

DISSERTATION

How Brain Rhythms Guide Memory and Decisions

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Abstract

In our daily lives we are faced with thousands of decisions: from complex ‘should I cross while it’s on a red light?’, to abstract ‘do I spell color with o or ou?’, to sensory dominated questions like ‘did my phone just vibrate?’. To navigate all of these different types of decisions, the brain has to incorporate a plethora of information from sensory and memory systems, requiring many neuronal populations from distinct cortical areas to work together. Neuroscientists posit that cortical oscillations play an important part in this process. I investigated the role of such cortical rhythms for the short retention of information in working memory and decision making with three experimental studies.

In all experiments, participants were asked to compare two sequentially presented stimuli. To solve this task, the first stimulus has to be kept in memory for a short while and is then compared to the second. While participants held the first stimulus in memory, magneto- and electroencephalographic recordings revealed a parametric modulation of parietal and prefrontal beta oscillations with the to-be-remembered stimulus feature. At the same time, we observed a previously unknown prefrontal gamma power decrease that was negatively correlated with the beta band effects. Therefore we suspect that there is a fronto-parietal network that communicates in these two frequency bands during working memory. In addition, we found decision-related activity in premotor beta power that encoded participants’ choices 0.7 seconds before they enacted their responses. Moreover, we also found a well-known parietal signal, which tracked the evolution of the decision over time. Interestingly, this signal was modulated by the difficulty of the decisions, indicating that present theories about perceptual decision making need to be extended.

Zusammenfassung

Der Mensch trifft täglich tausende Entscheidungen, von komplexen („Gehe ich über die rote Ampel?“), über abstrakte („Buchstabiere ich Foto mit F oder Ph?“), zu sensorisch geprägten („Hat mein Telefon gerade vibriert?“). Das Gehirn muss dabei flexibel auf eine Vielzahl von sensorischen Reizen und Entscheidungstypen reagieren. Um dies zu ermöglichen, arbeiten viele Neurone in ganz unterschiedlichen kortikalen Arealen zusammen. Neurowissenschaftler vermuten, dass kortikale Oszillationen dabei eine zentrale Rolle spielen. Sie reflektieren das Zusammenwirken vieler Neurone und werden zur Kommunikation neuronaler Populationen genutzt. In der vorliegenden Arbeit wurde die Rolle einzelner Rhythmen für das kurzfristige Speichern von Informationen im Arbeitsgedächtnis, sowie das Treffen von Entscheidungen untersucht.

Dieser Dissertation liegen drei Studien zugrunde, im Rahmen derer Versuchspersonen zwei nacheinander dargebotene Stimuli vergleichen sollten. Um diese Aufgabe zu bewältigen, muss der erste Stimulus kurz im Gedächtnis behalten werden. Dann kommt es zur eigentlichen Entscheidung, dem Abgleich der beiden Stimuli. Bei diesem Versuch konnten wir mit Hilfe von Magneto- und Elektroenzephalographie Oszillationen messen, die sich mit den Stimuluseigenschaften veränderten. Arbeitsgedächtnisprozesse waren dabei mit Beta-Oszillationen assoziiert. Insbesondere zeigten sich parietale und präfrontale Beta-Oszillationen, die mit Gamma-Oszillationen im präfrontalen Kortex zusammenspielten. Daher vermuten wir, dass ein fronto-parietales Netzwerk für das Behalten von Stimulus-Information von Bedeutung ist und diskutieren im Folgenden zugrundeliegende Mechanismen. Außerdem konnten wir während des Treffens von Entscheidungen prämotorische Beta-Oszillationen messen, die 0,7 Sekunden vor der Antwort der Versuchsteilnehmer die Entscheidung reflektierten. Darüber hinaus zeigten sich auch bekannte parietale Signale, die den Prozess der Entscheidungsfindung abbildeten. Interessanterweise waren diese Signale vom Schwierigkeitsgrad der Aufgabe abhängig. Dies spricht dafür, dass aktuelle Theorien zu neuronalen Grundlagen der Entscheidungsfindung ergänzt werden müssen.

Abbreviations

- BA Brodmann area
BOLD blood-oxygen-level dependent
CPP centro-parietal positivity
DDM drift-diffusion model
EEG electroencephalography
ERP event related potential
*f*1/*f*2 vibrotactile stimulus 1 / 2
FEF frontal eye fields
fMRI functional magnetic resonance imaging
IFG inferior frontal gyrus
IPL intraparietal lobule
IPS intraparietal sulcus
LIP lateral intraparietal area
MI primary motor cortex
MVPA multivariate pattern analysis
MEG magnetoencephalography
PFC prefrontal cortex
PMC premotor cortex
PPC posterior parietal cortex
RDM random-dot motion
RF receptive field
SI primary somatosensory cortex
SII secondary somatosensory cortex
*S*1/*S*2 RDM stimulus 1 / 2
SC superior colliculus
SDT signal detection theory
SFC sequential frequency comparison
SSEP/F steady-state evoked potential/field
TMS transcranial magnetic stimulation
WM working memory

List of Original Articles

This dissertation is based on the following peer-reviewed articles:

von Lautz AH, Herding J, Ludwig S, Nierhaus T, Maess B, Villringer A and Blankenburg F (2017): Gamma and Beta Oscillations in Human MEG Encode the Contents of Vibrotactile Working Memory. *Front. Hum. Neurosci.* 11:576. doi: 10.3389/fnhum.2017.00576

Herding J, Ludwig S, **von Lautz AH**, Spitzer B and Blankenburg F (under review): Centro-parietal EEG potentials index subjective evidence and difficulty during perceptual decision making. *Neuroimage*

von Lautz AH, Herding J and Blankenburg F (under review): Neuronal Signatures of a Random-Dot Motion Comparison task. *Neuroimage*

Introduction

In this particularly hot summer it is not beyond imagination that you choose to buy a watermelon from a small stand on the way home. Of course, you wish to buy not any watermelon, but a ripe and juicy one. According to humourist literature ("fixating the melon's secret", Kishon & Labatzke, 1975) the procedure of selecting a ripe and juicy melon consists of looking, feeling, smelling, and listening for a hollow sound and then comparing these features to another watermelon. Moreover, if the quality of tested watermelons doesn't suit you, you go to the next stand and try the ones there. This example encompasses several features of typical decision-making tasks used in neuroscience. To find just the right watermelon you need to *perceive* the colour, texture, smell, and sound. Then, you must keep this information for a short while in *memory* before testing the subsequent watermelon. Finally, you are tasked with judging which one was better: *making a decision*. Neuroscientists use such tasks in simple form to have control about the mental steps necessary to correctly solve this problem. For example, they would typically let participants only see the melons and let them decide between two, a challenge called 'sequential comparison task'. Or an experimenter would give participants the job of testing watermelons from multiple stands and deciding whether they were of good or poor quality. In this case, a person would need to *sequentially sample* watermelons up until she is confident that the particular stand sells good- or poor-quality fruit. In contrast with the study of psychophysics, which tests only the behaviour of participants, neuroscientists typically also record signals from the brain during such tasks and try to determine the neural basis of each mental step (e.g., *perceiving, memory, making a decision*).

In the present thesis, I will introduce how neuroscientists study such decisions in humans and other species. I will describe major lines of research investigating the neural substrates of the outlined mental steps using two well-studied experimental paradigms that fit to the aforementioned watermelon selection: sequential comparison and sequential sampling tasks. Then I will present my contribution to this field of research in the form of three

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studies that provide new insights into human working memory and decision making with magneto- and electroencephalography (M/EEG). Subsequently, I will link my findings to the larger context of current research and point to future avenues.

1.1 Researching perceptual decision making

The study of human decisions has a long history reaching back to ancient Greece (Aristotle, 1987; Epicurus, 1940). Whereas Greek philosophers argued for a nonmaterial soul determining all behaviour, the Enlightenment challenged this view and in particular Descartes (1649) advocated a dualist approach, where simple motor behaviours could be explained by actions of the material body (Descartes & Hall, 1664; Descartes & Monnoyer, 1988). In the 19th century Gustav Fechner went one step further and used empirical methods (Bacon, 1620) to unite behavioural measures with subjective, individual perception (Fechner, 1860). Similar to my introductory task with watermelons, Fechner tasked volunteers to lift two weights in succession and questioned them which was heavier, a sequential comparison task. This simple task provides a powerful tool to study human behaviour, because it allows to control an objective stimulus variable – the weight – and observe subjective perceptual differences between stimuli. Using this approach, Fechner was able to describe a logarithmic mapping between the physical magnitude of a stimulus and the extend of sensation it produces, the Weber-Fechner law that gave first insights into possible constraints of how information is processed by humans. Psychophysics, as Fechner called his mathematical descriptions of human psychology, has been aided in the study of the human brain by the invention of signal detection theory (SDT). Originally used to classify the detection of weak signals, the SDT proposes that an observer can respond to a stimulus in four ways: detect (hit), not detect (miss), detect the absence (correct reject), erroneously detect (false alarm). The advantage over conventional methods of only analysing hits and misses is that the SDT assumes an internal measurement of the stimulus feature that is proportional to the actual feature but includes noise. Therefore, also correct rejections and false alarms provide evidence for the internal measurement. The decision process for a

given stimulus can be modelled as taking a sample of two overlapping noisy (gaussian) distributions and applying a simple criterion. Most notably for the present thesis, we can take multiple samples from a stimulus over time and get ever-improving estimates of whether the stimulus belongs in one or the other part of the two overlapping distributions. Conceptually, this can be seen as accumulating evidence before applying a criterion. In the context of decision making studies, the internal measurement that we take for a stimulus is often referred to as a decision variable (DV). This DV has been linked closely to neuroscience, because an area involved in decision making should exhibit neural activity that correlates with the DV throughout an experimental task (Gold & Shadlen, 2007; Tanner & Swets, 1954). Experiments therefore are usually optimized to separate the mental steps involved in the decision processes in time or include only one stimulus feature that has to be detected by accumulating evidence. In the following, I will introduce results from two of the most common experiments operationalized to investigate the neural activity underlying decision making.

1.2 Sequential comparison tasks

Sequential comparison tasks, as Fechner used, are still an important tool to study psychophysics and have had a great impact onto neuroscience when used in conjunction with measurements of neural responses from the brain of primates and rodents. Mountcastle, Talbot, Sakata, and Hyvärinen (1969) were first to train monkeys in a vibrotactile version of this task, termed sequential frequency comparison (SFC) task, and recorded neural data (Mountcastle, Steinmetz, & Romo, 1990; Mountcastle, Talbot, Dar-Smith, & Kornhuber, 1967). In this setup (figure 1.1), a subject is presented with two vibrotactile frequencies in the flutter range (5-50 Hz), namely frequency 1 (f_1) and frequency 2 (f_2). The task is to decide whether the second (f_2) frequency is higher or lower than the first (f_1). To solve this challenge the subject must sequentially go through cognitive processes that are classically split into four parts. First, f_1 is perceived. Second, f_1 is being kept in memory, while the subject waits for the subsequent stimulus. Third, f_1 is compared with

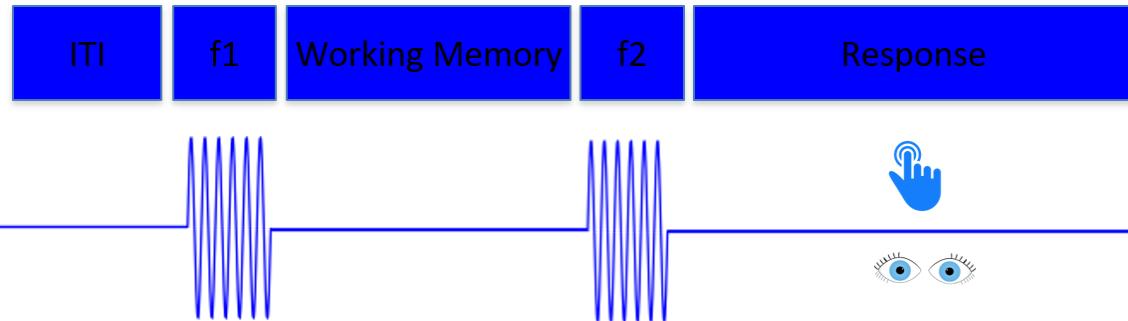


Figure 1.1: Sequential frequency comparison (SFC) task. Two vibrotactile frequencies are presented to the index finger in succession, f_1 and f_2 . The task is to decide whether f_2 is larger than f_1 or vice-versa. Between f_1 and f_2 is a working memory interval in which the frequency of the first stimulus has to be retained. After perception of f_2 , responses are made, typically via button press or saccade.

the perception of f_2 , thereby forming a decision. Fourth, the subject reports the choice, usually by pressing a button or enacting a saccade to a choice-specific visual target.

1.2.1 Sequential comparison tasks: perception

Perception of the first stimulus drives quickly adapting (QA) neurons in Brodmann areas 1 and 3b of the contralateral primary somatosensory cortex (SI). These neurons receive afferent signals from mechanoreceptors in the skin, which are routed via the Thalamus and are closely interconnected (Merzenich & Harrington, 1969; Mountcastle et al., 1967; Talbot & Mountcastle, 1968). The majority of monkey SI neurons align their spiking activity to the periodicity of the stimulus, which can also be observed in human M/EEG as steady-state evoked potentials/fields (SSEP/F) (Mountcastle et al., 1990; Nangini, Ross, Tam, & Graham, 2006; Tobimatsu, Zhang, & Kato, 1999). Moreover, a portion of S1 neurons increase their firing rate monotonically with increasing vibrotactile frequency (Hernández et al., 2010; Hernández, Zainos, & Romo, 2000; Lemus, Hernández, Luna, Zainos, & Romo, 2010; Luna, Hernández, Brody, & Romo, 2005; Salinas, Hernández, Zainos, & Romo, 2000). Notably, only those QA neurons that modulate their firing rates by the vibrotactile frequency showed differential patterns in error trials, indicating that the brain uses these neurons to inform behaviour (Salinas et al., 2000). Therefore, it is well-established that the firing rates and the rhythmic SSEF/Ps observed with M/EEG represent the encoding of

sensory evidence on which later decisions are based. Interestingly, the firing rate predicts the monkeys' behaviour better than the periodicity of the neural responses and while periodicity is high in SI, it is almost absent in SII, speaking against a communication mechanism through periodic firing as would be predicted from SSEF/Ps (Hernández et al., 2000; Luna et al., 2005; Salinas et al., 2000). An alternative possibility is that QA neurons encode stimuli by the number of discrete bursts of spikes instead of single spikes. Such a coding scheme has been observed in visual tasks and has been suggested to efficiently encode stimulus features (Kepecs & Lisman, 2003; Kepecs, Wang, & Lisman, 2002; Krahe & Gabbiani, 2004; Reinagel, Godwin, Sherman, & Koch, 1999; Romo & de Lafuente, 2013). Notably, because other relevant monkey work has focused on bursts (e.g., Lundqvist et al., 2016), the stimulation times extend beyond the time of a burst in these vibrotactile studies (always 500ms) and therefore a code based on spikes is indistinguishable to one based upon bursts (Romo & de Lafuente, 2013). However, it remains unclear if bursting covaries with behavioural performance on a trial-by-trial level as has been observed for spikes (Luna et al., 2005). Regardless whether bursting or spiking underlies an encoding by rate, such a code could be positively or negatively correlated in upstream areas, as is observed throughout the sensorimotor hierarchy in this task including SII, prefrontal and motor cortices (Hernández et al., 2010; Salinas et al., 2000).

1.2.2 Sequential comparison tasks: working memory

Such a dual rate code, with populations either increasing or decreasing with stimulus frequencies, was also observed in the absence of stimulation: during the short retention interval between f_1 and f_2 . In particular, Romo, Brody, Hernández, and Lemus (1999) recorded from the inferior convexity of the prefrontal cortex and identified neurons whose firing rate changed monotonically with the vibrotactile frequency held in working memory (WM). Visual tasks have long associated sustained prefrontal firing with WM (Funahashi, Bruce, & Goldman-Rakic, 1989; Fuster & Alexander, 1971; Goldman-Rakic, 1995), however, this study demonstrates that the contents of WM can directly map onto firing rate changes in single neurons. Further analyses indicate that the representation of stimulus information

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by population dynamics of prefrontal neurons degrades after stimulus presentation, but re-emerges with different tunings towards the end of the working memory delay (Barak, Tsodyks, & Romo, 2010). This is particularly interesting, because it challenges the view that WM is encoded in sustained firing throughout delay periods, with biophysically plausible alternatives both in rhythmicity (Fiebig & Lansner, 2017; Lundqvist, Herman, Warden, Brincat, & Miller, 2018; Lundqvist et al., 2016) and synaptic changes (Mongillo, Barak, & Tsodyks, 2008; Stokes, 2015). This current high-level debate (for either side, see: Constantinidis et al., 2018; Lundqvist, Herman, & Miller, 2018) is so interesting for vibrotactile SFC studies, because firing rates directly represent the contents of WM, not overall changes. Recent evidence, however, suggests that both single neurons and populations may be responsible for WM in this task. Haegens, Vergara, Rossi-Pool, Lemus, and Romo (2017) recorded local field potentials (LFPs), which reflect local neuronal ensembles, and single neurons from monkey premotor cortex during a multimodal version of the SFC task. They found a modulation of LFP beta oscillations reflecting the stimulus features during WM. In addition, premotor spike-field coherence with the beta band was also related to the stimulus features, indicating a tuning of firing rate to this rhythm. These findings suggest that both population-related beta modulations and the closely affiliated spike activity encode the contents of WM.

This close coupling of beta oscillations with spiking activity underlying tactile WM has also been suspected from a series of EEG studies. Spitzer, Wacker, and Blankenburg (2010) gave human volunteers a similar SFC task and found a parametric modulation of the beta band in the right inferior frontal gyrus (IFG), suggesting that both monkey and human prefrontal cortices (PFC) exhibit content-specific activity during WM. In a follow-up study, Spitzer and Blankenburg (2011) demonstrated that this prefrontal activity was independent of encoding processes, by retro-cueing to one of two presented vibrotactile stimuli. Furthermore, Spitzer and Blankenburg (2012) hypothesized that this parametric encoding of abstract magnitudes was supramodal. In addition to the tactile task, they implemented a sequential visual flicker and a sequential acoustic flutter comparison task. Across all these modalities, prefrontal beta power monotonically encoded the frequency

information of the stimulus. However, this parametric code consists of a monotonic increase in beta power with the vibrotactile stimulus held in working memory and did not exhibit the negative component of a dual code as had been observed in monkey PFC (Romo et al., 1999). Because the precise link between the large-scale signals recorded with EEG and single neuron firing rates are poorly understood, it remains unclear whether the difference in power reflects a population imbalance of the dual code observed in monkeys, where about 60% of modulated neurons reflected a monotonic increase (Romo et al., 1999; Spitzer et al., 2010). This is of particular note, because working memory has been associated with sustained firing rates in the PFC (Funahashi et al., 1989; Fuster & Alexander, 1971; Goldman-Rakic, 1995; Pasternak & Greenlee, 2005) and gamma, not beta, appears to be closely related to neural firing rates even when recorded with surface EEG (Whittingstall & Logothetis, 2009). However, increases in gamma activity during working memory do not necessarily reflect sustained firing rates, but a more dynamic system of neural firing patterns (Cromer, Roy, & Miller, 2010; Durstewitz & Seamans, 2006; Shafi et al., 2007; Stokes et al., 2013). Indeed, recent monkey recordings revealed a pattern of brief gamma bursts accompanying encoding and re-activation of stimulus information while beta bursts reflected a default state of maintenance that was interrupted by gamma (Lundqvist et al., 2016). Notably, it is quite possible that such short gamma bursts have been averaged out of datasets by summation over multiple trials to increase the signal to noise ratio in previous human recordings (Stokes & Spaak, 2016). Furthermore, during EEG recordings the skull acts as a low-pass filter (Pfurtscheller & Cooper, 1975), making it difficult to pick up on gamma oscillations. The only MEG study investigating gamma in an SFC task, found overall gamma increases in SI, SII and frontal cortices during working memory, but did not investigate the parametric encoding of stimulus features (Haegens, Osipova, Oostenveld, & Jensen, 2010). Therefore, it remains an open question how the parametric beta band modulations observed by Spitzer and colleagues are associated with dynamic changes in gamma frequencies.

1.2.3 Sequential comparison tasks: decision making

The next part of the SFC task, comparing f_1 and f_2 to form a decision is associated with neural firing in premotor cortices (PMC) that are modulated by subtracting f_1 from f_2 (Hernández et al., 2010; Hernández, Zainos, & Romo, 2002; Jun et al., 2010; Romo, Hernández, & Zainos, 2004), which has also been observed in SII (Romo, Hernández, Zainos, Lemus, & Brody, 2002). Notably, the decisions were indicated by button press and therefore likely associated with PMC rather than with FEF when responses are indicated with saccades (see also Gold & Shadlen, 2007). Underlining this function, the PMC firing rates were modulated reversely during incorrect trials, indicating that they followed the monkey's choice rather than the physical attributes of the stimuli (Hernández et al., 2002; Romo et al., 2004). Most interestingly, because the retention of vibrotactile stimuli was associated with beta power in humans (Spitzer et al., 2010), Haegens, Nacher, Luna, Romo, and Jensen (2011) recorded local field potentials (LFPs) from monkey PMC and found that beta band power reflected the difference between f_2 and f_1 . Importantly, when monkeys were instructed to respond independent of the task, neural firing and beta LFPs were not modulated by the decision process in PMC (see also Haegens et al., 2017). These findings in monkeys correspond well to recent EEG studies extending a role of the beta band for decision making to humans during this task (Herding, Ludwig, & Blankenburg, 2017; Herding, Spitzer, & Blankenburg, 2016). Agreeing with Haegens et al. (2011), Herding et al. (2016) demonstrated that beta band power in premotor areas was modulated by participants' choices, always with the decision outcome $f_2 > f_1$ resulting in a larger beta response than the outcome $f_2 < f_1$. These same findings were replicated for saccade responses, and in line with an intentional framework for decision making (Shadlen, Kiani, Hanks, & Churchland, 2008), the beta modulation was source localized to the FEF instead of PMC (Herding et al., 2017). Moreover, these studies used Bayesian modelling of participants' behaviour to estimate the subjective contribution of beta to choices, revealing both a clear pattern of beta invariant to the response mapping (index/middle finger) and a scaling by choice even when trials were incorrect. Yet, it remains unclear whether this choice-related beta band effect in the EEG extends beyond somatosensory processing,

which has been associated closely with this frequency band (Pfurtscheller, 1981).

Building upon this finding of choice-related beta modulation, Ludwig, Herding, and Blankenburg (2018) added a response delay to this task, in which the response mapping was not provided. With this slight change in setup, they found an almost identical beta band effect in the posterior parietal cortex (PPC), but not in premotor areas. This indicates that premotor areas are only directly involved in the decision process when the decision outcome is known. The PPC on the other hand appears to fulfil an effector-unspecific role and might have a more general role in the decision process. This is particularly interesting, because another parietal signal, the classic P300 (Chapman & Bragdon, 1964; Sutton, Braren, Zubin, & John, 1965), has long been associated with decision making (Donchin & Cohen, 1967; Rohrbaugh, Donchin, & Eriksen, 1974). More so, the P300, recently also termed centro-parietal positivity (CPP - more on it later), has been theorized not to reflect a unitary neural event after stimulus onset, but a dynamically changing neural signature of making a decision over time (Twomey, Murphy, Kelly, & O'Connell, 2015). Thus, the question remains how the choice related beta band effect in SFC tasks relates to decision signals in other paradigms, specifically the CPP and beta-gamma modulations observed with MEG in accumulation of evidence tasks (Donner, Siegel, Fries, & Engel, 2009; Donner et al., 2007; Kelly & O'Connell, 2013, 2015; O'Connell, Dockree, & Kelly, 2012; Philiastides, Heekeren, & Sajda, 2014; Twomey, Kelly, & O'Connell, 2016; Twomey et al., 2015)

1.3 Accumulation of evidence tasks

The other line of research I want to introduce builds also on Fechner's work on psychophysics, and in particular is the result of his legacy in mathematical psychology that drove ever-improving accounts of choice behaviour throughout the 20th century. This led to the development of signal detection theory, which as previously mentioned, has the advantage of taking into account noise behaviour and the structure of incorrect trials (Tanner & Swets, 1954). Neuroscientific experiments have used this theory to model perceptual

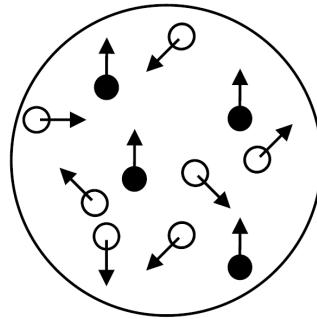


Figure 1.2: Example of random-dot motion kinematogram. The white dots represent the dots moving randomly, the black ones the coherently moving dots. The task is usually to detect coherent motion, varying the number of coherently moving dots determines the difficulty and time needed to perform the judgement.

decision making as a process of sequential sampling that results in an accumulation of evidence for a decision. Underlying this model is the idea that a decision variable (DV) represents the set of all evidence for a decision and for binary choices modern models posit a single mechanism that accumulates evidence over time for one choice over another (Shadlen & Kiani, 2013). For example, in our introductory example when we strive to find a good watermelon stand, we would sample melons from one stand sequentially, until we are sure the stand sells fruit of high or low quality. Every time we try a fruit, we would get a piece of evidence in favour of one possible choice, which over time accumulates to inform a decision – typically modelled as crossing an absolute bound. The neuroscientific hypothesis is that one decision variable tracks the current state of such evidence accumulation and that we can observe such a variable in the brain.

To track this neural correlate of perceptual decision making, neuroscientists have used predominantly one decision making task: the random-dot motion (RDM) direction discrimination. In the RDM task (figure 1.2) participants are shown dots on a monitor that move around. A portion of these dots move coherently in the same direction and the challenge is to detect this movement. Because the number of dots moving coherently is typically low and movement can only be spotted through a change over time, the perceptual challenge is usually difficult, and it can take between a few hundred milliseconds to seconds to detect the motion. Moreover, because the dots typically move randomly, it is possible to perceive a wrong direction.

This task is particularly powerful for psychophysics, because it requires no distinct working memory process and it lends itself well to be modelled as an accumulation-to-bound process (O'Connell, Shadlen, Wong-Lin, & Kelly, 2018). In such models it is assumed that subjects continuously sample from the dot-motion stimulus, perceive the motion direction of individual dots and accumulate evidence for one direction over time. When participants have a level of confidence in the direction, the decision bound is crossed and the decision communicated. This is usually done in monkey experiments by eye movements. The model can be further simplified by having the subjects decide between two opposite directions that are known in advance, thus becoming a binary accumulation process. Notably, because choices are typically indicated by performing a saccade to one of two targets associated with the choices, the decision process can be treated as a process of movement selection. Therefore, beyond motion sensitive neurons in MT/V5, recordings are primarily carried out in those areas associated with motor preparation and eye-movement execution, resulting in neural correlates of a decision variable in the superior colliculus (SC), frontal eye fields (FEF), lateral intraparietal area (LIP) and the dorsolateral prefrontal cortex (DLPFC) (for review see Gold & Shadlen, 2007).

1.3.1 Accumulation of evidence tasks with nonhuman primates

Employing the RDM task while recording from macaques, Britten, Shadlen, Newsome, and Movshon (1992) were able to link a small set of middle temporal visual area (MT/V5) neurons to concurrent choice behaviour. Even when the coherence was at 0% and all dots were moving randomly, MT firing rates predicted choices significantly (Britten, Newsome, Shadlen, Celebrini, & Movshon, 1996). Motion sensitive neurons in area MT are well-known to respond strongly to visual stimuli moving in a particular direction, exhibiting tuning to stimuli moving through their receptive fields (Baker, Petersen, Newsome, & Allman, 1981; Van Essen, Maunsell, & Bixby, 1981; Zeki, 1974, 1980). Using this knowledge of systematic motion direction organization in MT, microstimulation has been used to successively activate motion direction specific systems, thereby demonstrating a causal relationship of MT neurons for task performance (Ditterich, Mazurek, & Shadlen, 2003;

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Salzman, Britten, & Newsome, 1990; Salzman, Murasugi, Britten, & Newsome, 1992). Most interestingly, when using a version of the RDM task with the opportunity to respond as soon as possible, MT microstimulation influences both choice and RTs in the stimulated neurons' preferred motion direction. In turn, when MT neurons are deactivated, the decision making process is impaired, likely because the sensory encoding is interrupted (Katz, Yates, Pillow, & Huk, 2016). On a functional level these findings indicate that MT processes the motion information and thus provides the sensory evidence on which decisions are formed.

To find out the neural substrates of a decision variable, a large body of monkey recordings targeted the FEF, because it is well-connected to visual areas, and known to encode the saccade processing required to respond in the RDM paradigm (Felleman & Van Essen, 1991; Hanes & Schall, 1996; Schall, Hanes, Thompson, & King, 1995; Schall & Morel, 1995; Thompson, Hanes, Bichot, & Schall, 1996; Van Essen, Anderson, & Felleman, 1992). Moreover, suprathreshold electrical stimulation evokes saccades while subthreshold stimulation elicits changes to saccade selection and spatial attention (Burman & Bruce, 1997; Moore & Armstrong, 2003; Moore & Fallah, 2001; Robinson & Fuchs, 1969). Gold and Shadlen (2000) interrupted motion viewing during the evidence accumulation process while monkeys viewed the RDM stimuli. Then they immediately applied a short electrical current to the FEF, which resulted in a saccade whose direction and amplitude was influenced by the current state of the decision process, reflecting the evolution of a decision variable (Gold & Shadlen, 2000; Gold, Shadlen, & Munoz, 2003). However, while the FEF is clearly involved in the decision process, it appears that only a small part of FEF neurons track the DV, while others encode stimulus properties during and after the decision, possibly to evaluate the outcome (Ding & Gold, 2012). Together, these studies indicate that the FEF is related to action-performance in RDM tasks with saccade responses, but also encodes stimulus and outcome related information.

Besides the more perceptual aspects of MT and the action-related activity in FEF, the lateral intraparietal area (LIP) has been extensively studied in RT-dependent versions of the RDM task. LIP has been focused on, because anatomically it receives inputs from

MT and outputs to the FEF (Andersen, Brotchie, & Mazzoni, 1992; Blatt, Andersen, & Stoner, 1990; Lewis & Van Essen, 2000). In particular, the LIP is tightly coupled to areas involved in eye movement control (Andersen, Asanuma, Essick, & Siegel, 1990). LIP neurons fire when a saccade is planned into their receptive fields (Andersen, Essick, & Siegel, 1987) and its neurons fire persistently when an animal withdraws a saccade to a target (Barash, Bracewell, Fogassi, Gnadt, & Andersen, 1991; Gnadt & Andersen, 1988). Thus, LIP function appeared to be between perceptual processing and eye-movement execution, responsible for sensorimotor integration mediated by cognitive control (for review, Andersen & Buneo, 2002). Therefore, it was unsurprising when Shadlen and Newsome (1996, 2001) demonstrated that activity in LIP neurons, whose receptive fields were aligned with visual targets in the RDM task, increased before saccades to these targets were executed. Surprisingly however, single neuron activity was modulated by the presentation of dot-motion and correlated with RDM coherency. That is, activity reflected the difficulty of individual RDM patches by faster increases of firing rates in easy trials, indicating that LIP neurons tracked the evolution of the decision process. Most interestingly, LIP firing rates accumulated to a fixed threshold at the time of response independent of trial difficulty, fitting to drift-diffusion models of decision processing (Roitman & Shadlen, 2002a; Shadlen & Newsome, 1996, 2001). Contrary to MT however, LIP microstimulation appears to only slightly affect choice and RT (Hanks, Ditterich, & Shadlen, 2006). Moreover, when short motion perturbations were added to the RDM kinematogram, RT and choices were modulated by these over a sustained period of time (Huk, 2005). Together, these findings indicate that LIP neurons reflect the integration of decision information over time and microstimulaton perturbations drive the encoded decision variable with respect to a decision bound.

Most relevant to the present thesis (task design study 1 & 3), when responses could not be immediately taken and monkeys had to map targets to a spatially undetermined color-code, LIP neurons still represented the DV even though no specific saccade planning was possible (Bennur & Gold, 2011). This indicates that LIP function includes tracking the evolving DV independent of a specific motor response. However, a recent study

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using causal de-activation of LIP neurons during decision formation suggests that LIP neurons may not be critical for computing perceptual decisions, and may only reflect secondary processes that correlate with the actual computation (Katz et al., 2016). This is particularly interesting, because concurrent recordings from six regions involved in decision making including MT, FEF and LIP suggest that information is not confined to specific cortical regions but shared among relevant brain areas and transmitted via bursts (Siegel, Buschman, & Miller, 2015). This observation ties in well with earlier studies suggesting that decision information is present even in areas functionally specific to early visual processing and may be communicated there via feedback from downstream cortices (Donner, Sagi, Bonneh, & Heeger, 2008; Nienborg & Cumming, 2009; Siegel, Engel, & Donner, 2011). If information is shared along the whole perception-action loop in a network between distributed regions, studying the whole system instead of isolated areas might be necessary, as is done in human neuroimaging.

1.3.2 Accumulation of evidence tasks using M/EEG in humans

Studies of perceptual decision making with nonhuman primates have discovered that many different areas throughout the cortical hierarchy are involved and share information across large distances. Yet, we know little about how these areas dynamically interact to form decisions, because studies recording from single cells are always limited to small populations and few cortical areas. In contrast, studies using neuroimaging with human subjects can trace neuronal dynamics across the whole head and concurrently throughout cortices. In addition, human subjects can be asked directly on what their perceptions and decisions were, e.g. how confidently they made a choice, and are recorded in much larger number, leading to better inferences about common mechanisms. Notably however, little is known about how many of the rhythms measured with M/EEG correspond to single-cell recordings and how they compare to signals detected in fMRI BOLD contrasts (Buzsáki & Wang, 2012; Jann, Kottlow, Dierks, Boesch, & Koenig, 2010; Keller et al., 2013; Lee et al., 2014; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001; Scheeringa et al., 2011; Whittingstall & Logothetis, 2009).

Coherent oscillations between cortical areas may dynamically regulate the information flow across sets of neuronal populations (Engel, Fries, & Singer, 2001; Fries, 2015; Salinas & Sejnowski, 2001; Sejnowski, 2006; Varela, Lachaux, Rodriguez, & Martinerie, 2001) and MEG is well-suited to study such cortical dynamics (Siegel et al., 2011). Using MEG to discover the role of cortical oscillations for perceptual decision making, Donner et al. (2007) asked human volunteers to detect RDM motion (rather than choosing between directions) and found that beta power was elevated throughout the dorsal visual pathway including MT, intraparietal sulcus (IPS) and dlPFC for correct vs. incorrect trials. Interestingly, this activity predicted the accuracy and not the content of the upcoming choice, suggesting that beta reflected the computation of decisions rather than the content (see also Siegel et al., 2011). In another experiment, volunteers were shown an RDM patch at different coherence levels and had to indicate the motion direction (Siegel, Donner, Oostenveld, Fries, & Engel, 2007). After a typical event-related field, they observed a parametric scaling of occipital gamma power with the stimulus coherence and the opposite, but less robust, pattern in alpha and beta bands. Because the visual areas partial to this effect are known to be involved in motion processing, such as MT, this suggests that gamma reflects processing of the evidence on which decisions are based.

To investigate the action component of such perceptual choices, in another experiment Donner et al. (2009) presented RDM stimuli for a fixed time and before responses were given with either hand, a short delay was enforced onto the participants. Gamma band activity increased over the contralateral (pre-) motor cortex, and low frequency alpha and beta oscillations decreased with respect to the ipsilateral hemisphere. Notably, this pattern built up during stimulus viewing, likely reflecting the accumulation of evidence for a decision that would be source localized to FEF when responding with saccades instead (Herding et al., 2017). The lateralization of beta-band activity over central electrodes in particular appears to reflect an emerging motor plan that is directly associated with participants' choices. Building upon this finding, de Lange, Rahnev, Donner, and Lau (2013) demonstrated that pre-stimulus variance of lateralized power in the beta band predicted choices and that the accumulation of beta lateralization was modulated by

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motion coherence. In sum, these MEG studies demonstrate signals corresponding to the sensory processing in MT and the action-related activity in FEF as observed in nonhuman primates and suggest an active role of beta and gamma oscillations in encoding the stimulus content. However, monkey studies have found extensive correlates of neuronal activity in the posterior parietal cortex with the evolution of a decision variable, which could not be identified with MEG. This is particularly curious, because recent EEG studies have observed consistent evidence of a centro-parietal potential (CPP or P300) that may be a candidate signal for such a parietal mechanism (Kelly & O'Connell, 2015).

The CPP has been identified as a rhythm matching the evolution of a decision variable during perceptual decision making tasks (Kelly & O'Connell, 2013, 2015; Philiastides et al., 2014; Twomey et al., 2015). One strategy to find this signal in RDM tasks has been to eliminate the typically observed ERPs resulting from stimulus onsets by presenting a field of randomly moving dots before coherent motion onset, thereby allowing for a seamless transition (Kelly & O'Connell, 2013). Moreover, responses are often made by button press using either left or right hands, to enable observation of lateralized beta power (as in de Lange et al., 2013; Donner et al., 2009). Using this setup, Kelly and O'Connell (2013) recorded EEG while humans performed the RDM task. They found that the CPP exhibited an accumulation-to-bound with respect to the decision of up- vs downward motion. In addition, the rate of CPP build-up was modulated by the sensory evidence strength, exhibiting a defining property of theoretical accounts of a decision variable. Even though effector specific activity in form of the lateralized readiness potential (Eimer, 1998; Smulders & Miller, 2012) did also show a ramping up, this activity was driven by the abstract, centroparietal signal. Moreover, in a previous study with a change detection task, hand movement specific motor signals, such as the previously observed beta lateralization, also exhibited a pattern of build-up to a threshold just before responses were executed, however, were abolished when manual responses were not carried out (O'Connell et al., 2012). This indicates that the CPP appears one directional in this process and only represents the accumulation-to-bound in a positive manner. This means that it doesn't represent different choices – a signed value - but the absolute value of the DV. The effector-

specific beta activity on the other hand includes information about choices, because they have to be enacted on. Such an interpretation of the CPP is in line with observations in LIP neurons and theoretical accounts that posit the supramodal accumulation of evidence for distinct alternatives in the same cortical areas that race each other (Brown & Heathcote, 2008; Roitman & Shadlen, 2002b; Usher & McClelland, 2001). Moreover, recent evidence suggests that neural correlates of a DV are independent of motor plans in LIP (Bennur & Gold, 2011) and corresponding human area IPS includes distinct systems implementing motor and perceptual decisions, suggesting functional heterogeneity (Filimon, Philiastides, Nelson, Kloosterman, & Heekeren, 2013). Therefore, it remains unclear what exactly is encoded by the centroparietal signals observed with EEG from this area and what precise cognitive function underlies the ramping up of activity.

If the CPP is the same signal as the P300, as recently suggested (Twomey et al., 2015), then a large body of evidence has indicated a relationship with a plethora of alternative cognitive processes (Nieuwenhuis, 2011; Nieuwenhuis, Aston-Jones, & Cohen, 2005). One measure in particular appears to fit well to recent observations of the CPP: confidence (Hillyard, Squires, Bauer, & Lindsay, 1971; Squires, Hillyard, & Lindsay, 1973). Because the CPP is not selective in its accumulation for one choice over another, it may only reflect the absolute value of a DV. Such a signal is closely related to confidence, which can be viewed as the distance between the DV and the closest decision bound (Urai & Pfeffer, 2014). A confidence signal would therefore not be selective for choices; however, it would still be affected by them. If participants commit an error, the DV should reach the same threshold as in a correct trial, while confidence should be lower (Shadlen & Kiani, 2013). Most interestingly, Philiastides et al. (2014) used a face-house discrimination task in which participants also had to sequentially sample and integrate information over time. They found that a CPP gradually built-up over time with the amount of evidence for either choice, as predicted from drift-diffusion models (DDM) and corresponding to RDM tasks. However, the signal did not reach a fixed threshold, but was still modulated by the amount of evidence for a choice. Because a simple DDM could not account for this, the authors demonstrated that adding a proxy for confidence on each trial could. This indicates that

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at the time of response, the CPP includes information about choice confidence. However, participants weren't specifically asked how confident they were in their decisions, and it remains unclear whether this part of the CPP can be related directly to confidence judgements, as has been done in fMRI (e.g., Hebart, Schriever, Donner, & Haynes, 2016).

1.3.3 Accumulation of evidence tasks using fMRI in humans

Functional magnetic resonance imaging (fMRI) has indeed provided another avenue of human neuroimaging research to investigate perceptual decision making and confidence with high spatial acuity. Heekeren, Marrett, Bandettini, and Ungerleider (2004) gave participants a similar face-house discrimination task as described in the previous section (Philiastides et al., 2014) and used the spatial specificity of face processing in the fusiform face area (FFA) and house processing in the parahippocampal place area (PPA) to investigate relative blood-oxygen-level dependent (BOLD) increases. BOLD is known to increase in the FFA and PPA when faces and houses are perceived, respectively and can be related to single neuronal codes for either stimulus (Epstein & Kanwisher, 1998; Haxby, Hoffman, & Gobbini, 2000; Ishai, Ungerleider, Martin, Schouten, & Haxby, 1999; Kanwisher, McDermott, & Chun, 1997; Logothetis et al., 2001; Logothetis & Wandell, 2004; McCarthy, Puce, Gore, & Allison, 1997). A region responsible for decision making should covary with either FFA or PPA activity depending on whether faces or houses were perceived (Heekeren et al., 2004). Because the BOLD response is sluggish, it can only pick up on the overall activity during a trial and a modulation by evidence in either area is likely difficult to detect. However, the authors postulated that a candidate decision making area should show a pattern of easy trials associated with higher BOLD responses than hard trials, because in easy trials BOLD responses should reach a high level faster. They found that the left dorsolateral PFC (dlPFC) showed such an activity pattern and in a follow-up demonstrated that this was independent of the response modality (Heekeren, Marrett, Ruff, Bandettini, & Ungerleider, 2006). In addition, the role of the dlPFC appears to be one of integrating evidence, modeled as the drift in DDM, because when repetitive transcranial magnetic stimulation (TMS) was applied to this area to interrupt the decision process,

accuracy and response times were stymied in line with an interpretation as decreasing drift rate (Philiastides, Auksztulewicz, Heekeren, & Blankenburg, 2011). Notably in the context of the present thesis, this prefrontal activity appears to be co-activated with the IPS and FEF, suggesting a frontoparietal network involved in encoding of stimulus information and decision making (Heekeren et al., 2006; Ho, Brown, & Serences, 2009; Kayser, Buchsbaum, Erickson, & D'Esposito, 2010; Liu & Pleskac, 2011). In particular, Liu and Pleskac (2011) designed an RDM task where they gave information about the response modality, either button press or saccade, before or after the stimulus presentation (see design of study 1 of this thesis). Because participants could answer as fast as they wanted, with no forced delay as in Heekeren et al. (2004), the BOLD responses were increased for more difficult trials (Hanks & Summerfield, 2017), indicating that participants accumulated evidence for a longer time. Besides frontal areas and the anterior insula, the modulation was present in saccade-related areas FEF and IPS. Crucially, the foreknowledge and response modality did not have an effect on this activity pattern, suggesting no effector specificity of the neural system underlying evidence accumulation. These findings fit well with recent observations in monkey LIP, indicating that information about RDM direction was present before monkeys knew where the saccade target was going to be (Bennur & Gold, 2011).

Together, human neuroimaging provides a complimentary view to monkey recordings and provides evidence for the involvement of prefrontal and parietal areas in perceptual decision making¹. Most notably, the dlPFC appears to fulfil the role of a domain general evidence accumulator, not evident from monkey single-cell recordings. Apart from these prefrontal findings, human fMRI and M/EEG studies show a remarkable similarity with monkey recordings in the areas involved in perceptual decision making. Especially the pattern of parietal signals tracking the evidence accumulation of noisy input and (pre-) motor areas exhibiting variability with the execution of choices is consistent across species and methods. Moreover, it appears that the information about the current state of decision making, a DV, is available to many areas and not restricted to a central decision maker.

¹In addition, fMRI has revealed a role for the anterior insula during evidence accumulation (Ho et al., 2009; Liu and Pleskac, 2011). Because the insula is related to many different cognitive functions and because the present studies haven't found signals corresponding to such activity, I have left this introduction for another place (Menon and Uddin, 2010).

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This is particularly important, as neural oscillations studied with M/EEG often reflect the dynamics of a cortical representation. More so, the dynamics of a general decision making mechanism are likely to be similar across cognitive tasks, such as the RDM and the SFC task, even if sensory modality or stimuli involve distinct cortical areas.

1.3.4 Common neural codes across perceptual decision making tasks

Evidence of common neural codes was found in studies using the RDM stimulus in a sequential comparison setup. Zaksas and Pasternak (2006) recorded from areas MT and PFC, while monkeys performed a delayed match-to-sample task on the motion direction of two sequentially presented RDM stimuli. During perception of the first stimulus, MT and PFC neurons were direction selective, but selectivity in PFC emerged 40ms after MT. During the delay period, neurons in both areas were attuned to direction, but through transient, not sustained firing. Similarly, the decision information was present in both MT and PFC, but the PFC was modulated 100 ms later and predictive of the upcoming choice. This indicates that PFC neurons encode task-relevant features about visual motion and represent the decisions that are based on comparisons taking place in MT. In addition, Hussar and Pasternak (2012) recorded from two distinct principal types of PFC neurons, pyramidal and interneurons, during the same task. They found that while both were involved in perception, mostly pyramidal cells carried information throughout the delay period, in a transient, dynamic code. Furthermore, the cell type determined whether the neuron was attuned to matching versus non-matching RDM directions. This suggests that the PFC employs a dual code for decision making in which different cell types have distinct contributions. To investigate the network states involved in this visual comparison task, Wimmer, Ramon, Pasternak, and Compte (2016) analysed LFPs from the lateral PFC from monkeys comparing either the motion directions or speeds of two RDM patches. During perception, theta and gamma power was increased, while beta decreased. In the subsequent delay, beta power encoded the relevant RDM feature, agreeing with findings in human neuroimaging (Spitzer & Blankenburg, 2012; Spitzer et al., 2010). Broadband LFP activity reflected the difference between S2 and S1 and was split into an early signed

modulation (S2-S1) and a later absolute choice-related component that reflected the buildup of the perceptual decision. Albeit in different areas, these results appear remarkably similar to findings of decision beta in SFC tasks on the one hand (Haegens et al., 2011; Herding et al., 2016), and the CPP (Kelly & O'Connell, 2013) on the other. However, until the studies included in the present thesis, there have not been any human neuroimaging approaches investigating these common cortical dynamics.

1.4 Objectives of this dissertation

Throughout the research for this dissertation, my primary aim has been to find the neural substrates underlying working memory and decision making with the intention to understand these cognitive functions better. Neural oscillations have been associated with these specific mental tasks, however, several important questions on the role of beta and gamma oscillations, in particular, remain unanswered. I addressed these gaps in our knowledge in three studies using a sequential comparison task with tactile (study 1+2) and visual stimuli (study 3). Moreover, I bridged the gap of perceptual decision making research using the predominant random-dot motion stimuli in a new comparison task setup (study 3). In conjunction with neural oscillations, I investigated broadband centro-parietal signals, and related them to motor beta, trial difficulty and confidence (study 2+3). Finally, this thesis accumulates the information from these three very related studies and outlines common themes surrounding the beta and gamma band as well as possible common ground with the CPP.

Summary of Original Research

Articles

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2.1 Study 1: Gamma and Beta Oscillations in Human MEG Encode the Contents of Vibrotactile Working Memory

From single-cell recordings in monkeys to large-scale human EEG, the parametric encoding of vibrotactile frequency during working memory is well-established (Romo et al., 1999; Spitzer et al., 2010). As reviewed in the introduction, a number of recent EEG studies have identified cortical oscillations in the beta band to represent the frequency information during a short delay in a vibrotactile sequential frequency comparison task. However, visual and auditory working memory studies have found a crucial role of gamma oscillations for working memory, not observed in previous vibrotactile EEG studies (Roux & Uhlhaas, 2014). In addition, the only MEG study investigating tactile working memory found a modulation of SI and - most interestingly - of SII during stimulus retention, but didn't investigate a parametric modulation in prefrontal areas (Haegens et al., 2010). While the authors did find an overall increase in frontal gamma during WM, this was limited to contrasting periods of working memory with a prestimulus baseline and was not content specific. Therefore, our first goal was to investigate whether frontal gamma encodes stimulus features during WM. In addition to this aim, a line of monkey and human neuroimaging studies has identified the intraparietal sulcus (IPS) as a hub for numerosity processing, a mental task very similar to the vibrotactile features in our design (Nieder, 2016). However, studies using EEG have not been able to localize IPS activity reflecting the vibrotactile frequency held in WM as is known from fMRI (Wu et al., 2018). Therefore, we aimed at detecting both high frequency oscillations in the gamma band and stimulus information from the IPS for the first time.

We recorded 306-channel whole-head magnetoencephalography while participants performed a version of the vibrotactile frequency comparison task. Notably, our original task design intended to also investigate how beta-gamma codes of decision making were

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influenced by foreknowledge of the response modality, and therefore the task included responses with button press and saccades. However, due to technical problems, we had to discard the analysis of decision making related activity.

Our main analysis probed with a zero-mean contrast of the four different vibrotactile frequencies held in working memory at 15, 19, 23 and 27 Hz, whether there were channels, frequencies or time points in which a parametric code of vibrotactile frequencies was present. With a nonparametric cluster-based permutation test we identified three areas that showed such a pattern, all around the center of the WM interval. First, replicating previous EEG findings, beta power in the right IFG at around 30-35 Hz. Second, low beta power (10-20Hz) in bilateral parietal channels which was source localized to the IPS. Third, matching the beta effect in source location in the right IFG, gamma power (74-90 Hz) was negatively modulated by the vibrotactile frequency, thus showing the opposite pattern of the beta band effects. Notably, we did not replicate effects of overall broadband gamma power increases in SI, SII and frontal cortices as had been observed in a similar vibrotactile task (Haegens et al., 2010), while replicating the patterns typically observed in vibrotactile SFC tasks with M/EEG (Bauer, 2006; Spitzer et al., 2010).

These results indicate that there is a frontoparietal network underlying the retention of vibrotactile stimuli with an extended role of the beta band that may interact with gamma to enable working memory. We demonstrate for the first time with MEG that the IPS is also involved in this process and that the gamma band, which is associated more directly with neuronal firing than beta, might drive the prefrontal processing (Lundqvist et al., 2016; Whittingstall & Logothetis, 2009).

2.2 Study 2: Centro-parietal EEG Potentials Index Subjective Evidence and Difficulty

Recent studies indicate that the CPP in human EEG tracks the integration of noisy sensory input over time. It remains unclear however, whether the comparison of two short

2.2 Study 2: Centro-parietal EEG Potentials Index Subjective Evidence and Difficulty

vibrotactile frequencies elicits a similar response, as this percept does not include the accumulation of noisy evidence over an extended period. Moreover, it remains unknown whether the premotor beta band that scales with subjects' upcoming choices is related to the CPP. This is particularly interesting, because the CPP reflects the absolute, unsigned strength of accumulated evidence ($|S2 - S1|$), while choice dependent beta is a signed value ($S2 - S1$) reflecting the direction of the decision (e.g., Siegel et al., 2011; Urai & Pfeffer, 2014).

In this study, we used EEG data from six variants of the SFC task (n=116) and applied a model based on Bayesian inference to the behavioural data to estimate the subjectively perceived frequency differences (SPFDs). We found that parietal ERPs reflected the SPFCs shortly after the second stimulus offset (168-709ms) in a signed fashion, thus indicating the direction of choice. Crucially, this early parietal signal was correlated with choice-related beta power on a single trial level. While not implying causation, this can be viewed as first evidence for a previously unknown EEG signature that indexes the updating of subjective evidence in relation to the ensuing choice. The timing of these two signals as well as their source locations in parietal and premotor cortex further underline the possibility that the early ERPs serve to communicate the evidence for one motor plan or its alternative and the premotor beta band reflects the choice planning based upon this evidence.

In addition to this early parietal modulation by signed difference, we observed later parietal ERPs (273-953ms after stimulus offset) that correlated with the absolute strength of evidence. Interestingly, this later modulation was source localized not only to parietal areas, but also included the bilateral IFG, which relates it to the parametric encoding of the vibrotactile frequencies during WM. Similar to study 3 we also did not observe an absolute threshold of CPP accumulation, but rather a scaling of the late ERPs by subjective task difficulty. Further analysis revealed that this effect complied with the definition of statistical decision confidence in all aspects (Hangya, Sanders, & Kepcs, 2016; Sanders, Hangya, & Kepcs, 2016).

In summary, these findings indicate that early centroparietal ERPs reflect the evidence on which decisions are based, while later modulations might refer to the strength of evidence

informing a decision, which is closely related to measures of confidence.

2.3 Study 3: Neuronal Signatures of a Random-Dot Motion Comparison Task

Both the vibrotactile frequency comparison task and the random-dot motion task have been studied extensively in humans and monkeys, as I introduced earlier. However, there is remarkably little research aiming at finding common codes across these perceptual decision making tasks. So far, no human neuroimaging study has investigated the RDM task with vibrotactile stimuli nor studied the sequential comparison of random-dot motion stimuli. This is particularly curious, because pupillometry in humans and electrophysiological recordings in monkeys using a combination of these classical tasks have produced high-impact studies that gave novel insights into the encoding of decision information (Urai, Braun, & Donner, 2017; Wimmer et al., 2016). Here, we recorded EEG while human volunteers were tasked to compare the coherence of two sequentially presented random-dot motion stimuli (S_1, S_2) and responded by button press. If findings from SFC studies indeed transfer to the visual domain, we should observe a parametric beta band code in PFC as well as a modulation of premotor beta by choice. Moreover, RDM stimuli should elicit typical visual effects as well as a correlate of the accumulation of evidence in the form of a CPP. Crucially, the decision variable in this task reflects the comparison of the first with the second stimulus, thus we should not observe a CPP during perception of S_1 . Moreover, the CPP should scale with the difference between the two, not the coherence of S_2 .

We asked 28 subjects to perform this task and used their behavioral data to model the subjectively perceived coherence difference (SPCD) for each subject and trial. Using variational Bayes, our model accounted for the time-order effect/error (Hellström, 1985), a bias typically observed in sequential comparisons. In analogy to study 1, our WM analysis was a parametric contrast of the four S_1 coherence levels. To look into the decision making

2.3 Study 3: Neuronal Signatures of a Random-Dot Motion Comparison Task

interval, we performed a 2×2 GLM of choice ($S2 > S1$ vs $S2 < S1$) and performance (correct vs incorrect). Moreover, we investigated the CPP and contrasted it by subjects' choices and each trial's SPCD in three levels of 'easy', 'medium' and 'hard'.

In our WM analysis we found a significant cluster of prefrontal channels that were modulated by the level of $S1$ coherence retained throughout the inter-stimulus-interval. In agreement with previous EEG studies using vibrotactile stimuli (Spitzer & Blankenburg, 2012; Spitzer et al., 2010), this effect source localized to the right IFG, suggesting that the working memory related beta is supramodal and can be observed with stimuli not relying on frequency magnitudes. We also found a negative modulation of gamma, replicating findings from study 1. However, this effect was mainly driven by the lowest coherence stimuli and will require further investigation. Curiously, we also found a negative modulation of low beta band activity by the $S1$ coherence level in centroparietal channels, source localizing to bilateral MI and precuneus.

The analysis of decision-related activity found a modulation of premotor beta band activity 700ms before responses were made that was elevated for choices of $S2 > S1$ in comparison to those of $S2 < S1$. This is in line with recent vibrotactile SFC studies in humans, corresponding in time, frequency and location (Herding et al., 2016) and also agrees with monkey LFPs (Haegens et al., 2011; Haegens et al., 2017). There was no effect when splitting trials into 3 levels by SPCD (easy, medium, hard), thus reflecting the choices in a binary code. The CPP was modulated both in response to the perception of $S2$ and with respect to responses. $S2$ -locked activity accrued during the stimulus presentation and stayed on a fixed level afterwards. Crucially, the amplitude of this level was modulated by the trials' difficulty ($S2 - S1'$) and not by the coherence of $S2$. Furthermore, the $S2$ -locked CPP was modulated by choice and reached a higher amplitude for choices $S2 < S1$ than $S2 > S1$, the opposite of the beta band effect. Response-locked CPP showed a pattern of signal accumulation to a peak at the time of response. Notably, this peak was both influenced by choice and the difficulty of trials. At the time of response the CPP did not reach a fixed threshold, like in simple boundary-crossing models, but was scaled by the SPCD, with difficult trials exhibiting smaller amplitudes and incorrect trials demonstrating

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even smaller amplitudes. This effect was only evident in the last 300ms before responding and in particular, seemed to be driven by a lower starting point to the accumulation rather than variance during the accumulation.

Our findings indicate an extended role of the beta band for both working memory and decision making in comparison tasks, regardless of sensory modality. Beta has been suggested to reflect the “status quo” of information (Engel & Fries, 2010). In our studies however, it appears to reflect more than that. It is modulated by the abstract magnitudes in comparison tasks (vibrotactile frequency or RDM coherence) and therefore reflects the WM content, as well as the content of decision making, already very early, 700ms before responding. In conjunction with fast, transient gamma it might therefore reflect the re-activation of content (Spitzer & Haegens, 2017) and/or the maintenance state (also of choice) that is interrupted by gamma (Lundqvist, Herman, & Miller, 2018).

The CPP was strongly modulated by trial difficulty at the time of response, suggesting it reflects a cognitive process that is not wholly explained by crossing a bound in a simple drift-diffusion model. More complex models based on sequential Bayesian updating or with collapsing bounds may be necessary to keep the drift-diffusion view in place. Moreover, it is possible that the CPP reflects an accumulation to an absolute bound, but the signal we observed included other parietal signals encoding the decision confidence. Finally, the CPP was also modulated by participants’ choices, indicating a relationship with premotor beta that is yet to be investigated.

In sum, this study was able to bridge gap between decision making paradigms and sensory domains, indicating a common role for beta band driven content encoding and the CPP as an evidence accumulation mechanism that has ties to confidence.

General Discussion

In the research summarized in the previous section, we gained new insights into the role of neural oscillations ascribed to cognitive functions, especially working memory modulated beta and gamma, decision-related beta power and the supramodal nature of the CPP for tracking decisions.

In the first study, we were able to uncover previously hypothesized but never demonstrated modulations of prefrontal gamma and parietal beta power by vibrotactile frequencies held in working memory. Most interestingly, the parietal beta modulations could be source localized to the IPS, an area known to be involved in numerosity processing. These results indicate that a frontoparietal network underlies working memory that employs beta and gamma oscillations in a mechanistic fashion.

The second study encompassed six EEG experiments, whose analysis consistently showed a CPP that accumulated during decision making. With respect to the second stimulus, we observed a scaling of the CPP, first by the subsequent choice and later by trial difficulty, which we relate to confidence. In addition, we found a correlation between choice-related beta and the CPP, suggesting common codes during decision processing. Our findings point to a role of the CPP that goes beyond signaling the status of a DV and insinuate that such a role is related to the decision outcome.

In the most recent experiment, we showed that the functional roles attributed to beta oscillations in the tactile task hold up in a visual variant, indicating a general, supramodal mechanism. Similarly, we demonstrated that non-lateralized choice-dependent beta can also account for decisions when using RDM stimuli. In addition, both stimulus- and response-locked CPPs reflected the tracking of a decision variable during a comparison task that was informed by working memory. This is of particular note, because there was no relationship of the CPP during RDM perception, suggesting independence from sensory processes. Finally, the CPP scaled with subjectively perceived difficulty at the time of response, which further indicates that the CPP incorporates confidence signals.

3.1 Unifying accounts of prefrontal beta band oscillations during working memory

All experiments reviewed here replicated the finding that beta band power from IFG is parametrically modulated by abstract quantitative information (vibrotactile frequency or RDM coherence) held in working memory during a short interval between two stimuli. Spitzer et al. (2010) had identified this effect at 20-25 Hz with EEG during a similar vibrotactile SFC task. Interestingly, when we used a visual variant of the task, but the same EEG equipment as these authors, the effect was surprisingly similar at 18-26 Hz, however, was found significantly higher (30-35 Hz) in MEG recordings on almost the same vibrotactile task. Because in EEG the skull acts as a low-pass filter (Pfurtscheller & Cooper, 1975) and the observed effect may be an epiphenomenon of averaging further temporally smeared beta bursts, it is quite possible that the prefrontal oscillations even extend into the gamma range. Recent monkey recordings appear to concur with a representation in higher beta oscillations, with a medial premotor beta peak above 25 Hz (Haegens et al., 2017). This may particularly important, as lower beta modulations (13-20 Hz) occur jointly with alpha (Hanslmayr, Spitzer, & Bäuml, 2009) and decrease in task-relevant areas while higher beta-band rhythms (20-35) mirror gamma and increase with engagement (Tallon-Baudry, Bertrand, Peronnet, & Pernier, 1998). It may therefore be necessary, in the future, to separate lower beta activity more clearly from higher beta oscillations to avoid grouping them in one beta band.

Our findings in the prefrontal cortex were clearly in the upper beta band and appeared to be related to active processing rather than inhibitory in nature. Enhanced beta has been hypothesized to signal the “status quo” of maintaining the current sensorimotor or cognitive state (Engel & Fries, 2010). However, our findings go beyond overall changes. We provide evidence that beta oscillations hold information about the content (vibrotactile frequency or RDM coherence) of working memory on a given trial, joining a growing body of evidence for such a role (Spitzer & Blankenburg, 2011; Spitzer et al., 2010; Wimmer et al., 2016). This type of feature specific activity has also been found in neuronal spiking and high frequency LFPs (Nieder & Miller, 2003; Pesaran, Pezaris, Sahani, Mitra, & Andersen,

3.2 Diverging findings with MEG and EEG

2002; Romo et al., 1999) and has been studied extensively with fMRI (Christophel, Hebart, & Haynes, 2012; Christophel, Klink, Spitzer, Roelfsema, & Haynes, 2017; Uluc, Schmidt, Wu, & Blankenburg, 2018; Wu et al., 2018). Yet, it remains unclear how neural activity measured as spike firing rates and BOLD signals relate to the previously observed EEG beta band oscillations. In particular, it is unknown, whether beta activity correlates positively or negatively with these activity measurements (Spitzer & Haegens, 2017). Upper beta band oscillations are likely to correspond closer to those in gamma, who have been associated with higher spike rates and increases in BOLD, while low beta may be associated negatively with activity, corresponding to alpha (Hanslmayr et al., 2011; Michels et al., 2010). However, it is also possible that beta is neither associated with activity increases nor decreases, as observed in some studies (Rule, Vargas-Irwin, Donoghue, & Truccolo, 2017; Whittingstall & Logothetis, 2009). Therefore our findings with MEG are of particular note, because we demonstrated that both high prefrontal and low parietal beta were associated with the abstract magnitudes held in working memory in the same fashion. We did not, however, observe overall changes, further underlining that beta fulfills a content-specific role. I therefore suspect that the functional role of beta is not directly related to overall spiking/BOLD activity increases as has been observed in gamma, but reflects the updating of content (Spitzer & Haegens, 2017).

3.2 Diverging findings with MEG and EEG

One major difference between our MEG recordings and previous EEG studies was that we observed parametric changes in gamma spectral power by the to-be-maintained frequency f_1 . One explanation why parametric WM in high frequency gamma oscillations was not detected in the large amount of previous vibrotactile EEG studies (Herding et al., 2016; Spitzer & Blankenburg, 2011, 2012; Spitzer, Fleck, & Blankenburg, 2014; Spitzer et al., 2010) is the previously mentioned nature of the human skull to act as a low-pass filter (Pfurtscheller & Cooper, 1975). Specifically, EEG and MEG can exhibit distinct frequency versus power relationships in high frequencies, because the capacitive properties of the

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extracellular medium, i.e. skin and scalp muscle artefacts, distort the EEG, but not the MEG signal (Buzsáki & Wang, 2012; Dehghani, Bédard, Cash, Halgren, & Destexhe, 2010; Demanuele, James, & Sonuga-Barke, 2007). In addition, we used a multitaper approach based on Slepian sequences with a fixed window of 200 ms in the MEG study compared to a window of 400 ms in previous EEG recordings. This shorter time window results in less smoothing in the time domain, which gives rougher estimates, but may have provided us with the possibility to detect more short-lived effects. Because of these differences, we also used the shorter window for exploratory analysis in more recent experiments, for example study 3, resulting in the same negative gamma modulation by the abstract quantity held in working memory as observed with MEG. For prospective WM studies or an eventual meta-analysis of the present findings I therefore also recommend trying out a short window for multitaper analysis of higher frequencies.

In addition to gamma, the MEG recordings differed from EEG recordings in one more area: the IPS. We found that low beta band power (10-20) from this area was parametrically modulated by the abstract quantity retained in WM. There are two methodological reasons that could account for why we detected this modulation with MEG and not EEG (cf. Spitzer et al., 2014). One, MEG has a higher signal-to-noise ratio for shallow sources (Goldenholz et al., 2009). Two, MEG is more sensitive to sulcal than gyral sources, because it is blind to radial dipoles, biasing source analysis in favor of sulcal sources (Ahlfors, Han, Belliveau, & Hämäläinen, 2010). However, while unexpected from the previous EEG literature, the involvement of the IPS in quantity processing was not wholly surprising. Concurrent to our research, fMRI studies found a role of the IPS for vibrotactile, visual, and auditory frequency maintenance (Uluc et al., 2018; Wu et al., 2018). Moreover, similar to the abstract stimuli we employ, tasks using concrete numbers have found a direct link between multivariate BOLD-responses in the IPS and quantity (Eger et al., 2009). This finding builds upon a body of work with nonhuman primates that has revealed a crucial involvement of intraparietal regions for the encoding of quantitative features that are ordered along a continuum (Jacob, Vallentin, & Nieder, 2012; Nieder, 2016), including supramodal frequency (Vergara, Rivera, Rossi-Pool, & Romo, 2016). Furthermore, the IPS has been

3.2 Diverging findings with MEG and EEG

well-established as a hub for working memory in conjunction with the prefrontal cortex in studies on capacity limits and appears to be essential for short term object retention (Todd & Marois, 2004, 2005; Vogel & Machizawa, 2004; Xu & Chun, 2006). Therefore, a role of the IPS in conjunction with the PFC has been well-established, yet it remains unclear what role beta band oscillations at low frequencies contribute to working memory in this area. In particular, the low beta we observed with MEG includes frequencies associated with the mu rhythm (Chatrian, Petersen, & Lazarte, 1959; Gastaut & Bert, 1954), whose functional role has been viewed as alpha-like suppression for somatosensation¹. Contrary to this interpretation, we did not observe overall ERD/ERS, but a parametric modulation of lower beta/mu power by the content held in working memory. It is therefore unlikely that the observed effect reflects a generic inhibition or gating mechanism. One possibility is that the inhibition is content specific, explicitly because another stimulus is being presented subsequently that is sure to be different in vibrotactile frequency. Thus, the stimulus frequency held in working memory could be inhibited. However, the parametric modulation of IPS did not extend to the time of f2 stimulation, rendering this interpretation unlikely. Similarly, the mu rhythm is associated with attention (Anderson & Ding, 2011) and it is possible that participants paid more attention to higher frequencies. This is unlikely for two reasons. First, we did not observe behavioral effects in this direction, and second, prefrontal gamma band and occipital alpha would be expected to be similarly modulated, which we also did not observe (in this direction). Therefore, a role of the IPS for numerosity processing and working memory is well-established and it appears that our observations are difficult to reconcile with the inhibitory nature of low frequencies. I speculate that our observations reflect an active maintenance mechanism, possibly interacting with prefrontal gamma.

¹Note that there is a different view on mu as a correlate of the mirror neuron system: (Naeem, Prasad, Watson, and Kelso, 2012; Pineda, 2005)

3.3 A frontoparietal beta-gamma code

One idea could be that the IPS maintains the information and is top-down controlled by prefrontal areas in a periodic replay based upon interactions of beta and gamma. This idea is analogous to computational modeling of neuronal firing patterns in animals proposing that working memory arises from periodically reactivating the content held in working memory, guided by gamma and theta oscillations (Fuentemilla, Penny, Cashdollar, Bunzeck, & Düzel, 2010; Jensen & Lisman, 2005; Lisman, 1999; Lisman & Idiart, 1995). This concept likely extends beyond the theta-related hippocampus to other areas and frequency bands (Lundqvist et al., 2016; Mongillo et al., 2008) and could be modulated on short time scales by attention (Awh, Jonides, & Reuter-Lorenz, 1998). Moreover, there is evidence of PFC-PPC coupling in the beta and delta bands, with delta reflecting task-irrelevant stimulus dimensions and beta only those immediately relevant (Antzoulatos & Miller, 2016). Yet so far, a gamma-beta relationship has only been shown within the prefrontal cortex (Lundqvist et al., 2016) and not across frontoparietal areas. However, this same idea may serve to explain the pattern of concurrent high beta band increases and gamma decreases with the abstract quantity held in working memory I observed both with MEG and EEG in separate tactile and visual studies. Lundqvist et al. (2016) observed brief gamma (45-100 Hz) and beta (20-35 Hz) bursts during single cell and LFP recordings of monkeys performing a working memory task. The gamma bursts increased during encoding and recall, while the beta bursts reflected a default network state that was interrupted by gamma. My findings could be an epiphenomenon of such a coding scheme, but reflected in mean power differences due to averaging over trials smoothing out individual bursts. Further analysis using SFC tasks in humans should concentrate on understanding the single trial dynamics. Because signal to noise ratios in M/EEG can be low, this has proven difficult in the past. One avenue may lie in observing the cross-frequency coupling, both in power changes and rhythmicity (Fransen, van Ede, & Maris, 2015). Another promising method to investigate the network configuration of oscillations may lie in the extraction of frequency-specific timecourses with high temporal resolution (Vidaurre et al., 2018; Vidaurre et al., 2016). However, perhaps more importantly,

mechanistic accounts of PPC-PFC function will have to evaluate whether gamma from superficial cortical layers and beta from deep layers also enact a similar relationship in other cortical areas (Christophel et al., 2017; Miller, Lundqvist, & Bastos, 2018).

Under close examination this idea of a dynamic frontoparietal beta-gamma code speaks against working memory as a function grounded in sustained prefrontal firing rates (Funahashi et al., 1989; Fuster & Alexander, 1971; Goldman-Rakic, 1995; Pasternak & Greenlee, 2005). Studies demonstrating continuous delay activity have relied heavily on trial and spike averaging, convoluting more complex single trial dynamics (Rainer & Miller, 2002; Shafi et al., 2007). Indeed, similar to the previously mentioned beta-gamma patterns (Lundqvist et al., 2016), most neurons are variable in their spiking behavior in both timing and duration throughout retention intervals and show dynamic coding schemes transitioning between coding states (Cromer et al., 2010; Durstewitz & Seamans, 2006; Spaak, Watanabe, Funahashi, & Stokes, 2017; Stokes et al., 2013). Moreover, recent neuroimaging studies suggest that working memory can be ‘activity silent’ when stimuli are unattended or irrelevant for current task demands (Lewis-Peacock, Drysdale, Oberauer, & Postle, 2012; Stokes, 2015; Wolff, Ding, Myers, & Stokes, 2015; Wolff, Jochim, Akyürek, & Stokes, 2017). While the role of such silent states is currently under high-level debate (Christophel, Iamshchinina, Yan, Allefeld, & Haynes, 2018), evidence converges on the idea that working memory does not rely on sustained prefrontal firing as a solitary mechanism (Lundqvist, Herman, & Miller, 2018; Spaak et al., 2017). My data agrees with this notion. First, contrary to Haegens et al. (2010) we did not observe an overall increase of gamma power during working memory as would be expected from sustained firing, while EEG findings for alpha and beta were replicated. Second, irrespective of whether gamma power changes reflected bursting, the observed changes in gamma were in a finite time window and not sustained throughout the whole interval. Third, while single-trial dynamics remain unclear, the pattern of gamma decrease with concurrent beta increase in PFC and PPC hint at a relationship between these frequency bands for working memory. The key to a unifying explanation for these effects may be provided by a very recent monkey study: Lundqvist, Herman, and Miller (2018) found that gamma increased, and beta

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decreased shortly before items in working memory had to be used for decision making, while gamma decreased and beta increased when stimuli were not needed anymore. The authors interpret this as beta oscillations regulating control over gamma and working memory, a view summarily fitting to our results and recent investigations into the role of beta “beyond the status quo” (Haegens et al., 2017; Ludwig et al., 2018; Lundqvist, Herman, & Miller, 2018; Spitzer & Haegens, 2017). In this view, beta oscillations provide a mechanism to guide neural ensembles for the (re-)activation of maintained information. This builds on the observation that beta facilitates top-down driven communication across long distances and cortical areas (Antzoulatos & Miller, 2016; Arnal & Giraud, 2012; Bastos et al., 2015; Engel & Fries, 2010; Michalareas et al., 2016; Sejnowski, 2006; Siegel, Donner, & Engel, 2012; Varela et al., 2001; Wang, 2010), but beyond static maintenance can be characterized as a dynamic mechanism that can facilitate content-specific encoding and read-out by “waking up” in the form of short temporal bursts (Fries, 2015; Jones, 2016; Lundqvist, Herman, & Miller, 2018; Spitzer & Haegens, 2017). The question remains however, whether beta facilitates information “wake up” over long range connections, e.g. from sensory areas or if it is a mechanism of central processing in the prefrontal cortex. This is particularly interesting, because during visual and tactile tasks I have found consistent parametric modulations of beta oscillations in the PFC while none from sensory areas.

3.4 Distributed codes or central working memory?

While we observed working memory related activity consistently only in the prefrontal cortex, recent accounts also focus on a role for parietal and sensory cortices (Bettencourt & Xu, 2015; Christophel et al., 2017; Sreenivasan, Curtis, & D’Esposito, 2014; Xu & Jeong, 2015). In particular, studies using MVPA on fMRI recordings during the maintenance of precise visual details could reliably decode stimulus content from sensory cortices, yet failed in frontal areas (Christophel et al., 2012; Emrich, Riggall, LaRocque, & Postle, 2013; Riggall & Postle, 2012). When operationalizing the retention of vibrotactile frequencies

however, fMRI has revealed multivariate parametric codes in prefrontal and sensory areas (Schmidt, Wu, & Blankenburg, 2017; Wu et al., 2018). Thus, multiple avenues of research into working memory have found very distinct regions to be involved - how can these findings be consolidated? One idea is that the locus of working memory follows the processing in terms of the cortical hierarchy (Eriksson, Vogel, Lansner, Bergström, & Nyberg, 2015; Fuster & Bressler, 2012; Zimmer, 2008). Moreover, Christophel et al. (2017) postulate that for one, all cortical regions can maintain information over a short period of time. And for two, that the nature of the task dictates the relevant region in the cortical hierarchy depending on low level sensory features and the level of abstraction of the to-be-remembered stimulus. With such an interpretation of previous results, the areas involved in working memory can range from the prefrontal cortex for abstract, complex stimuli to low-level features in primary sensory cortices. Contrary to early MVPA fMRI studies tasking volunteers to remember low-level sensory details, we used abstract magnitude information, either in the form of vibrotactile flutters or the perceived coherence of a random dot kinematogram. Therefore, it is expected from this account that the representation in our studies materializes in areas such as the PFC and higher-order parietal regions, which process abstract, supramodal information. Furthermore, this idea may serve to explain the beta band modulation in motor areas before pressing a button we observed in terms of active perceptual memory. In this case, the motor-specific areas would also maintain information over a short period of time relevant to their place in the cortical hierarchy: the motor code for a subsequent button press.

3.5 Beta band during decision making

Beyond a role for working memory, we found an involvement of premotor beta band activity during decision making in a visual task and used previous findings of decision-related beta in tactile tasks to establish an association with concurrent centroparietal signals. Unfortunately, due to technical difficulties with both the vibrotactile stimulation device and the eye-tracking system, an analysis of our MEG data set in relation to decision making

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was unsuccessful (cf. Chandler, Hayes, Townsend, & Thwaites, 2015). This is particularly lamentably, because Donner et al. (2007) used MEG in a RDM task and found that beta band activity predicted the accuracy and not the content of upcoming perceptual reports, for which we found no evidence with EEG.

The modulation of upper beta band power by subjects' choices we observed in sequential comparison tasks is in accord with choice signals in monkey LFPs (Haegens et al., 2011) in frequency, timing and cross-species location. Moreover, the increase in beta power for choices $S2 > S1$ vs. $S2 < S1$ follows the same direction common to all previous studies (Haegens et al., 2011; Herding et al., 2017; Herding et al., 2016; Ludwig et al., 2018). Remarkably, when comparing patterns of visual (study 3, figure 4) and tactile studies (Herding et al., 2016, figure 4) the time-frequency maps and topographies appear incredibly similar even though stimulus processing relied on distinct sensory modalities and the tasks had divergent timings.

This similarity between tactile and visual decision making indicates that the underlying process is supramodal and might indeed depend on the motor output rather than the sensory domain as predicted from the intentional framework of decision making (Shadlen et al., 2008). Further evidence stems from data used in study 2, experiments 1 and 2. Published also as Herding et al. (2016, 2017), this data demonstrates that depending on the response modality, the choice-selective beta band modulation can be source localized either to the premotor cortex for button press or the FEF for saccade responses. While these tasks used essentially the same sequential frequency comparison, we can now add that also in the comparison of sequentially sampled RDM stimuli the decision-related beta band modulation can be observed. This is particularly interesting, because during motor processing the beta frequency band does not solely represent motor preparation, as historically thought (Pfurtscheller, 1981). Indeed, when participants responded with either their left or right hand, lateralized beta band power over contralateral MI scaled with the process of accumulating evidence for a decision, tracking the evolving decision variable (Donner et al., 2009; O'Connell et al., 2012). In our recordings with button-press responses, we used the right index and middle fingers, which in addition were counterbalanced

across volunteers, eliminating the possibility that contralateral sensorimotor beta band modulations accounted for choice-dependent beta exclusively. Moreover, because in study 3 we used a visual task and found almost identical results, we can separate such decision-beta from the beta oscillations observed during somatosensory perception. If this modulation is indeed independent from perception and is related to the choice information, then we should only be able to find it if a response mapping is provided. Therefore, in study 2, experiments 3+4, also published as Ludwig et al. (2018), participants were only provided with the response mapping after a short delay and had to transform the decision information onto a colour code. Interestingly, in those trials where responses could not be immediately transformed into motor commands the beta band was also similarly modulated, but in posterior parietal cortex, not premotor areas. Taken together with our visual and tactile experiments employing direct mappings, this implies that the way we respond determines where in the sensorimotor hierarchy the decision is processed and supports an intentional framework (Shadlen et al., 2008). Furthermore, our findings indicate that the beta band reflects the categorical, abstract content of a decision, even in the absence of a motor plan. This is particularly interesting, because also broadband centroparietal signals (CPP) have been theorized to reflect the closely related process of accumulating evidence.

3.6 Common ground for CPP and decision beta

Both the premotor beta oscillations and the CPP we observed are candidate signals to reflect large-scale neural ensembles expressing the repeated sequential sampling and integration in sensorimotor neurons observed in studies with nonhuman primates (Gold & Shadlen, 2007; Hanks & Summerfield, 2017; Kelly & O'Connell, 2015; Spitzer & Haegens, 2017). In particular, they correspond well to studies focusing on the role of the PPC for decision formation. As introduced earlier, the LIP is closely connected to the accumulation of motion information from direction-selective neurons in MT, but also with frontal areas such as the FEF (Ding & Gold, 2012). Notably, the LIP and FEF can both exhibit ramping

3 General Discussion

up of neural activity and can reach a fixed level prior to saccade responses (Ding & Gold, 2010, 2012; Hanes & Schall, 1996; Roitman & Shadlen, 2002b). While the function of single neurons in these areas has been studied extensively, the precise role of the large-scale signals recorded with EEG, decision beta and CPP, remains uncertain.

The closest link between monkey and our human studies might be found between my third study and Wimmer et al. (2016). They recorded LFPs from monkey lateral prefrontal cortex during a sequential comparison task of the speed and direction of two RDM patches. During stimulus perception beta power was reduced, but theta and gamma increased. Throughout the working memory interval beta power encoded the task-relevant *S1* feature, matching our findings in visual and tactile recordings. After *S2* onset broadband LFP activity tracked the difference between *S1* and *S2* with an early sensory-related component reflecting the stimulus difference and a later component associated with the behavioural decision build-up. This is remarkably similar to our findings concerning the CPP, but in a wholly different area. However, the lPFC is very well-connected with the PPC (Cole, Pathak, & Schneider, 2010) and my own findings add to a well-established relationship between these areas (Cole et al., 2013; Cole & Schneider, 2007; Duncan, 2010; Muhle-Karbe, Duncan, De Baene, Mitchell, & Brass, 2017; Nieder, 2016). These results, in conjunction with ours, indicate that during cognitive tasks a network of prefrontal and parietal areas transition dynamically between neural coding states in a variety of frequency bands rather than one type of oscillation or broadband signal underlying perceptual decision making.

The coupling between CPP and choice-related beta in our findings, however, indicates that broadband signals and the beta band fulfil very related roles. I speculate that the CPP reflects the absolute value of a DV - maybe confidence - in an accumulation-to-bound manner, while the choice-related beta band serves to communicate the result of this process, continuously over time as is crucial for response preparation. This serves to explain, why choice-related beta appears so early in all our recordings (studies 2 & 3), about 150 ms after onset of the second stimulus, and disappears long before motor action is taken. This observation indicates that choice-related beta is strongest, when the CPP accumulates the most and the most updating of information is necessary (Twomey et al., 2015). Moreover,

this explains also why premotor beta band modulations could only be observed when the response modality was clear (Ludwig et al., 2018): the information was retained in the PPC till responses could be made. If the choice-related beta was exclusively related to response preparation, we would have observed such a modulation before subjects responded, regardless. However, further research into the beta band – CPP relationship will be necessary, to which I want to point in the next section.

3.7 Future Avenues

The present studies call for follow-up experiments. First, similar to our task design in study 1 (see attached study: von Lautz et al., 2017), it may be interesting to know where choice-beta will originate if there is a delay before responding and the response modality (button press / saccade) is either known or unknown on a trial-by-trial basis. I would hypothesize that in trials with unknown response modality beta band modulations source localize to the PPC, while in trials where subjects know how to answer, this effect originates from premotor areas or FEF.

Second, we observed a scaling of the CPP with subjectively perceived stimulus differences and related these changes to statistical decision confidence. A crucial next step will be to record actual ratings of confidence on single trials to uncover how confidence interacts with the accumulation of evidence tracked by the CPP. In particular, it remains unclear whether at the time of response a fixed threshold bound is reached or if the signal is modulated by confidence (Gherman & Philiastides, 2015; Kelly & O'Connell, 2013, 2015; Philiastides et al., 2014; Twomey et al., 2016). For example, our recordings in study 3 demonstrate that the CPP builds-up as expected from an accumulation process, but is scaled by trial difficulty at the time of response. A drift-diffusion model with non-collapsing bounds would have predicted that a fixed threshold of CPP amplitude is reached independent of trial difficulty as observed in similar recordings (Kelly & O'Connell, 2013). For future mechanistic explanations and the large body of modelling work on such decision processes

3 General Discussion

we should identify if confidence signals, e.g. from the ventral striatum as observed with fMRI (Hebart et al., 2016), are either mixed with or alternatively directly influence the CPP.

Third, it will be important to investigate gamma oscillations in this task more thoroughly, because – as previously discussed – the beta band is theorized to reflect the re-activation of content (Spitzer & Haegens, 2017) and might reflect a maintenance state that is interrupted by short gamma bursts (Lundqvist, Herman, & Miller, 2018; Lundqvist et al., 2016). Because re-activation of content may only be necessary across timespans above one second, it will be important to investigate gamma during a longer WM interval. Moreover, gamma has not been investigated during decision making in the SFC task and a possible relationship with the CPP should be investigated. MEG however, appears unsuited to detect a centro-parietal field², and previous MEG studies were not able to find such a parietal signal (e.g., Donner et al., 2009). One avenue would be to record concurrent M/EEG and use both signals to detect high-frequency gamma and the CPP. In addition, recent developments based on the Hidden Markov Model have been used to identify fast transient states in M/EEG data (Vidaurre et al., 2018; Vidaurre et al., 2016), and could be a promising method to characterize such a mechanism.

3.8 General Summary

As climate change leads to ever higher temperatures (Parmesan & Yohe, 2003), buying good quality watermelons will become more important. So, what can we say about the neural basis of finding the right melon? First, when we feel the watermelon, the power of neural oscillations in the alpha band increase over task-irrelevant visual areas. Concurrently, low beta (mu) oscillations increase over the ipsilateral hemisphere of the hand doing the feeling, while decreasing over the contralateral. Then, while we keep how the watermelon felt in memory before selecting another to test, beta band power increases with this abstract

²It would be called ‘field’, and not ‘potential’ because flux is measured in terms of space

quantity, while gamma decreases. Finally, before we point to the watermelon we want to buy, broadband centroparietal signals characterize the process of accumulating evidence for one melon or the other while beta band activity from premotor areas reflects our choice. These large-scale neural oscillations reflect the dynamic, fast-paced changes in single neurons and neuronal populations that unite their rhythms, making them detectable with neuroimaging methods from outside the human skull. This suggests that the brain uses neural oscillations to communicate information between different areas and that the more we understand about these rhythms the better we can understand the language the brain uses.

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Gamma and Beta Oscillations in Human MEG Encode the Contents of Vibrotactile Working Memory

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Ample evidence suggests that oscillations in the beta band represent quantitative information about somatosensory features during stimulus retention. Visual and auditory working memory (WM) research, on the other hand, has indicated a predominant role of gamma oscillations for active WM processing. Here we reconciled these findings by recording whole-head magnetoencephalography during a vibrotactile frequency comparison task. A Braille stimulator presented healthy subjects with a vibration to the left fingertip that was retained in WM for comparison with a second stimulus presented after a short delay. During this retention interval spectral power in the beta band from the right intraparietal sulcus and inferior frontal gyrus (IFG) monotonically increased with the to-be-remembered vibrotactile frequency. In contrast, induced gamma power showed the inverse of this pattern and decreased with higher stimulus frequency in the right IFG. Together, these results expand the previously established role of beta oscillations for somatosensory WM to the gamma band and give further evidence that quantitative information may be processed in a fronto-parietal network.

Keywords: working memory, MEG, somatosensory, gamma, beta, oscillations

INTRODUCTION

The ability to maintain behaviorally important sensory information over short periods of time is a key component of working memory (WM). The neural basis of this cognitive function has been attributed to the lateral prefrontal cortex (PFC), whose neural firing rates are modulated during stimulus retention (for review, see D'Esposito, 2007). Research in the somatosensory domain provides evidence that single neurons in the PFC can encode WM content by monotonically increasing and decreasing their firing rate (Romo et al., 1999; Brody et al., 2003). In these studies responses of neurons from the right inferior convexity of the PFC were recorded in behaving monkeys trained to decide whether the second (f2) of two sequentially presented frequencies was higher or lower than the first (f1). Hence, this task requires remembering f1 throughout a short retention interval between both stimuli. Firing rates observed during this retention interval changed as a function of f1 and were directly related to behavior, in line with an interpretation as a neural substrate of parametric WM (for review, see Romo and de Lafuente, 2013).

Complementing these findings from non-human primates, human electroencephalography (EEG) recordings during the same task have revealed a parametric increase of oscillatory

power in the beta band (15–35 Hz) as a function of f1 (Spitzer et al., 2010; Spitzer and Blankenburg, 2012). The source of this modulation was consistently found in the right inferior frontal gyrus (IFG) of the PFC. Expanding on these findings, Spitzer and Blankenburg (2012) and Spitzer et al. (2014) demonstrated this effect across sensory modalities and stimulus features, indicating a generalized role of prefrontal beta oscillations for maintaining quantitative information.

Magnetoencephalography (MEG) studies on the other hand have identified modulations of high frequency gamma oscillations (>40 Hz) accompanying somatosensory WM (Bauer et al., 2006; Haegens et al., 2010). In a vibrotactile delayed match-to-sample task, Haegens et al. (2010) demonstrated that relative to a pre-stimulus baseline, gamma power increased during the WM interval in the secondary somatosensory (SII) and frontal cortices. Furthermore, the frontal power increase correlated positively with behavioral performance, suggesting a functional role for gamma oscillations around 65–80 Hz. These results corroborate findings from other sensory domains (for reviews, see Benchenane et al., 2011; Roux and Uhlhaas, 2014; Lara and Wallis, 2015) and intracranial recordings in monkeys (Pesaran et al., 2002). Specifically, MEG studies in humans have shown that visual and auditory WM is accompanied by sustained gamma band activity in modality specific sensory areas (Lutzenberger et al., 2002; Kaiser et al., 2003; Jokisch and Jensen, 2007).

However, the available evidence for an involvement of high frequency oscillations in somatosensory WM is limited to contrasting periods of high vs. low WM load. Indeed, while investigations into the functional role of the beta-band demonstrated a parametric mapping of stimulus identity to oscillatory power, the role of gamma in maintaining stimulus features remains unclear.

In the present study, we investigated the role of cortical oscillations for the parametric encoding of human somatosensory WM. Subjects performed a vibrotactile frequency comparison task with stimuli consisting of different frequencies delivered to the left index finger. The neural substrates of performing this task were measured non-invasively with whole-head MEG, allowing for the tracking of fast oscillatory changes in high frequencies. We hypothesized that in addition to the well-established modulation of frontal beta band power by f1, oscillations in the gamma band would also be modulated by the to-be-maintained stimulus frequency.

MATERIALS AND METHODS

Participants

Twenty-three healthy volunteers (12 females, 23–37 years of age, median: 28) participated in the study and underwent a 30-min behavioral training session to learn the task one week before the MEG recording. All participants reported being right-handed, according to the Edinburgh Handedness Inventory (Oldfield, 1971), having no history of neurological illness and normal or corrected-to-normal vision. Volunteers provided written

informed consent as approved by the local ethics committee of the Freie Universität Berlin in accordance with the Human Subjects Guidelines of the Declaration of Helsinki.

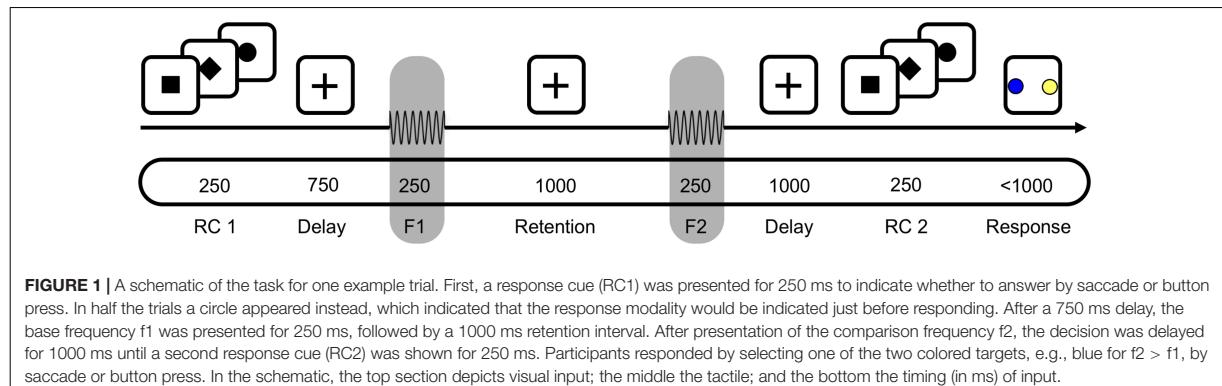
Experimental Paradigm

Participants were asked to decide whether the second of two sequentially presented vibrotactile frequencies was higher or lower than the first, either by making a saccade to a visual target or by selecting the target via button press (Figure 1). Each trial started with a fixation cross being presented at the center of a screen in front of the participant for a variable duration (750–1250 ms) at a viewing distance of 90 cm. The response type (saccade or button press) for a given trial was indicated subsequently by a square or diamond presented at the location of the fixation cross for 250 ms (first response cue, RC1; Figure 1). Alternatively, in 50% of trials, a circle appeared at this time, indicating that the response mapping would only be disclosed via a second response cue just before participants were allowed to respond (RC2; Figure 1). Then, the two vibrotactile flutter stimuli (with frequencies 11–31 Hz) were briefly presented to the left index finger (250 ms each), separated by 1000 ms. The frequency of the first stimulus (f1) was varied between 15 and 27 Hz in steps of 4 Hz while the frequency of the second stimulus (f2) was either 2 or 4 Hz higher or lower than f1. The f2 presentation was followed by a delay of 1000 ms, after which the second response cue was presented for 250 ms (RC2; Figure 1). If the first response cue had already provided the response mapping (i.e., RC1 = diamond or square), a circle was presented. In case the first response cue was uninformative (i.e., RC1 = circle), the second response cue revealed whether participants should respond via button press or saccade (i.e., RC2 = diamond or square). Following this, two colored target dots were presented at the left and right side of the screen with eccentricity of 12° visual angle ('go'-cue). One dot was blue, and the other one yellow, with the specific spatial configuration being counterbalanced across trials (i.e., blue dot was equally likely on either side). Each participant applied one of two possible color mappings (i.e., if f2 > f1, choose blue; if f2 < f1, choose yellow, or vice versa) that were counterbalanced across participants, and selected one of the colored dots according to their decision as soon as the target dots appeared (i.e., either by button press or saccade, depending on the cued response modality).

Participants completed six blocks with 128 trials each. Within each block, half the trials were answered by button press, the other half by saccades (64/64). Similarly counterbalanced was the position of the informative response cue, with half the response types indicated before and the other half after stimulus presentation (64/64). The total of 768 trials per participant resulted in a scanning time of about 75 min.

Stimuli

All stimuli were created using a PC running the MATLAB-based Psychophysics toolbox (Brainard, 1997). Vibrotactile stimulation was delivered by a piezoelectric Braille stimulation device (QuaeroSys, Schotten, Germany) to the left index finger. The 16 pins of the 4 × 4 Braille display were driven



by a constant 121 Hz carrier signal whose amplitude was modulated by sinusoids with frequencies between 11 and 31 Hz, resulting in a percept of vibrotactile flutter at the modulation frequency (Tobimatsu et al., 1999). The stimuli were loaded into the buffer of the Braille stimulation device 1 s before the presentation of f1, as the communication of PC and Braille stimulator created noticeable artifacts. To mask the noise of the Braille display, white noise was replayed at 66 dB from electromechanical transducers and transmitted via sound conducting tubes to the ears inside the MEG helmet.

Data Acquisition

Participants were positioned upright in the MEG system with their arms placed comfortably on a table in front of them. They were instructed to keep fixation on the presentation screen and not to move during the experiment. Magnetoencephalography was recorded using a whole-head MEG Vectorview NM2169N (Elekta Neuromag Oy, Helsinki, Finland) with a total of 306 MEG channels (102 magnetometers, 204 planar gradiometers). A band-pass filter of 0.03–500 Hz was applied during acquisition at 1500 samples/second and five head position indicator (HPI) coils attached to the scalp, three on the forehead and one on each mastoid, tracked the head movements continuously. Three fiducials (nasion, left and right preauricular points) as well as over 500 scalp points were measured with a Polhemus FASTRAK 3D digitizer to obtain the head shape of each participant. We did not employ electrooculography, because initial tests revealed that electrodes placed on the head increased artifacts from the QuaeroSys stimulation device (cf. Chandler et al., 2015).

Participants' responses were tracked via a NNL-Response Grip from Nordic Neuro Lab (BNC – serial port) and an iView X MEG eye-tracking system (SensoMotoric Instruments GmbH, Berlin, Germany) sampled at 50 Hz. Saccades to the left or to the right further than nine degrees off-center were interpreted as a response to the according side. Trials in which participants showed lateral eye movements before the colored targets appeared and those in which the wrong response modality was used were excluded from further analysis. Before each block started, the eye-tracker

was calibrated and validated with a standard five-point procedure.

Data Processing

All MEG data were preprocessed using the Oxford Centre for Human Brain Activity software library (OSL)¹ drawing on the Fieldtrip toolbox² (Oostenveld et al., 2011) and SPM12 (Wellcome Department of Cognitive Neurology, London, United Kingdom³).

As a first preprocessing step, we identified noisy channels and periods of strong artifacts by visually inspecting the continuous recordings. Then, using the MaxMove software (Elekta Neuromag), noise sources outside the skull were removed by applying signal-space separation with its temporal extension. Head movement compensation based on continuous tracking of the HPI coils was used and each individual's data transformed to the co-ordinate frame of their third scanning block. Subsequently the continuous data were bandpass filtered at 0.1–165 Hz, down-sampled to 512 samples per second and cut into epochs with respect to f1 onset in a time window of −1000 to +1500 ms. After visual inspection of individual trials to identify extreme muscle artifacts, squid jumps and signal drop out, an independent component analysis (ICA), as implemented in the EEGLAB toolbox (Delorme and Makeig, 2004), was calculated to identify blink, saccade and heart beat components, which were excluded in the remixing of the data. We conservatively rejected only those components that showed a very typical artifactual nature. In a final visual inspection, trials with persisting artifacts were manually removed.

To obtain a time-frequency (TF) representation of spectral power we used a sliding window Fourier transform at steps of 20 ms and applied a Hann taper with seven cycles length for frequencies 5–40 Hz. For higher frequencies, we used a multitaper Fourier transform with a fixed sliding window of 200 ms and ±10 Hz smoothing.

Evoked power was calculated for each f1-f2 stimulus pair by computing the TF representation of the according event related

¹<http://ohba-analysis.github.io/>

²<http://www.fieldtriptoolbox.org>

³www.fil.ion.ucl.ac.uk/spm/

fields (ERFs). ERFs were obtained by averaging all baseline-corrected trials (with respect to 650–150 ms prior to f1) for each stimulus pair in the time domain. Induced power was calculated by subtracting the ERFs of each stimulus pair from according single trials before transforming the single-trial data into the TF domain. The resulting single-trial TF representations were averaged for each condition (i.e., per stimulus pairs) to yield estimates of average induced power per condition. Finally, we applied a frequency-specific baseline correction by subtracting the average power in each frequency band 650–150 ms before f1 onset from the whole trial. For further analyses and display purposes, we combined the set of two orthogonal gradiometers at each location, resulting in 102 rectified planar gradiometers.

Statistical Analysis

Time-frequency maps were convolved with a 3 Hz × 300 ms Gaussian smoothing kernel (Kilner et al., 2005) to reduce variability between trials. To investigate parametric coding of f1 frequency during the retention interval, we implemented a general linear model (GLM) with a one-factorial repeated measures design for individual trials with the four f1 conditions as factor levels (i.e., f1 = 15, 19, 23, or 27 Hz). The accordingly estimated parameter maps (beta images) were weighted with a zero-mean contrast vector of [−0.75, −0.25, 0.25, 0.75]. The resulting contrast images depict the parametric difference across the four conditions in each TF bin.

These images from all individuals were statistically validated via a cluster-based permutation test procedure over all subjects (Maris and Oostenveld, 2007). This test controls the false-alarm rate by using a cluster statistic that is evaluated under a permutation distribution of summary statistics of the observed data, which we established with 5000 randomly sign-flipped permutations. A cluster was defined as a group of adjacent time-frequency bins whose cluster-defining threshold surmounted $p_{\text{threshold}} < 0.05$. Clusters exceeding the family-wise error (FWE) corrected threshold of $p_{\text{FWE}} < 0.05$ (corrected for time, frequency, and channels) were considered to be statistically significant. Cluster-based inference, which serves to reject the null hypothesis of the whole time-frequency-channel window, was supplemented by conventional linear trend analysis over time, pooled over the channels and frequency bands in which a significant effect had been observed. The aforementioned analysis steps were also applied to equal-sized subsets of correct and incorrect trials. For each cluster, the statistical comparisons were then based upon those channels and frequencies exhibiting a significant effect in the main parametric contrast of induced power. This cluster analysis was supplemented by conventional *t*-tests between correct and incorrect trials on all timepoints where significant clusters had been identified and were subjected to Bonferroni-Holm correction.

To maximize the power of these parametric contrasts, we pooled trials over both response modalities (i.e., saccades and button presses) and response cues (i.e., before and after stimulus presentation). To ensure that there were no differences between the underlying subgroups for the parametric WM effects, we applied the same procedure for these separate

conditions. Moreover, to verify that response times (RTs) – as a measure of WM load – did not have an influence on the parametric coding of vibrotactile frequencies, we contrasted the four estimated parameter maps from the GLM inversion (i.e., one beta image for each base frequency) by the according individual mean RTs, instead of the actual f1 frequencies as in the main analysis. Both control analyses did not reveal any significant clusters during the WM period of this task.

Source Reconstruction

The 3-D sources of the observed effects at the sensor level were reconstructed using T1-weighted structural magnetic resonance (MR) images. The images were acquired with a Siemens 3.0 Tesla TIM Trio or Verio scanner, either using a T1-weighted MPRAGE sequence (TR = 2300 ms, TE = 2.96 ms, flip angle = 9°, FOV = 256 mm × 240 mm × 176 mm, voxel size = 1.0 mm isotropic) or a T1-weighted MP2RAGE sequence (TR = 5000 ms, TE = 2.92 ms, TI1 = 700 ms, TI2 = 2500 ms, flip angle 1 = 4°, flip angle 2 = 5°, matrix size = 240 × 256 × 176, voxel size = 1.0 mm isotropic). The individual structural MR images were used to create cortical meshes of 8196 vertices by warping meshes from a brain template to the inverse spatial normalization of individual brains. The MEG recording sites were co-registered with the MRI using three fiducials: the nasion as well as the left and right pre-auricular points. The forward model (i.e., leadfield matrix) was estimated as a realistic single shell (Nolte, 2003).

The inversion of the forward model was based on the preprocessed MEG data in the time domain, prior to TF transformation. Before model inversion, the time domain signal was bandpass-filtered and epoched to representative time-frequency windows that reflected the features of the sensor space analysis; namely the significant times and frequencies of the cluster-based permutation test for the localization of the WM effect, and the time of f1 presentation in combination with according frequency bands (i.e., frequency of f1 ± 1 Hz) for the localization of somatosensory steady-state evoked fields (SSEFs). The forward model was inverted using multiple sparse priors (MSP; Friston et al., 2008) under group constraints (Litvak and Friston, 2008) as implemented in SPM12 for each condition separately. For each participant, the results of model inversion were summarized by 3-D images reflecting the spectral source amplitude averaged over the corresponding TF windows of interest. These matched the significant clusters of the sensor level analysis for the WM effect, and were according to time and frequency of f1 presentation for the localization of SSEFs. For the source reconstruction of the WM effect, the summary images were contrasted in analogy to the sensor space analysis, namely by a parametric contrast corresponding to the four different f1 values (i.e., f1 = 15, 19, 23, 27 with contrast vector = [−0.75, −0.25, 0.25, 0.75]). For the source reconstruction of SSEFs, the 3-D summary images of spectral source power during f1 presentation (at corresponding frequencies) were weighted by the individual amplitudes of SSEFs as observed at the sensor level. Since somatosensory SSEFs (i.e., somatosensory steady-state evoked potentials recorded with EEG) are known to show a bell-shaped amplitude profile over stimulus frequencies in

the flutter range when recorded at the scalp (e.g., Snyder, 1992; Tobimatsu et al., 1999), this specific amplitude profile was also used to identify the most likely cortical sources of SSEFs. On the group level, individual source estimates were contrasted using conventional *t*-tests. Sources that exceeded a statistical threshold of $p < 0.01$ ($p < 0.001$ for SSEFs; both uncorrected) were displayed to indicate the most likely sources underlying the effects observed at the sensor level. References to anatomical landmarks were established with the SPM anatomy toolbox (Eickhoff et al., 2005) and are expressed in the Montreal Neurological Institute and Hospital (MNI) coordinate system.

RESULTS

Behavior

Participants correctly discriminated on average 69% ($SD = 7\%$, **Table 1**) of all presented stimulus pairs and each participant's correct responses exceeded the guess rate of 50%. A within-subjects ANOVA with the factors 'base stimulus frequencies' in Hz (15, 19, 23, 27) and 'difficulty' (± 4 Hz vs. ± 2 Hz) was performed on percentages of correct responses (PCR), logit-transformed to account for the non-normality of the residuals. This analysis revealed no effect of base stimulus frequency (i.e., f1) on the percentage of correct responses [$F(3,66) = 1.25$, $p > 0.05$]. However, as expected, participants were more successful on easy trials ($f_2-f_1 = \pm 4$ Hz) as compared to difficult trials [$f_2-f_1 = \pm 2$ Hz; $F(1,22) = 101.64$, $p < 0.001$]. Similarly, we

performed a 2×2 within-subjects ANOVA with factors 'response type' (button vs. saccade) and 'response cue' (before vs. after stimulus presentation) on the logit transformed PCRs, which revealed no significant differences (all $p > 0.05$, see **Table 1**).

On average, participants responded 430 ms after the 'go'-cue, i.e., after displaying the response mapping on the screen. Because we applied a forced-delay decision task, RTs were not expected to show large variability across different stimulus conditions. Accordingly, a within-subjects ANOVA with factors 'base stimulus frequencies' and 'difficulty' of the median RTs did not reveal any significant differences (all $p > 0.05$, see **Table 1**). The same analysis with the factors 'response type' and 'response cue' showed faster answers by button press than saccades [$F(1,22) = 24.82$, $p < 0.001$]. One reason for this difference was that detecting saccades accurately was slower than reading out button presses. Participants also gave faster responses when the response cue was delivered before stimulus presentation [$F(1,22) = 30.71$, $p < 0.001$, for a list of all RTs see **Table 1**].

Stimulus-Evoked Fields

Stimulus evoked MEG activity from all planar gradiometers are depicted in **Figure 2A** for one exemplary stimulus pair ($f_1 = 23$ Hz; $f_2 = 27$ Hz). The vibrotactile stimulus evoked strong frequency-specific steady-state evoked fields (SSEFs), contralateral to the stimulated hand (**Figure 2B**). Source reconstruction localized the steady-state evoked response focally to the right somatosensory cortex, with a cluster spanning areas 3b, 1 and 2 (peak: 24, -38, 57). Crucially, evoked responses were limited to the duration of stimulus presentation and were absent during the retention interval.

We were interested whether subjects' performance was related to their steady-state evoked responses as previously reported with EEG (Spitzer et al., 2010). **Figure 2C** shows the grand average narrow band evoked activity at the frequency of f1 and f2 stimulation, computed over all stimulus conditions for equal subsets of correct and incorrect trials. The illustrated time-courses are based on averages from planar gradiometers over right somatosensory areas, where SSEFs were most pronounced. Statistical analysis revealed differences between correct and incorrect trials during both base (f1) and comparison (f2) stimulus presentation ($p < 0.05$). This difference is likely due to participants increased attention during correct trials, which has been shown to enhance somatosensory evoked potentials (Bardouille et al., 2010). Additionally, we tested whether individual SSEFs were related to behavioral performance across participants. The correlation between subject's PCRs and SSEF amplitude was not significant [Pearson's $r(21) = 0.34$, $p = 0.11$; **Figure 2D**], however, there was a trend toward stronger SSEFs in subjects with higher performance.

Induced MEG Responses

The overall induced responses observed in higher and lower frequencies pooled over all trials are illustrated in **Figure 3**. Transient and steady-state evoked potentials were eliminated by subtracting the average waveform before time-frequency transformation for each base and comparison frequency pair.

TABLE 1 | Average task performance.

Behavioral performance

Frequency (Hz)	% Correct	RT (ms)
15	67 (12)	437 (106)
19	69 (9)	430 (97)
23	71(9)	428 (93)
27	66 (7)	425 (93)
Total	69 (7)	430 (97)
<i>f₁-f₂ (Hz)</i>		
-4	69 (11)	432 (98)
-2	62 (9)	433 (101)
2	65 (9)	435 (100)
4	79 (11)	420 (90)
Response cue before		
Button press	69 (8)	379 (109)
Saccade	69 (7)	443 (91)
Response cue after		
Button press	68 (8)	419 (110)
Saccade	69 (8)	478 (99)

The top part shows the performance for the four base (f1) frequencies as proportion of correct responses (PCRs; in %) as well as the median reaction times (RTs) in milliseconds. The middle part depicts PCRs and RTs as a function of the difference between base (f1) and comparison (f2) frequency. The bottom part shows the performance for the different response modalities, separate for whether the response cue appeared before or after vibrotactile stimulation. All entries are followed by the corresponding standard deviation in brackets.

Because the piezoelectric stimulation device created an artifact that varied trial-by-trial, subtracting the average waveform left a residual artifact that was restricted to the time of stimulus presentation (**Figure 3B**).

In comparison to a prestimulus baseline, vibrotactile stimulation induced the typically observed changes in the beta band (15–25 Hz) over somatosensory areas (see Spitzer et al., 2010). During and immediately after stimulation, we observed a beta power decrease over bilateral somatosensory channels (**Figures 3B,C**; peak: 42, -26, 52), which was followed by a rebound, dominantly contralateral to the side of stimulation (**Figures 3B,D**; peak: 46, -34, 63). Moreover, alpha band (7–12 Hz) activity was increased during the retention phase in posterior channels (**Figures 3B,E**). Source reconstruction of this effect revealed a distributed activation pattern over visual regions that was most robust ipsilateral to the stimulated hand (peak: -12, -90, 45). Furthermore, this effect was more pronounced in correct than incorrect trials ($p_{\text{FWE}} < 0.05$). As visual input was inconsequential for task performance during this time, alpha power appears to reflect top-down inhibition of task-irrelevant cortical areas (Klimesch et al., 2007; Jensen and Mazaheri, 2010).

While there were no changes in induced gamma power (>40 Hz, **Figure 3A**) with respect to the prestimulus baseline, frontal gamma power between 70 and 110 Hz was related to task performance. In particular, we found higher broadband gamma band power for correct as compared with incorrect trials ($p_{\text{FWE}} < 0.01$). However, this effect neither correlated with changes in occipital alpha power across subjects, nor with participants' overall performance (both $p > 0.05$), as had been reported previously (Haegens et al., 2010).

Parametric Contrast of Induced Beta Oscillations

The central aim of this study was to identify changes in oscillatory power that scale with the stimulus held in WM throughout the delay period. **Figure 4** illustrates such a parametric WM effect for low frequencies (5–40 Hz). A cluster-based permutation test revealed TF windows in which the effect was statistically significant (**Figure 4A**). Interestingly, this analysis indicated two distinct clusters in the beta band (both $p_{\text{FWE}} < 0.05$), centered at the middle of the retention interval. One cluster spanned frequencies in the lower beta band (10–20 Hz) and showed the strongest modulation over bilateral parietal channels (**Figure 4E**). Source localization of this effect indicated focal activity in the right intraparietal sulcus of posterior parietal cortex (PPC; **Figure 4E**; peak: 50, -44, 53), an area closely linked to numerosity processing (Nieder, 2016). Markedly, the average time courses of lower beta power scaled monotonically with the frequency held in WM (**Figure 4D**), as confirmed by linear trend analysis (600–1050 ms, $p < 0.05$). The second cluster extended to the upper beta frequency range (30–35 Hz) and peaked in right frontal channels (**Figure 4C**). The most likely source of this effect was located in the right IFG of the lateral PFC (**Figure 4C**; peak: 48, 12, 35). Similar to the effect in the lower beta band, high beta power scaled with the remembered

stimulus frequency throughout a large portion of the retention interval (**Figure 4B**).

To investigate a link to behavior, we compared the observed modulations of beta band power between correct and incorrect trials. When the analysis was based exclusively on incorrect trials, the observed parametric contrast did not reveal any significant effects. However, while analyses of only correct trials revealed the same pattern as the main analysis, the difference between correct and incorrect was not significant. Note that this analysis was limited to a fraction of trials to match the amount of correct with incorrect trials, which strongly reduced statistical power. **Figure 4F** illustrates an example of the performance related differences and displays the parametric contrast statistic at 30–35 Hz for equal-numbered subsets of correct and incorrect trials separately.

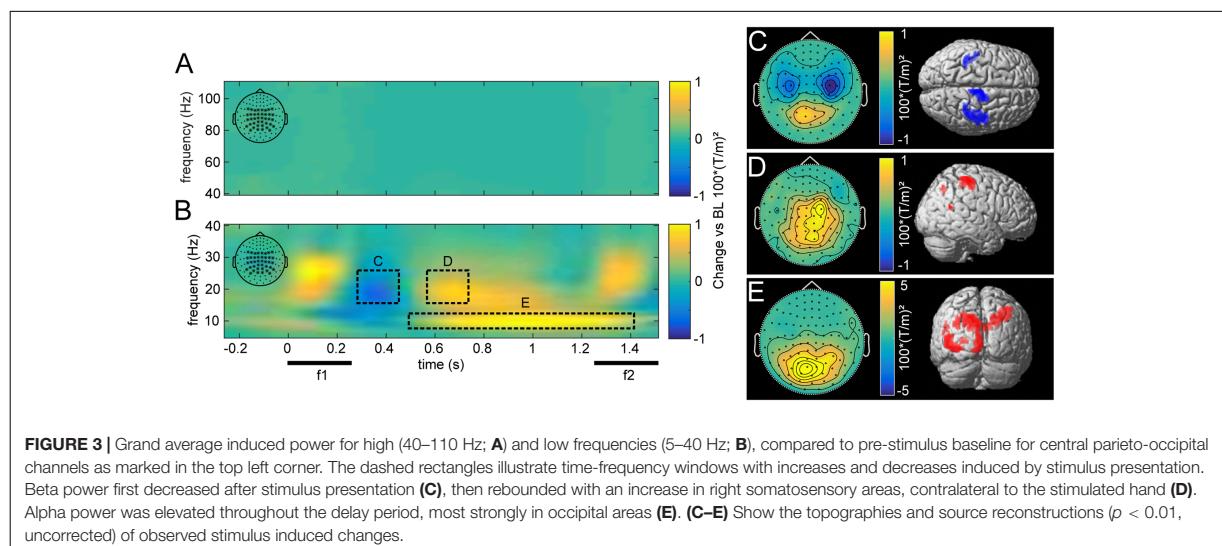
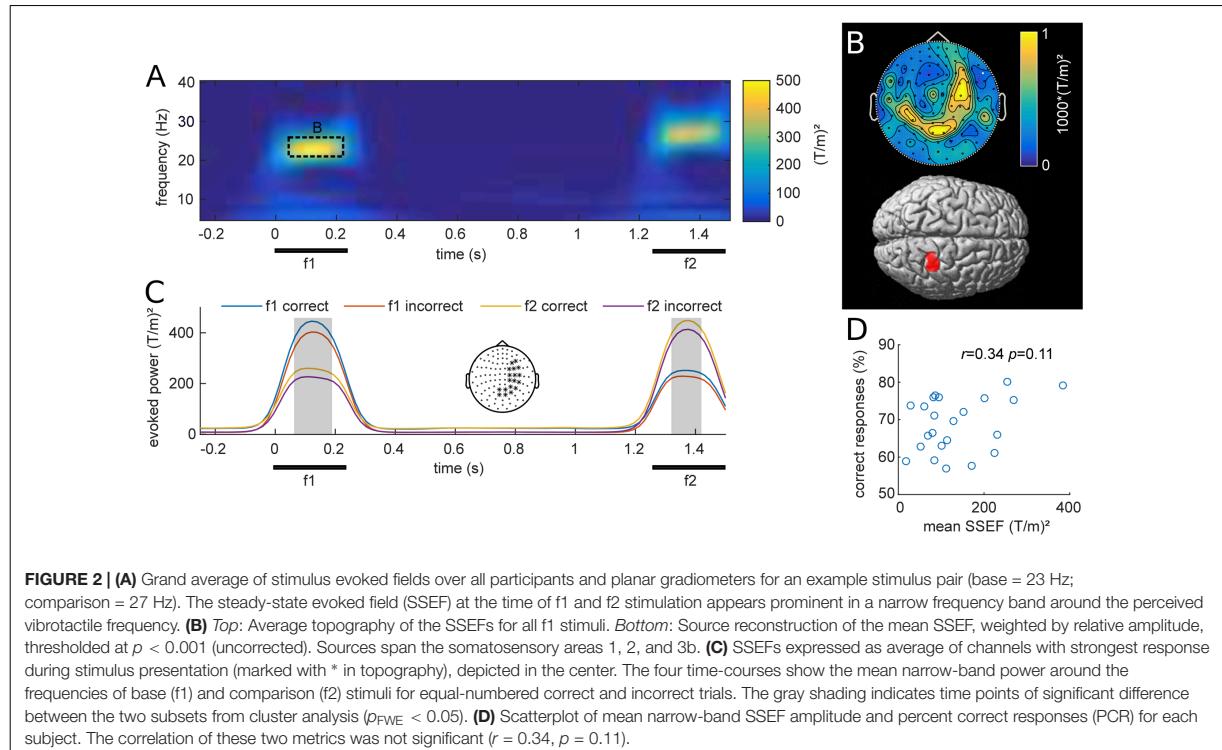
Parametric Modulations of Induced Gamma Activity by f1

The main focus of the present MEG study was the possible parametric modulation of higher frequency oscillations throughout f1 retention, complementing the previously established effects in lower frequencies with EEG. Statistical analysis of frequencies in the gamma band revealed a cluster of prefrontal channels, whose power at 74–90 Hz declined monotonically with increasing f1 frequency (**Figures 5A,E**; $p_{\text{FWE}} < 0.05$). Source reconstruction of the TF cluster identified the right IFG as the origin of this negative gamma band modulation (**Figure 5B**; peak: 50, -44, 53). In comparison with the high beta effect, which showed the opposite pattern (i.e., an increase with stimulus frequency), the modulation of gamma band activity was localized to more anterior and inferior areas, also reflecting the differences in their respective scalp topographies (viz. **Figures 4C, 5B**). Linear trend analysis of the average power in this frequency range for each of the four f1 stimuli was significant between 550 and 800 ms after f1 onset (**Figure 5C**).

The separate analysis of equal-numbered subsets of correct and incorrect trials resulted in the same pattern as observed in lower frequencies. While an analysis based exclusively on correct trials appeared more similar to the effects of all trials (i.e., showed a modulation by f1), incorrect trials did not show this pattern. However, because this analysis was based upon random permutations of a fraction of trials, statistical power was strongly reduced and no significant differences manifested between the two subsets (**Figure 5D**).

DISCUSSION

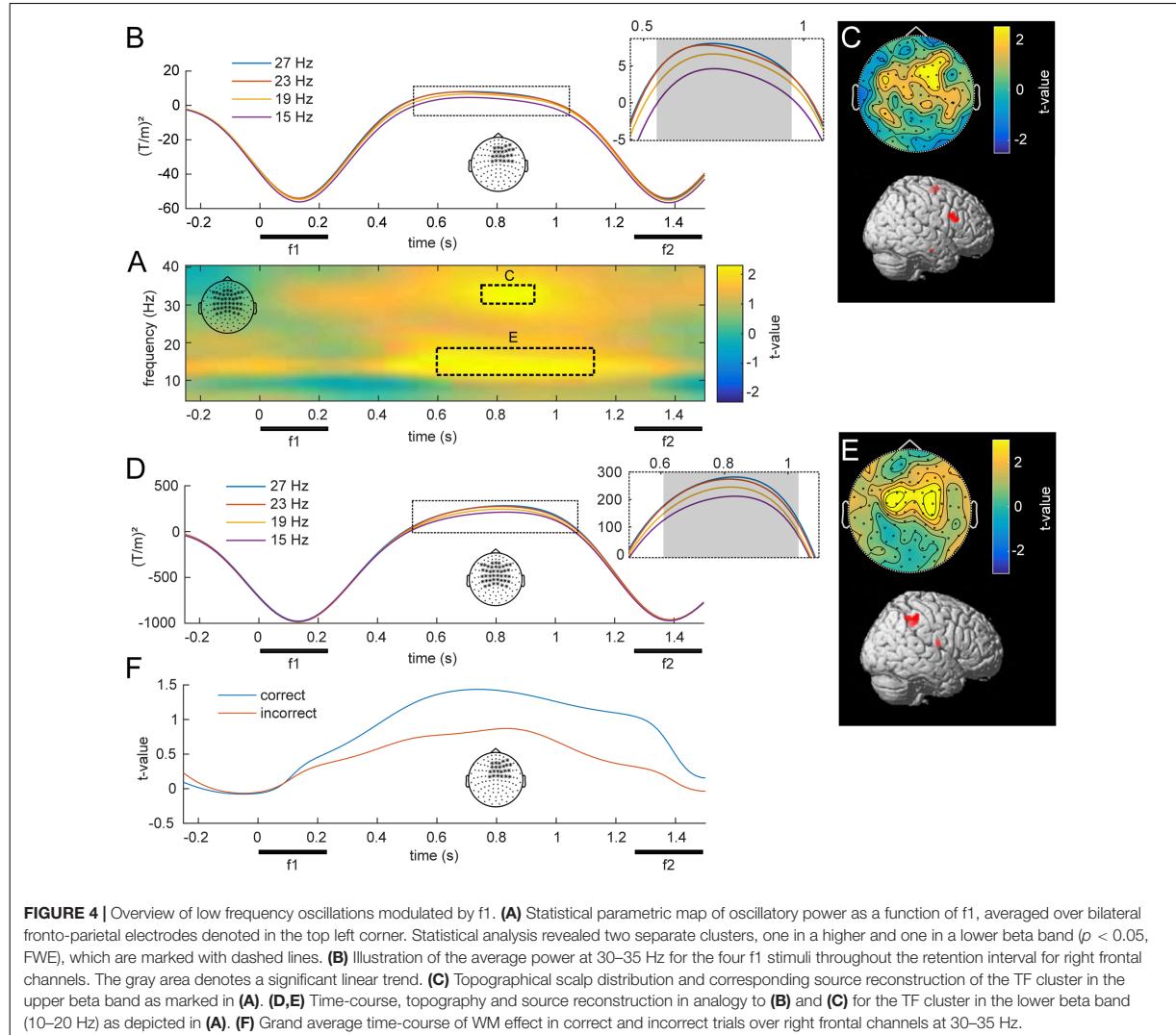
In the present study, we recorded MEG in humans to determine the neural oscillations underlying vibrotactile frequency maintenance during WM. In a sequential frequency comparison task, we identified modulations of spectral power by the to-be-remembered vibrotactile stimulus frequency (i.e., f1) in the beta (at 10–20 and 30–35 Hz) and gamma (at 74–90 Hz) range during the WM period of the task. Oscillatory power in the beta band parametrically increased in parietal and prefrontal areas with



the magnitude of f1. In contrast, prefrontal gamma oscillations parametrically decreased with increasing f1.

The sequential frequency comparison task employed in this study required participants to maintain the stimulus frequency of the first stimulus (i.e., f1) in WM. Consistent with previous EEG studies of somatosensory WM (Spitzer et al., 2010; Spitzer and Blankenburg, 2011, 2012) we identified oscillations

in the beta band (10–35 Hz) that encoded the frequency of f1 in a parametric manner during the delay period of the task. The parametric change of high beta power was localized to the IFG in full agreement with previous EEG (Spitzer et al., 2010), fMRI (Kostopoulos et al., 2007) and electrophysiological recordings (Romo et al., 1999; Brody et al., 2003) that demonstrated a crucial role of the IFG for parametric

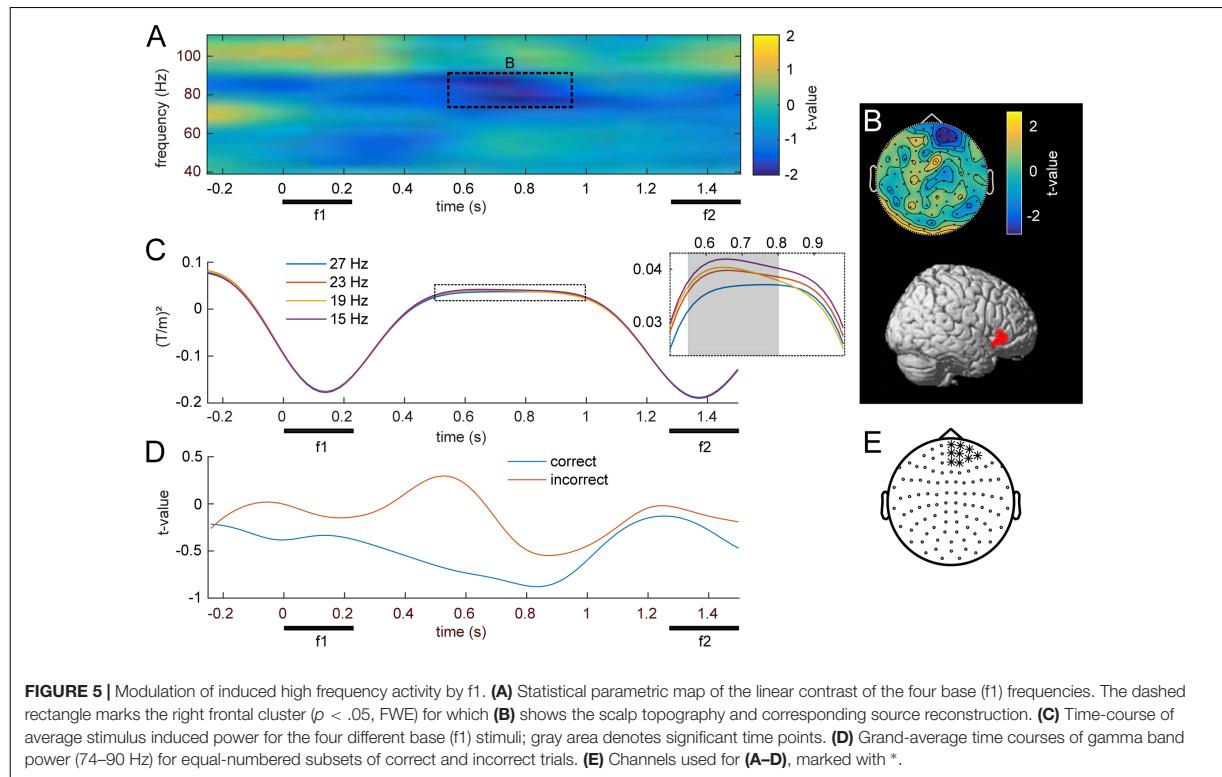


somatosensory WM. Contrary to previous EEG recordings (Spitzer et al., 2010; Spitzer and Blankenburg, 2011, 2012), in which the skull typically acts like a low-pass filter (Pfurtscheller and Cooper, 1975), the observed effect extended above 30 Hz and might therefore be termed a change in the gamma, not the beta band.

Interestingly, we also observed modulations of high frequency gamma power in the right IFG. However, this effect displayed the opposite pattern of the parametric modulation of spectral power in the beta band, i.e., gamma band power decreased monotonically with stimulus frequency. The observed effect in the gamma band appeared in the same frequency range (74–90 Hz) as other correlates of WM in MEG (Kaiser et al., 2003; Fuentemilla et al., 2010; Haegens et al., 2010) and was estimated to be located slightly anterior to the high beta band modulation. Whereas the overall induced gamma power was additionally

related to performance within subjects, it neither correlated with performance across subjects, nor with alpha power as was previously observed in a similar task by Haegens et al. (2010). The same study also observed a sustained broad band gamma increase in SII during the retention phase for which we found no evidence in the present study. The lack of such a sustained signal favors the notion that WM exhibits dynamic oscillatory changes – not sustained activity – as evidenced in single-cell recordings (cf. Shafi et al., 2007; Stokes et al., 2013; Lundqvist et al., 2016).

As signal detection with MEG depends on large-scale oscillatory changes, we speculate that our observations reflect a population-level correlate of the heterogeneous encoding as a complex pattern of increases and decreases in firing rate observed in single cells (Barak et al., 2010). This is in line with previous EEG studies (Spitzer and Blankenburg, 2011, 2012) hypothesizing



that parametric prefrontal WM effects may indicate an abstract internal scaling of analog quantity information, according to task demands. While the basis of this interpretation was confined to prefrontal oscillations in the beta band, the present results extend this view to prefrontal gamma. This is particularly interesting, because gamma amplitudes recorded with EEG, but not beta, have been found to predict neural responses from multiunit activity recordings in monkeys (Whittingstall and Logothetis, 2009), thus being more likely to represent commonalities between monkey and human research.

Contrary to previous EEG studies, we found that low beta band power (10–20 Hz) was also parametrically modulated by the stimulus frequency held in WM. Interestingly, this effect localized to the right intraparietal sulcus (IPS), an area well-established in its role for supramodal number processing (Eger et al., 2003; Castelli et al., 2006; Nieder, 2012). In particular, blood-oxygen-level dependent (BOLD) responses in the IPS can be used for multi-voxel pattern analysis to distinguish between quantities (Eger et al., 2009) and have been shown to activate in conjunction with inferior frontal areas in numerosity tasks (Piazza et al., 2007; Knops et al., 2014). The present results therefore join growing evidence that indicates a common representation of abstract quantity in the IPS and PFC.

It is unclear, however, why previous EEG studies (Spitzer et al., 2010, 2014; Spitzer and Blankenburg, 2011, 2012; Herding et al., 2016) did not detect the observed changes in the IPS. Besides the higher signal-to-noise ratio for shallow sources with

MEG compared to EEG, one reason may be that MEG is more sensitive to sulcal than gyral sources, making the detection of oscillations from the intraparietal sulcus more likely than those from, e.g., the IFG (Hämäläinen et al., 1993; Goldenholz et al., 2009).

Notably, the parametric changes in low beta (10–20 Hz) included frequencies as low as those in the alpha range (8–12 Hz – also called ‘mu’), which are commonly associated with the functional disengagement of particular brain areas (Klimesch et al., 2007). However, the low beta signal was parametrically modulated by the stimulus frequency, suggesting a feature-specific role of the underlying neural process. We suggest that our findings may be explained by frequency specific inhibitory processes in sensorimotor areas themselves, as proposed by the discrete coding and periodic replay hypothesis (Sandberg et al., 2003; Lundqvist et al., 2011), and might be an expression of passive maintenance states as theorized by the dynamic coding framework (Stokes, 2015). In agreement with this idea, the observed beta-gamma dynamics may reflect feature specific differences in brief beta and gamma bursts, which would agree with recent observations in monkeys (Lundqvist et al., 2016). Overall, it appears that an intricate interplay of beta and gamma oscillations in fronto-parietal areas underlies tactile WM, as has recently been observed for attention (van Ede et al., 2014).

In summary, we have shown that beta and gamma oscillations in the IFG parametrically encode stimulus features while

retaining vibrotactile frequencies in working memory. Interestingly, in contrast to increases in the beta band, gamma oscillations decreased with the to-be-maintained frequency. Additionally, we found a modulation of spectral power by stimulus frequency in a lower frequency range in the intraparietal sulcus, which underlines the close coupling of IPS and IFG for the processing of abstract quantities. Our findings suggest a functional role of neural oscillations for WM in a fronto-parietal network, with an extended role of beta and gamma oscillations for the somatosensory domain.

ETHICS STATEMENT

This study was carried out in conformance with the recommendations of the ethics committee of the Freie Universität Berlin with written informed consent from all subjects and in accordance with the Declaration of Helsinki.

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AUTHOR CONTRIBUTIONS

AvL, JH, SL, TN, and FB: experiment design, data collection, data analysis, article preparation. BM and AV: data collection, data analysis, article preparation.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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