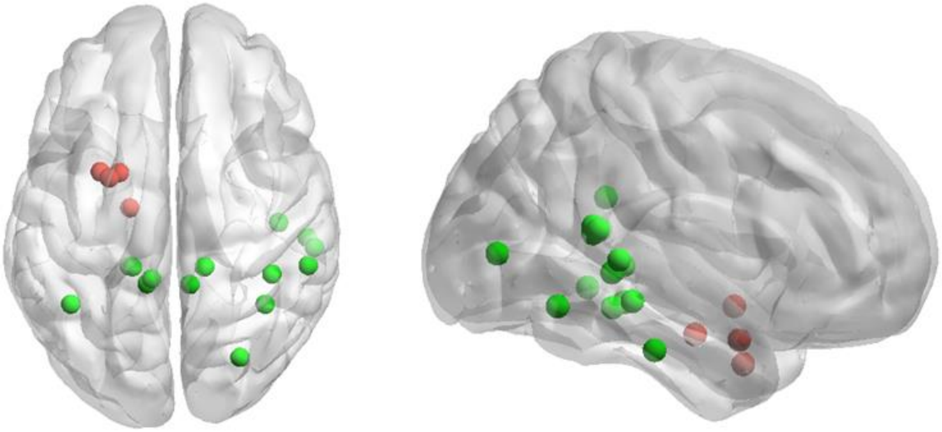

Figure 5.12. During the late delay (3.55 – 4s) the perirhinal and the enthorinal cortex (red nodes; BA 28, 34, 35, 36) were connected more strongly with the rest of the brain in the TT condition as compared to the T-0 condition. The green nodes represent the areas that accounted for 50% of the cluster's global connection strength difference between the two conditions. Left: top view; right: right lateral view.

5.4.2. Late delay gamma hubs in both modality contrasts

In the gamma band consistent results were observed across the two contrasts (figure 5.13). In the AA vs A0 contrast a late delay hub emerged (3.8 – 3.95s) located in the right auditory areas, while the TT vsT0 contrast highlighted a cluster over the somatosensory and posterior parietal cortex (3.7 – 3.9s). This implies that the sensory cortices stimulated were more connected with the rest of the brain in the gamma frequency range just prior to the onset of the second stimulus. The pattern of largest connection strengths (green nodes) did not reveal any clear patterns. By tendency, the auditory hub showed stronger connectivity differences with frontal areas, while the tactile hub connectivity strength differences were driven mostly by links to the posterior parts of the brain.

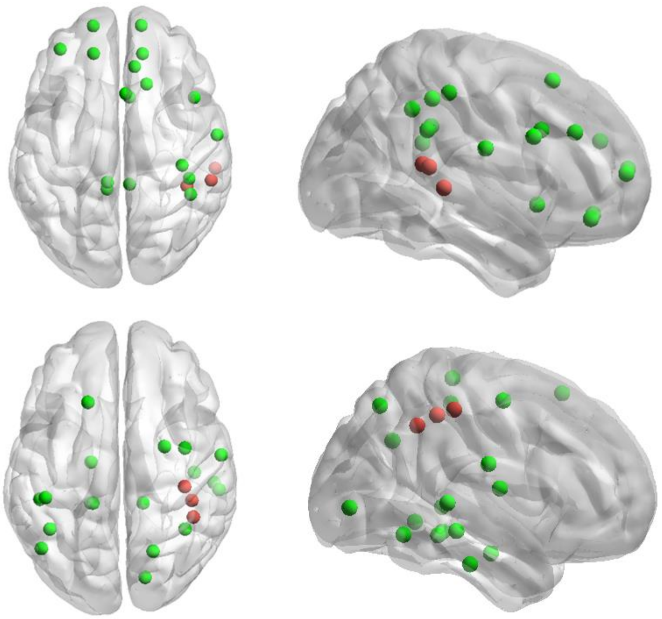

Figure 5.13. During the late delay (3.5 – 4s) the sensory cortices of the respective conditions were connected more strongly with the rest of the brain in the working memory task as compared to the ramp detection task. The green nodes represent the areas that accounted for 50% of the cluster's global connection strength difference between the two conditions. Top row – top and right lateral view of TT vs T0 connectivity contrast: a hub over the right somatosensory cortex emerged (BA 2, 3, 40); bottom row: top and right lateral view of TT vs T0 connectivity contrast: a hub over the right auditory cortex emerged (BA 22, 41, 42).

5.5. Discussion

5.5.1. Theta sources reveal hippocampal involvement in the tactile WM task

A clear topography of theta sources emerged both during the early and late delay period. Bilateral sources were identified in the temporal pole and over the medial temporal cortex, which strongly suggests differential involvement of the hippocampal area in the two tasks contrasted. This is in line with a number of studies suggesting hippocampal involvement in WM tasks (Tesche et al., 2000; Leszczyński and Fell, 2015). Working memory encoding and maintenance via theta rhythm is typically observed in the case of ordered items such as sequence memorization – the phase of the theta cycle becomes uniquely linked with ensembles of neurons which reactive sequentially through the oscillatory cycle thus maintaining the memorized sequence (Lisman, 2005). It is possible that the present task engaged the theta WM coding mechanism due to the noisy stimulus being perceived as a sequence of vibratory patterns. This hypothesis would have to be tested in an experiment with regular amplitude stimuli, which exhibit no inner order or apparent structure.

Late delay theta sources in the tactile contrast also showed an unexpected accuracy and precision for EEG, since the source topography reflected a medial prefrontal cluster as observed in numerous studies (Doppelmayr, 2008; Cavanagh and Chackman, 2014). The general functions associated with theta activity in the mPFC are those of cognitive control, attention, and, in general, inward directed mental effort (Cavanagh and Frank, 2015). This provides a close match between the established role of mPFC activity and the cognitive functions associated with the late delay period of a WM task (maintenance of attention and WM representation, while coordinating this activity with the anticipation of the comparison stimulus). While the discussion on functional differences between hippocampal and frontal midline theta remains ongoing (Mitchell et al., 2008; Leszczinsky, 2011), the present experiment contributes to this discussion by showing that through contrasting different task types both WM maintenance related phenomena appear as clearly distinct and can be studied in close temporal proximity to each other.

The auditory contrast did not show a similar pattern of activation and therefore throws into doubt the generality of the observations made in the tactile task contrast. Nevertheless, the areas identified in the auditory WM vs non-WM contrast – ventrolateral PFC and the right temporal lobe – corresponded well to those identified in auditory WM research literature. Studies suggest that non-spatial auditory WM relies on sensory, temporal and prefrontal regions, with ventrolateral PFC showing the densest connections with temporal lobe areas associated with auditory processing (Timiht et al., 2000). In particular, ventrolateral PFC has been shown to play a central role in non-spatial auditory WM (Cohen et al., 2009), while delay period involvement of the superior temporal gyrus has been established through auditory WM fMRI studies (Arnott et al., 2005).

What demands further investigation is the radically different pattern of hippocampal and mPFC involvement in SWM. These areas are most readily associated with theta band activity and memory functions, yet the reliance of these mechanisms appears to be highly modality specific. Indeed, it has been shown that transient storage of auditory stimuli relies on a temporal-prefrontal neocortical network, with hippocampal lesions having no impact on behavioral responses or neurophysiological delay period measures (Alain et al., 1998). Somatosensory stimulation, on the other hand, relies on and interacts closely with hippocampal activity patterns (Guterstam et al., 2015).

5.5.2. Delay period alpha differences reflect task demands when contrasting different modalities

The reduced extent of the somatosensory cluster in the A0 vs T0 contrast suggests that attending to the stimulus is not sufficient grounds for the emergence of post stimulation/early delay alpha power differences. This is reinforced by the fact that in the ramp detection task the best ramp detection strategy should result from comparing the first intensity values to the last intensity values of the stimulus. This implies that more attention might be directed to the end of the stimulus in the ramp detection task as compared to the intensity task. Yet, despite attentional requirements suggesting an opposite pattern, alpha power reduction was more extensive over the stimulated area in the AA vs TT task both in terms of topography and duration. This strongly suggests both that early delay alpha power reduction reflects stimulus encoding in WM and that the encoding process involves the stimulus receiving sensory cortex. The cessation of early delay differences also suggests that later delay period storage of a SWM representation relies on the sensory cortices to a lesser degree. Alternatively, the SWM representation could be just as dependent on sensory cortex engagement also later in the delay period without this engagement being reflected through altered alpha power topography (for instance, phase synchronization between different areas can happen independently from power fluctuations). In either case, it is clear that an early delay transient effect in the alpha band fulfills a specific role in stimulus encoding, which goes beyond the mere detection of a certain stimulus feature.

5.5.3. Ambiguous within-modality WM task effects

While the AA vs TT and A0 vs T0 contrasts revealed that the involvement of the somatosensory cortex is reduced under non-WM condition, the same effect was not observed in the TT vs T0 contrast. Instead, task contrasts both in the tactile and in the auditory modality identified a source over the left auditory area, secondary somatosensory cortex, as well as parts of the parietal cortex. In addition, in the tactile modality a late delay cluster emerged over a fronto-central area, without any similar frontal activity being present in the auditory modality. The ipsilateral auditory areas were relatively more inhibited in the SWM task indicating a more lateralized focus on the contralateral side in the task requiring more elaborate stimulus processing (i.e., WM encoding and decoding). Similarly, the tactile sources could be interpreted as representing different degrees of lateralization depending on task demands; the source in this case would have to be attributed to ipsilateral secondary somatosensory cortex.

While the general idea of lateralization of alpha ERS/ERD effects as a function of task difficulty is plausible, the present observations suggest an asymmetric effect in that only the unattended but not the attended side manifests an effect of task demands. Studies taking advantage of alpha lateralization typically do so in the context of a single task (Händel et al., 2011; Müller and Weisz, 2012), for which reason direct evidence of the proposed hypothesis is missing. Lastly, while the early delay parietal source in the tactile contrast could be interpreted as reflecting the inhibition of contralateral somatosensory cortex, more accurate source localization needs to be achieved before making any stronger claims with regard to the correlation between specific task demands and asymmetric alpha power lateralization effects.

5.5.4. Gamma band effect corroborate the role of the premotor region in WM maintenance

In both modalities SWM vs non-SWM contrasts identified sources of enhanced gamma band activity in the frontal and left prefrontal areas. A prefrontal area located in the premotor cortex (BA6) was common to both early and late delay periods across both modalities. This observation shows stark similarities with two recent animal studies. Recording from Macacca Mulatta supplementary premotor area Vergara et al. showed that neurons in this area show a parametric coding properties with regard to both the frequency of tactile and auditory stimuli (Vergara et al., 2016). Neurons from the left hemisphere s-PMA were in particular modality agnostic. In the second study monkeys performed a visual WM task and neuronal activity in frontal areas corresponding to human dlPFC and inferior frontal sulcus were recorded (Lundqvist et al., 2016). Crucially, a subset of the recording sites showed transient bursts of gamma band activity and it was only at these sites that spiking activity reflected the properties of the encoded stimulus. Interestingly, the timing of the strongest gamma effects in the present experiment did not correspond to early and late delay periods as observed in other frequency bands and the above two studies. The absence of very early (first 200ms) and very late (last 300ms) delay differences was unexpected and deserves further investigation.

Despite the timing differences observed, the match between the examined sensory modalities, the topography of gamma band sources, as well as their close association with the neuronal spiking activity carrying WM stimulus properties all strongly suggest that the gamma effect identified in the present experiment is a reflection of a homologue WM activity pattern in the human species. While several MEG studies have reported an increase in gamma band during the delay period (Tallon-Baudry et al., 1998; Bauer et al., 2006), this increase was related to activity in the sensory cortices; nevertheless, changes in frontal gamma activity have also been reported (Ishii et al., 2014) and were particularly associated with demanding higher level cognitive functions such as focused attention, mental calculation, and working memory.

5.5.5. Sensory cortices and the hippocampus as WM delay period hubs

Theta

A few preliminary observations were made with regard to connectivity patterns in the theta and gamma bands. In line with the theta band power effects observed at the source level, a left hippocampal cluster with stronger global connectivity in the WM condition was identified. Interestingly, the differential connectivity strength manifested itself during the later delay period (while hippocampal power differences were identified during the early delay). This suggests that power difference between conditions as a potentially confounding factor can be excluded (Schoffelen and Gross, 2009). However, when visualizing the connections accounting for 50% of the global connection strength difference between the WM and non-WM conditions, no neurophysiologically meaningful pattern emerged. This observation provides further support to the idea that hippocampus is both involved in (tactile) WM and that its role is potentially not limited to a specific temporal window during the WM delay.

Gamma

In both contrasts, enhanced connectivity with the rest of the brain was served around the sensory cortices of the respective modality contrast. This is most likely a reflection of gamma band carrying stimulus related information during the delay period (Fries, 2009). In particular, the late delay emergence of the sensory gamma hubs supports the notion of reactivation of sensory level WM representations at the end of the delay period, possibly via a persistent top-down control signal (Mongillo et al., 2008; Lara and Wallis, 2015; Riley and Constantinidis, 2016).

The largest connection strength differences (figure 5.13., green nodes) between the WM and non-WM tasks did not reveal any specific pattern, indicating that the sensory WM hubs identified were preferentially interacting with a wide range of cortical areas. Given the connectivity effects observed in the theta and gamma bands in the present experiment, testing more specific connectivity hypothesis can potentially provide further information about inter-area communication during the present SWM task. The present results have identified theta-gamma cross frequency coupling as a candidate mechanism worth further exploration (Lisman and Jensen, 2013).

6. SUMMARY AND CONCLUSION

In this study three experiments were conducted with the overall goal of characterizing SWM delay period oscillatory activity. A number of questions were addressed with a particular focus on the alpha band, since the ‘gating by inhibition’ hypothesis allowed to give a more precise interpretation of the cognitive meaning of the neurophysiological results obtained. Nevertheless, whenever there was a specific hypothesis with regard to a particular experimental design or contrast of conditions, oscillatory effects were also examined in other frequency bands. EEG source reconstruction results allowed to reach valid conclusions through combining patterns of results across different condition contrasts. Lastly, a few observations were also made with regard to overall brain connectivity in order to indicate possibilities for future research.

In experiment 2 participants had to compare the intensity of auditory, tactile, or bimodal (tactile + auditory) stimuli in interleaved blocks separating the stimulation modalities. Results revealed that differences in the alpha band were statistically different only during the early and the late part of the delay period. Under the tactile vs auditory delay period comparison, only power reduction in the somatosensory cortex could be detected. This was most likely due to the strength of the relative signal change in the somatosensory cortex masking a comparable, albeit weaker effect in the auditory modality due to volume conduction. Source level power reconstruction revealed that the differential somatosensory activity was caused by both ERS in the auditory condition as well as ERD in the tactile condition. Comparing the auditory condition relative to its own baseline revealed that the delay period alpha ERS was not specific to the somatosensory cortex, but instead a more widespread posterior area showed this effect. This observation reduced the likelihood that somatosensory cortex inhibition was caused by the experimental context, i.e., by having somatosensory stimulation blocks in between auditory blocks throughout the experiment. A differential involvement of the frontal cortex was detected in the tactile vs bimodal contrast, but specific conclusions were not reached due to the lack of generality across both unimodal vs bimodal contrasts.

A parametric effect was observed in the beta band in the right posterior parietal cortex in the bimodal condition during the early delay. Since this effect was absent in the two unimodal conditions, it could be a reflection of multimodal integration related processing. Behaviorally, the strength of the contraction bias was reduced in the bimodal condition reflecting improved WM representation maintenance. The correlation between behavioral performance and a bimodal condition specific neurophysiological effect in the beta band warrants further investigation of this phenomenon.

Experiment 3 addressed further questions about delay period effects in the alpha band. Cross-modal WM conditions were introduced in which participants had to compare auditory to tactile stimulus intensity, and vice versa. Results revealed that late delay differences were not caused exclusively by modality specific stimulus anticipation, but instead were also affected by the modality of the first stimulus. Secondly, statistical contrasts involving switching focus from one modality to the other (i.e., cross-modal conditions) revealed qualitatively similar alpha band effects also in the auditory cortex. This gives credence to the speculation that continuous attention on the somatosensory cortex leads to the masking of the auditory alpha effect.

Secondly, involvement of the parietal cortex during the late delay was observed in the tactile-to-auditory cross modal comparison condition. This is an important result as it extends the realm of what modality specific alpha band effects beyond the sensory cortices can be observed. Interestingly, no late delay differences were observed in within-task contrasts despite the anticipation of different modalities. This suggests that, in addition to modality anticipation differences, also differences due to the task played a crucial role in bringing about the effects observed in the alpha band. Lastly, an early frontal theta source was identified when contrasting conditions in which identical first stimuli were followed by differing second stimuli. The result suggests a role of the hippocampus in the activation of stimulus representations deemed to be relevant for the anticipated comparison period.

In experiment 4, in which the unimodal WM task was compared to a non-WM equivalent, similar theta topography – suggestive of both hippocampal and mPFC activity – was observed, yet only in the tactile condition. In the light of the theta effect observed in experiment 3 in contrasts involving both modalities, a reconciliation between two results is needed. If the theta band effect of experiment 3 is interpreted as reflecting frontal midline theta, which has been frequently associated with task difficulty and demanding mental processing (e.g. performing mathematical operations), it explains why this effect was present in the unimodal vs cross-modal task comparisons in both modalities. A cross-modal task is clearly cognitively more challenging and would therefore lead to additional frontal processing demands. Returning to experiment 4, the theta observed could be associated with both hippocampal and frontal midline sources due to differences in both memory involvement and task difficulty; nevertheless, the absence of a mPFC theta source in the auditory condition precludes a fully congruent explanation and further experiments in this regard are needed.

With regard to the alpha band, a discrepancy between two sets of results was noted. While contrasts between different modalities under WM and non –WM task demands suggested a reduced involvement of the somatosensory cortex under no-WM conditions, the same result was not observed when contrasting the tactile WM condition with the tactile non-WM condition. The best explanation of these diverging results is that of a stronger cortical signal (or signals) effectively masking the detection of those less pronounced. As noted, delay period activity in the WM vs non-WM contrasts produced lasting differences between the conditions throughout the delay period. Thus, it is likely that differential activity at multiple cortical sources were at play in this contrast, which lead to the identification of more diffuse and ambiguous differential source level activity.

Unique to experiment 4 was the difference detected in the lower gamma when contrasting WM and non-WM tasks. This was the case in both auditory and tactile WM vs non-WM task contrasts. Surprisingly, both modalities, and both early and late delay periods showed an overall similar source level topography over the premotor cortex, amongst other left lateralized fronto-central areas. This is an encouraging result as it falls in line with both human and recent animal studies suggesting gamma involvement in the maintenance of WM representations.

Overall, this study demonstrated that alpha band dynamics is an effective way of exploring cortical activity patterns during the SWM delay. It also highlighted the fact that under specific stimulation combinations, the involvement of posterior areas can be detected in tactile, bimodal, and cross-modal WM tasks. With regard to experimental design, a valuable insight that this study provides is that combining auditory and tactile stimulation must be implemented with great consideration of stimulation strength and persistence due to the differences in induced response amplitudes between the two sensory areas. While experiment 4 revealed additional SWM effects in the gamma band, the contrast between a WM and a non-WM task also showed that the differences in such a comparison were too widespread in time and across frequencies for specific conclusions to emerge, especially in the alpha band. Nevertheless, some encouraging results were observed with regard to connectivity patterns, which provides useful insights for future connectivity studies.

7. FUTURE DIRECTIONS

The three experiments allowed us to inch ever closer to an optimal design for examining SWM. Differences in the nature of auditory and somatosensory responses led to complications in interpreting the results in a way that could be generalized across conditions. Contrasting different tasks within the same modality, on the other hand, can lead to broad differences that are hard to interpret. An analysis approach that could overcome the above difficulties is that of contrasting correct and incorrect trials within the same modality. Here, both the stimulation level differences are kept constant and the interpretation of the observed differences could be clearly attributed to effective carrying out of encoding, maintenance, or retrieval processes, depending on the timing of the effect.

The bimodal integration effect must be tested under “bimodal stimulation – unimodal WM” conditions, with one modality serving as a distractor to be ignored. This would clarify the role of parietal beta oscillatory activity during the early SWM delay period.

The identification of global gamma hubs over the sensory cortices during the late delay, as well as a theta hub in the tactile task contrast contributes to the result and suggests that a more targeted assessment of connectivity through the examination of cross and within frequency coupling could provide a productive venue of future research. The data collected already allows more targeted analyses to be carried out. For instance, can enhanced beta band phase synchrony be detected between the posterior parietal cortex and the sensory cortices under bimodal SWM conditions? Is there any enhanced theta-gamma cross frequency coupling present in the WM conditions of experiment 4? If the answer to the latter question is affirmative, it would have certain implications for the way in which the noisy stimuli are possibly encoded into WM (i.e., as a sequence of vibratory patterns as opposed to a scalar intensity value, which would thus be a test of the theta–gamma encoding hypothesis; see Lisman and Jensen, 2013).

Lastly, the WM vs non-WM tasks must be compared also using cross-modal stimulation in order to determine whether the parietal involvement under tactile cross-modal WM conditions in experiment 3 depends on WM task demands or it is a reflection of anticipatory attentional shifts without necessarily reflecting WM related processing.

REFERENCES

Alain, C., Woods, D. L., & Knight, R. T. (1998). A distributed cortical network for auditory sensory memory in humans. *Brain Research*, *812*(1), 23–37. http://doi.org/10.1016/S0006-8993(98)00851-8

Arnott, S. R., Grady, C. L., Hevenor, S. J., Graham, S., & Alain, C. (2005). The Functional Organization of Auditory Working Memory as Revealed by fMRI. *Journal of Cognitive Neuroscience*, *17*(5), 819–831. http://doi.org/10.1162/0898929053747612

Bauer, M., Oostenveld, R., Peeters, M., & Fries, P. (2006). Tactile Spatial Attention Enhances Gamma-Band Activity in Somatosensory Cortex and Reduces Low-Frequency Activity in Parieto-Occipital Areas. *Journal of Neuroscience*, *26*(2). Retrieved from http://www.jneurosci.org/content/26/2/490.short

Benchenane, K., Peyrache, A., Khamassi, M., Tierney, P. L., Gioanni, Y., Battaglia, F. P., & Wiener, S. I. (2010). Coherent Theta Oscillations and Reorganization of Spike Timing in the Hippocampal- Prefrontal Network upon Learning. *Neuron*, *66*(6), 921–936. http://doi.org/10.1016/j.neuron.2010.05.013

Benedek, M., Schickel, R. J., Jauk, E., Fink, A., & Neubauer, A. C. (2014). Alpha power increases in right parietal cortex reflects focused internal attention. *Neuropsychologia*, *56*(100), 393–400. http://doi.org/10.1016/j.neuropsychologia.2014.02.010

Bonnici, H. M., Richter, F. R., Yazar, Y., & Simons, J. S. (2016). Multimodal Feature Integration in the Angular Gyrus during Episodic and Semantic Retrieval. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *36*(20), 5462–71. http://doi.org/10.1523/JNEUROSCI.4310-15.2016

Buzsáki, G. (2002). Theta Oscillations in the Hippocampus. *Neuron*, *33*(3), 325–340. http://doi.org/10.1016/S0896-6273(02)00586-X

Buzsáki, G., & Schomburg, E. W. (2015). What does gamma coherence tell us about inter-regional neural communication? *Nature Publishing Group*, *18*. http://doi.org/10.1038/nn.3952

Cavanagh, J. F., & Frank, M. J. (2014). Frontal theta as a mechanism for cognitive control. *Trends in Cognitive Sciences*, *18*(8), 414–21. http://doi.org/10.1016/j.tics.2014.04.012

Cavanagh, J. F., & Shackman, A. J. (2015). Frontal midline theta reflects anxiety and cognitive control: Meta-analytic evidence. *Journal of Physiology-Paris*, *109*(1), 3–15. http://doi.org/10.1016/j.jphysparis.2014.04.003

Cohen, M. X., Elger, C. E., & Fell, J. (2009). Oscillatory Activity and Phase–Amplitude Coupling in the Human Medial Frontal Cortex during Decision Making. *Journal of*

Cognitive Neuroscience, *21*(2), 390–402.

Croxson, P. L., Johansen-Berg, H., Behrens, T. E. J., Robson, M. D., Pinsk, M. A., Gross, C. G., … Rushworth, M. F. S. (n.d.). Behavioral/Systems/Cognitive Quantitative Investigation of Connections of the Prefrontal Cortex in the Human and Macaque using Probabilistic Diffusion Tractography. http://doi.org/10.1523/JNEUROSCI.1311-05.2005

D'Esposito, M., & Postle, B. R. (2015). The Cognitive Neuroscience of Working Memory. *Annual Review of Psychology*, *66*(1), 115–142. http://doi.org/10.1146/annurev-psych-010814-015031

David, A., & Pierre, L. (2006). Hippocampal Neuroanatomy. In *The Hippocampus Book* (pp. 37–114). Oxford University Press. http://doi.org/10.1093/acprof:oso/9780195100273.003.0003

David, O., & Friston, K. J. (n.d.). A neural mass model for MEG/EEG: coupling and neuronal dynamics. http://doi.org/10.1016/j.neuroimage.2003.07.015

Dé, F., Roux, R., & Uhlhaas, P. J. (2014). Working memory and neural oscillations: alpha–gamma versus theta–gamma codes for distinct WM information? *Trends in Cognitive Sciences*, *18*, 16–25. http://doi.org/10.1016/j.tics.2013.10.010

Denker, M., Roux, S., Lindén, H., Diesmann, M., Riehle, A., & Grün, S. (2011). The Local Field Potential Reflects Surplus Spike Synchrony. *Cerebral Cortex*, *21*(12), 2681–2695. http://doi.org/10.1093/cercor/bhr040

Doppelmayr, M., Finkenzeller, T., & Sauseng, P. (2008). Frontal midline theta in the pre-shot phase of rifle shooting: Differences between experts and novices. *Neuropsychologia*, *46*(5), 1463–1467. http://doi.org/10.1016/j.neuropsychologia.2007.12.026

Eimer, M., & Forster, B. (2003). Modulations of early somatosensory ERP components by transient and sustained spatial attention. *Exp Brain Res*, *151*, 24–31. http://doi.org/10.1007/s00221-003-1437-1

Engel, A. K., & Fries, P. (2010). Author's personal copy Beta-band oscillations — signalling the status quo? *Current Opinion in Neurobiology*, *20*, 156–165. http://doi.org/10.1016/j.conb.2010.02.015

Engel, A. K., Senkowski, D., & Schneider, T. R. (2012). *Multisensory Integration through Neural Coherence*. *The Neural Bases of Multisensory Processes*. CRC Press/Taylor & Francis. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22593880

Fassihi, A., Akrami, A., Esmaeili, V., & Diamond, M. E. (2014). Tactile perception and working memory in rats and humans. *Proceedings of the National Academy of Sciences of the United States of America*, *111*(6), 2331–6. http://doi.org/10.1073/pnas.1315171111

Fell, J., & Axmacher, N. (2011). The role of phase synchronization in memory processes. *Nature Reviews Neuroscience*, *12*(2), 105–118. http://doi.org/10.1038/nrn2979

Fink, A., Grabner, R. H., Neuper, C., & Neubauer, A. C. (2005). EEG alpha band dissociation with increasing task demands. *Cognitive Brain Research*, *24*(2), 252–259. http://doi.org/10.1016/j.cogbrainres.2005.02.002

Fougnie, D. (n.d.). The Relationship between Attention and Working Memory. Retrieved from http://www.psy.vanderbilt.edu/students/fougnidl/Fougnie-chap1.pdf

Fries, P. (2009). Neuronal Gamma-Band Synchronization as a Fundamental Process in Cortical Computation. *Annual Review of Neuroscience*, *32*(1), 209–224. http://doi.org/10.1146/annurev.neuro.051508.135603

Gazzaley, A., & Nobre, A. C. (2012). Top-down modulation: bridging selective attention and working memory. *Trends in Cognitive Sciences*, *16*(2), 129–35. http://doi.org/10.1016/j.tics.2011.11.014

Gevins, A., Smith, M. E., McEvoy, L., & Yu, D. (1997). High-resolution EEG mapping of cortical activation related to working memory: effects of task difficulty, type of processing, and practice. *Cerebral Cortex*, *7*(4), 374–385. http://doi.org/10.1093/cercor/7.4.374

Gross, J. (2014). Analytical methods and experimental approaches for electrophysiological studies of brain oscillations. *Journal of Neuroscience Methods*, *228*(100), 57–66. http://doi.org/10.1016/j.jneumeth.2014.03.007

Gross, J., Kujala, J., Hamalainen, M., Timmermann, L., Schnitzler, A., & Salmelin, R. (2001). Dynamic imaging of coherent sources: Studying neural interactions in the human brain. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(2), 694–9. http://doi.org/10.1073/pnas.98.2.694

Guterstam, A., Björnsdotter, M., Bergouignan, L., Gentile, G., Li, T.-Q., & Ehrsson, H. H. (2015). Decoding illusory self-location from activity in the human hippocampus. *Frontiers in Human Neuroscience*, *9*, 412. http://doi.org/10.3389/fnhum.2015.00412

Haegens, S., Händel, B. F., & Jensen, O. (2011). Top-Down Controlled Alpha Band Activity in Somatosensory Areas Determines Behavioral Performance in a Discrimination Task. *Journal of Neuroscience*, *31*(14). Retrieved from http://www.jneurosci.org/content/31/14/5197.long

Haegens, S., Osipova, D., Oostenveld, R., & Jensen, O. (2009). Somatosensory working memory performance in humans depends on both engagement and disengagement of regions in a distributed network. *Human Brain Mapping*, *31*(1), NA–NA. http://doi.org/10.1002/hbm.20842

Harris, J. A., Miniussi, C., Harris, I. M., & Diamond, M. E. (2002). Transient Storage of a Tactile Memory Trace in Primary Somatosensory Cortex. *Journal of Neuroscience*, *22*(19). Retrieved from http://www.jneurosci.org/content/22/19/8720.short

Herweg, N. A., Apitz, T., Leicht, G., Mulert, C., Fuentemilla, L., & Bunzeck, N. (2016). Theta-Alpha Oscillations Bind the Hippocampus, Prefrontal Cortex, and Striatum during Recollection: Evidence from Simultaneous EEG-fMRI. *Journal of Neuroscience*, *36*(12), 3579–3587. http://doi.org/10.1523/JNEUROSCI.3629-15.2016

Honkanen, R., Rouhinen, S., Wang, S. H., Palva, J. M., Palva, S., M, H., … JR, P. (2015). Gamma Oscillations Underlie the Maintenance of Feature-Specific Information and the Contents of Visual Working Memory. *Cerebral Cortex*, *25*(10), 3788–3801. http://doi.org/10.1093/cercor/bhu263

Hoshiyama, M., Kakigi, R., Koyama, S., Watanabe, S., & Shimojo, M. (1997). Activity in Posterior Parietal Cortex Following Somatosensory Stimulation in Man: Magnetoencephalographic Study Using Spatio-Temporal Source Analysis. *Brain Topography*, *10*(1), 23–30. http://doi.org/10.1023/A:1022206906360

Hsieh, L.-T., & Ranganath, C. (2014). Frontal midline theta oscillations during working memory maintenance and episodic encoding and retrieval. *NeuroImage*, *85 Pt 2*(0 2), 721–9. http://doi.org/10.1016/j.neuroimage.2013.08.003

Huang, J., Gamble, D., Sarnlertsophon, K., Wang, X., & Hsiao, S. (2012). Feeling Music: Integration of Auditory and Tactile Inputs in Musical Meter Perception. *PLoS ONE*, *7*(10), e48496. http://doi.org/10.1371/journal.pone.0048496

Hyun, J.-S., & Luck, S. J. (2007). Visual working memory as the substrate for mental rotation. *Psychonomic Bulletin & Review*, *14*(1), 154–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/17546746

Ishii, R., Canuet, L., Ishihara, T., Aoki, Y., Ikeda, S., Hata, M., … Takeda, M. (2014). Frontal midline theta rhythm and gamma power changes during focused attention on mental calculation: an MEG beamformer analysis. *Frontiers in Human Neuroscience*, *8*, 406. http://doi.org/10.3389/fnhum.2014.00406

Javitt, D. C., & Sweet, R. A. (2015). Auditory dysfunction in schizophrenia: integrating clinical and basic features. *Nature Reviews Neuroscience*, *16*(9), 535–550. http://doi.org/10.1038/nrn4002

Jeneson, A., & Squire, L. R. (2012). Working memory, long-term memory, and medial temporal lobe function. *Learning & Memory (Cold Spring Harbor, N.Y.)*, *19*(1), 15–25. http://doi.org/10.1101/lm.024018.111

Jensen, O., Kaiser, J., & Lachaux, J.-P. (2007). Human gamma-frequency oscillations associated with attention and memory. *Trends in Neurosciences*, *30*(7), 317–324. http://doi.org/10.1016/j.tins.2007.05.001

Jensen, O., & Mazaheri, A. (2010). Shaping Functional Architecture by Oscillatory Alpha Activity: Gating by Inhibition. *Frontiers in Human Neuroscience*, *4*, 186.

http://doi.org/10.3389/fnhum.2010.00186

Kaiser, J., & Lutzenberger, W. (2005). Cortical oscillatory activity and the dynamics of auditory memory processing. *Reviews in the Neurosciences*, *16*(3), 239–54. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16323563

Kaplan, R., Bush, D., Bonnefond, M., Bandettini, P. A., Barnes, G. R., Doeller, C. F., & Burgess, N. (2014). Medial prefrontal theta phase coupling during spatial memory retrieval. *Hippocampus*, *24*(6), 656–65. http://doi.org/10.1002/hipo.22255

Kayser, C., & Logothetis, N. K. (2009). Directed interactions between auditory and superior temporal cortices and their role in sensory integration. *Frontiers in Integrative Neuroscience*, *3*, 7. http://doi.org/10.3389/neuro.07.007.2009

Khader, P. H., Jost, K., Ranganath, C., & Rösler, F. (2010). Theta and alpha oscillations during working-memory maintenance predict successful long-term memory encoding. *Neuroscience Letters*, *468*(3), 339–43. http://doi.org/10.1016/j.neulet.2009.11.028

Kilner, J., Bott, L., & Posada, A. (2005). Modulations in the degree of synchronization during ongoing oscillatory activity in the human brain. *European Journal of Neuroscience*, *21*(9), 2547–2554. http://doi.org/10.1111/j.1460-9568.2005.04069.x

Kisley, M. A., & Cornwell, Z. M. (2006). Gamma and beta neural activity evoked during a sensory gating paradigm: effects of auditory, somatosensory and cross-modal stimulation. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology*, *117*(11), 2549–63. http://doi.org/10.1016/j.clinph.2006.08.003

Kiyonaga, A., & Egner, T. (2013). Working memory as internal attention: Toward an integrative account of internal and external selection processes. *Psychonomic Bulletin & Review*, *20*(2), 228–242. http://doi.org/10.3758/s13423-012-0359-y

Klimesch, W. (2012). Alpha-band oscillations, attention, and controlled access to stored information. *Trends in Cognitive Sciences*, *16*(12), 606–617. http://doi.org/10.1016/j.tics.2012.10.007

Klimesch, W., Sauseng, P., & Hanslmayr, S. (2007). EEG alpha oscillations: The inhibition–timing hypothesis. *Brain Research Reviews*, *53*(1), 63–88. http://doi.org/10.1016/j.brainresrev.2006.06.003

Koelewijn, T., Van Schie, H. T., Bekkering, H., Oostenveld, R., & Jensen, O. (2007). Motor-cortical beta oscillations are modulated by correctness of observed action. http://doi.org/10.1016/j.neuroimage.2007.12.018

Krause, C. M., Sillanmäki, L., Koivisto, M., Saarela, C., Häggqvist, A., Laine, M., & Hämäläinen, H. (2000). The effects of memory load on event-related EEG desynchronization and synchronization. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology*, *111*(11), 2071–8.

Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11068244

Ku, Y., Zhao, D., Hao, N., Hu, Y., Bodner, M., & Zhou, Y.-D. (2015). *Sequential Roles of Primary Somatosensory Cortex and Posterior Parietal Cortex in Tactile-visual Cross-modal Working Memory: A Single-pulse Transcranial Magnetic Stimulation (spTMS) Study*. *Brain Stimulation* (Vol. 8). Retrieved from http://www.sciencedirect.com/science/article/pii/S1935861X14003076

Lara, A. H., & Wallis, J. D. (2015). The Role of Prefrontal Cortex in Working Memory: A Mini Review. *Frontiers in Systems Neuroscience*, *9*, 173. http://doi.org/10.3389/fnsys.2015.00173

Lehtelä, L., Salmelin, R., & Hari, R. (n.d.). Evidence for reactive magnetic 10-Hz rhythm in the human auditory cortex. Retrieved from http://ac.els-cdn.com/S0304394097133614/1-s2.0-S0304394097133614-main.pdf?_tid=1f2a22d8-5055-11e7-90c6-00000aacb35e&acdnat=1497371398_a2b24b13c27a475c6a6297aa77e037d2

Leszczynski, M. (2011). How does hippocampus contribute to working memory processing? *Frontiers in Human Neuroscience*, *5*, 168. http://doi.org/10.3389/fnhum.2011.00168

Leszczyński, M., Fell, J., & Axmacher, N. (2015). Rhythmic Working Memory Activation in the Human Hippocampus. *Cell Reports*, *13*(6), 1272–1282. http://doi.org/10.1016/j.celrep.2015.09.081

Levy, D. A. (2012). Towards an understanding of parietal mnemonic processes: some conceptual guideposts. *Frontiers in Integrative Neuroscience*, *6*, 41. http://doi.org/10.3389/fnint.2012.00041

Li, D., Christ, S. E., & Cowan, N. (2014). Domain-general and domain-specific functional networks in working memory. *NeuroImage*, *102*, 646–656. http://doi.org/10.1016/j.neuroimage.2014.08.028

Lisman, J. (2005). The theta/gamma discrete phase code occuring during the hippocampal phase precession may be a more general brain coding scheme. *Hippocampus*, *15*(7), 913–922. http://doi.org/10.1002/hipo.20121

Lisman, J. E., & Jensen, O. (2013). The θ-γ neural code. *Neuron*, *77*(6), 1002–16. http://doi.org/10.1016/j.neuron.2013.03.007

Lopes da Silva, F. (2013). EEG and MEG: Relevance to Neuroscience. *Neuron*, *80*(5), 1112–1128. http://doi.org/10.1016/j.neuron.2013.10.017

Ludwig, S., Spitzer, B., Jacobs, A. M., Sekutowicz, M., Sterzer, P., & Blankenburg, F. (2016). Spectral EEG abnormalities during vibrotactile encoding and quantitative working memory processing in schizophrenia. *NeuroImage. Clinical*, *11*, 578–87. http://doi.org/10.1016/j.nicl.2016.04.004

Lundqvist, M., Rose, J., Herman, P., Brincat, S. L., Buschman, T. J., Miller, E. K., …

Ekstrom, A. D. (2016). Gamma and Beta Bursts Underlie Working Memory. *Neuron, 90*(1), 152–164. http://doi.org/10.1016/j.neuron.2016.02.028

M?ller, N., & Weisz, N. (2012). Lateralized Auditory Cortical Alpha Band Activity and Interregional Connectivity Pattern Reflect Anticipation of Target Sounds. *Cerebral Cortex, 22*(7), 1604–1613. http://doi.org/10.1093/cercor/bhr232

Maier, J. X., Chandrasekaran, C., & Ghazanfar, A. A. (2008). Integration of Bimodal Looming Signals through Neuronal Coherence in the Temporal Lobe. *Current Biology*, *18*(13), 963–968. http://doi.org/10.1016/j.cub.2008.05.043

Malmivuo, J. A., & Suihko, V. E. (2004). Effect of Skull Resistivity on the Spatial Resolutions of EEG and MEG. *IEEE Transactions on Biomedical Engineering, 51*(7), 1276–1280. http://doi.org/10.1109/TBME.2004.827255

Marchetti, G. (2014). Attention and working memory: two basic mechanisms for constructing temporal experiences. *Frontiers in Psychology*, *5*, 880. http://doi.org/10.3389/fpsyg.2014.00880

McCabe, D. P., Roediger, H. L., McDaniel, M. A., Balota, D. A., Hambrick, D. Z., & Hambrick, D. Z. (2010). The relationship between working memory capacity and executive functioning: evidence for a common executive attention construct. *Neuropsychology*, *24*(2), 222–43. http://doi.org/10.1037/a0017619

McLelland, D., VanRullen, R., Kubo, M., Diesmann, M., Aertsen, A., & Buzsaki, G. (2016). Theta-Gamma Coding Meets Communication-through-Coherence: Neuronal Oscillatory Multiplexing Theories Reconciled. *PLOS Computational Biology, 12*(10), e1005162. http://doi.org/10.1371/journal.pcbi.1005162

Miller, E. K., & Cohen, J. D. (2001). An Integrative Theory of Prefrontal Cortex Function. *Annual Review of Neuroscience, 24*(1), 167–202. http://doi.org/10.1146/annurev.neuro.24.1.167

Mima, T., Nagamine, T., Nakamura, K., & Shibasaki, H. (1998). Attention Modulates Both Primary and Second Somatosensory Cortical Activities in Humans: A Magnetoencephalographic Study. *Journal of Neurophysiology*, *80*(4). Retrieved from http://jn.physiology.org/content/80/4/2215.short

Mitchell, D. J., McNaughton, N., Flanagan, D., & Kirk, I. J. (2008). Frontal-midline theta from the perspective of hippocampal "theta." *Progress in Neurobiology*, *86*(3), 156–185. http://doi.org/10.1016/j.pneurobio.2008.09.005

Miyauchi, E., Kitajo, K., & Kawasaki, M. (2016). TMS-induced theta phase synchrony reveals a bottom-up network in working memory. *Neuroscience Letters*, *622*, 10–14. http://doi.org/10.1016/j.neulet.2016.04.008

Mognon, A., Jovicich, J., Bruzzone, L., & Buiatti, M. (n.d.). ADJUST: An automatic EEG artifact detector based on the joint use of spatial and temporal features. http://doi.org/10.1111/j.1469-8986.2010.01061.x

Mongillo, G., Barak, O., & Tsodyks, M. (2008). Synaptic Theory of Working Memory. *Science*, *319*(5869). Retrieved from http://science.sciencemag.org/content/319/5869/1543.full

Moore, B. C. J. (2013). *Basic aspects of hearing : physiology and perception*. Springer. Retrieved from https://books.google.it/books?id=fm20cAYBj2oC&pg=PA460&lpg=PA460&dq=auditory+tactile+integration+brain&source=bl&ots=7j9Sv_00V4&sig=SrWHuSjARuephnZnW1p_68Q_3KY&hl=de&sa=X&ved=0ahUKEwiVvNC6vZDUAhWDXBQKHQs4CTUQ6AEIfDAJ#v=onepage&q=auditory tactile integration brain&f=false

Nauhaus, I., Busse, L., Carandini, M., & Ringach, D. L. (2009). Stimulus contrast modulates functional connectivity in visual cortex. *Nature Neuroscience*, *12*(1), 70–76. http://doi.org/10.1038/nn.2232

Nieder, A. (2017). Magnitude Codes for Cross-Modal Working Memory in the Primate Frontal Association Cortex. *Frontiers in Neuroscience*, *11*, 202. http://doi.org/10.3389/fnins.2017.00202

Oberauer, K., & Hein, L. (2012). Attention to Information in Working Memory The Three-Embedded-Components Model of Working Memory. *Current Directions in Psychological Science*, *21*(3), 164–169. http://doi.org/10.1177/0963721412444727

Onton, J., Delorme, A., & Makeig, S. (2005). Frontal midline EEG dynamics during working memory. *NeuroImage*, *27*(2), 341–356. http://doi.org/10.1016/j.neuroimage.2005.04.014

Oostenveld, R., Fries, P., Maris, E., & Schoffelen, J.-M. (2011). FieldTrip: Open Source Software for Advanced Analysis of MEG, EEG, and Invasive Electrophysiological Data. *Computational Intelligence and Neuroscience*, *2011*, 1–9. http://doi.org/10.1155/2011/156869

Osipova, D., Takashima, A., Oostenveld, R., Fernandez, G., Maris, E., & Jensen, O. (2006). Theta and Gamma Oscillations Predict Encoding and Retrieval of Declarative Memory. *Journal of Neuroscience*, *26*(28), 7523–7531. http://doi.org/10.1523/JNEUROSCI.1948-06.2006

Pascual-Marqui, R. D. (2007). Discrete, 3D distributed, linear imaging methods of electric neuronal activity. Part 1: exact, zero error localization. Retrieved from http://arxiv.org/abs/0710.3341

Pasternak, T., & Greenlee, M. W. (2005). Working memory in primate sensory systems. *Nature Reviews Neuroscience*, *6*(2), 97–107. http://doi.org/10.1038/nrn1603

Peled, A., Geva, A. B., Kremen, W. S., Blankfeld, H. M., Esfandiarfard, R., & Nordahl, T. E. (2001). Functional connectivity and working memory in schizophrenia: an EEG study. *The International Journal of Neuroscience*, *106*(1-2), 47–61. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11264908

Percival, D. B., & Walden, A. T. (1993). *Spectral analysis for physical applications : multitaper and conventional univariate techniques*. Cambridge University Press. Retrieved from https://books.google.it/books/about/Spectral_Analysis_for_Physical_Applicati.html?id=86IOtxblyQcC&redir_esc=y

Pfurtscheller, G. (2001). Functional brain imaging based on ERD/ERS. *Vision Research*, *41*(10-11), 1257–1260. http://doi.org/10.1016/S0042-6989(00)00235-2

Prueckl, R., Kapeller, C., Kamada, K., Takeuchi, F., Ogawa, H., Scharinger, J., & Guger, C. (2015). Distinction of individual finger responses in somatosensory cortex using ECoG high-gamma activation mapping. In *2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)* (pp. 5760–5763). IEEE. http://doi.org/10.1109/EMBC.2015.7319701

Quak, M., London, R. E., & Talsma, D. (2015). A multisensory perspective of working memory. *Frontiers in Human Neuroscience*, *9*, 197. http://doi.org/10.3389/fnhum.2015.00197

Raghavachari, S., Lisman, J. E., Tully, M., Madsen, J. R., Bromfield, E. B., & Kahana, M. J. (2006). Theta Oscillations in Human Cortex During a Working-Memory Task: Evidence for Local Generators. *Journal of Neurophysiology*, *95*(3). Retrieved from http://jn.physiology.org/content/95/3/1630

Rawley, J. B., & Constantinidis, C. (2009). Neural correlates of learning and working memory in the primate posterior parietal cortex. *Neurobiology of Learning and Memory*, *91*(2), 129–38. http://doi.org/10.1016/j.nlm.2008.12.006

Riley, M. R., & Constantinidis, C. (2016). Role of Prefrontal Persistent Activity in Working Memory. *Frontiers in Systems Neuroscience*, *9*, 181. http://doi.org/10.3389/fnsys.2015.00181

Romo, R., Brody, C. D., Hernández, A., & Lemus, L. (1999). Neuronal correlates of parametric working memory in the prefrontal cortex. *Nature*, *399*(6735), 470–473. http://doi.org/10.1038/20939

Ros, T., J. Baars, B., Lanius, R. A., & Vuilleumier, P. (2014). Tuning pathological brain oscillations with neurofeedback: a systems neuroscience framework. *Frontiers in Human Neuroscience*, *8*, 1008. http://doi.org/10.3389/fnhum.2014.01008

Roux, F., Uhlhaas, P. J., Baddeley, A., Wager, T. D., Smith, E. E., Luck, S. J., … al., et. (2014). Working memory and neural oscillations: alpha–gamma versus theta–gamma codes for distinct WM information? *Trends in Cognitive Sciences*, *18*(1), 16–25. http://doi.org/10.1016/j.tics.2013.10.010

Roux, F., Wibral, M., Mohr, H. M., Singer, W., & Uhlhaas, P. J. (2012). Gamma-Band Activity in Human Prefrontal Cortex Codes for the Number of Relevant Items Maintained in Working Memory. *Journal of Neuroscience*, *32*(36), 12411–12420. http://doi.org/10.1523/JNEUROSCI.0421-12.2012

Sacchet, M. D., LaPlante, R. A., Wan, Q., Pritchett, D. L., Lee, A. K. C., Hämäläinen, M., … Jones, S. R. (2015). Attention drives synchronization of alpha and beta rhythms between right inferior frontal and primary sensory neocortex. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *35*(5), 2074–82. http://doi.org/10.1523/JNEUROSCI.1292-14.2015

Sauseng, P., Klimesch, W., Doppelmayr, M., Pecherstorfer, T., Freunberger, R., & Hanslmayr, S. (2005). EEG alpha synchronization and functional coupling during top-down processing in a working memory task. *Human Brain Mapping*, *26*(2), 148–155. http://doi.org/10.1002/hbm.20150

Schoffelen, J.-M., & Gross, J. (2009). Source connectivity analysis with MEG and EEG. *Human Brain Mapping*, *30*(6), 1857–1865. http://doi.org/10.1002/hbm.20745

Senkowski, D., Molholm, S., Gomez-Ramirez, M., & Foxe, J. J. (2005). Oscillatory Beta Activity Predicts Response Speed during a Multisensory Audiovisual Reaction Time Task: A High-Density Electrical Mapping Study. *Cerebral Cortex*, *16*(11), 1556–1565. http://doi.org/10.1093/cercor/bhj091

Sesack, S. R., Deutch, A. Y., Roth, R. H., & Bunney, B. S. (1989). Topographical organization of the efferent projections of the medial prefrontal cortex in the rat: An anterograde tract-tracing study withPhaseolus vulgaris leucoagglutinin. *The Journal of Comparative Neurology*, *290*(2), 213–242. http://doi.org/10.1002/cne.902900205

Shaw, J. C. (John C. (2003). *The brain's alpha rhythms and the mind : a review of classical and modern studies of the alpha rhythm component of the electroencephalogram with commentaries on associated neuroscience and neuropsychology*. Elsevier.

Simson, R., Vaughan, H. G., & Ritter, W. (1977). The scalp topography of potentials in auditory and visual discrimination tasks. *Electroencephalography and Clinical Neurophysiology*, *42*(4), 528–535. http://doi.org/10.1016/0013-4694(77)90216-4

Spitzer, B., & Blankenburg, F. (2012). Supramodal Parametric Working Memory Processing in Humans. *Journal of Neuroscience*, *32*(10). Retrieved from http://www.jneurosci.org/content/32/10/3287

Spitzer, B., Wacker, E., & Blankenburg, F. (2010). Oscillatory Correlates of Vibrotactile Frequency Processing in Human Working Memory. *Journal of Neuroscience*, *30*(12). Retrieved from http://www.jneurosci.org/content/30/12/4496.short

Stipacek, A., Grabner, R. H., Neuper, C., Fink, A., & Neubauer, A. C. (2003). *Sensitivity of human EEG alpha band desynchronization to different working memory components and increasing levels of memory load*. *Neuroscience Letters* (Vol. 353). Retrieved from http://www.sciencedirect.com/science/article/pii/S0304394003011352

Supèr, H., Spekreijse, H., & Lamme, V. A. F. (2001). A Neural Correlate of Working Memory in the Monkey Primary Visual Cortex. *Science*, *293*(5527). Retrieved from http://science.sciencemag.org/content/293/5527/120

Tallon-Baudry, C., Bertrand, O., Peronnet, F., & Pernier, J. (1998). Induced γ-Band Activity during the Delay of a Visual Short-Term Memory Task in Humans. *Journal of Neuroscience*, *18*(11). Retrieved from http://www.jneurosci.org/content/18/11/4244.long

Teplan, M. (2002). FUNDAMENTALS OF EEG MEASUREMENT. *MEASUREMENT SCIENCE REVIEW*, *2*(2). Retrieved from http://www.edumed.org.br/cursos/neurociencia/MethodsEEGMeasurement.pdf

Tesche, C. D., & Karhu, J. (2000). Theta oscillations index human hippocampal activation during a working memory task. *Proceedings of the National Academy of Sciences of the United States of America*, *97*(2), 919–24. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10639180

van Ede, F., Szebényi, S., & Maris, E. (2014). Attentional modulations of somatosensory alpha, beta and gamma oscillations dissociate between anticipation and stimulus processing. *NeuroImage*, *97*, 134–141. http://doi.org/10.1016/j.neuroimage.2014.04.047

Vergara, J., Rivera, N., Rossi-Pool, R., & Romo, R. (2016). A Neural Parametric Code for Storing Information of More than One Sensory Modality in Working Memory. *Neuron*, *89*(1), 54–62. http://doi.org/10.1016/j.neuron.2015.11.026

Vertes, R. P. (2005). Hippocampal theta rhythm: A tag for short-term memory. *Hippocampus*, *15*(7), 923–935. http://doi.org/10.1002/hipo.20118

Vinck, M., Oostenveld, R., van Wingerden, M., Battaglia, F., & Pennartz, C. M. A. (2011). An improved index of phase-synchronization for electrophysiological data in the presence of volume-conduction, noise and sample-size bias. *NeuroImage*, *55*(4), 1548–65. http://doi.org/10.1016/j.neuroimage.2011.01.055

Yuvaraj, R., Murugappan, M., Ibrahim, N. M., Omar, M. I., Sundaraj, K., Mohamad, K., … Satiyan, M. (n.d.). On the analysis of EEG power, frequency and asymmetry in Parkinson's disease during emotion processing. http://doi.org/10.1186/1744-9081-10-12

Zaepffel, M., Trachel, R., Kilavik, B. E., Brochier, T., & Dijkerman, H. (2013). Modulations of EEG Beta Power during Planning and Execution of Grasping Movements. *PLoS ONE*, *8*(3), e60060. http://doi.org/10.1371/journal.pone.0060060

Zanto, T. P., Rubens, M. T., Thangavel, A., & Gazzaley, A. (2011). Causal role of the prefrontal cortex in top-down modulation of visual processing and working memory. Nature Publishing Group, 14. http://doi.org/10.1038/nn.2773