SENSORY AND WORKING MEMORY IMPAIRMENTS, DELAYED DECISIONS, AND DIFFERENT ACTION MODALITIES WITHIN THE SOMATOSENSORY PERCEPTION-ACTION CYCLE

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Contents

Abbreviations

DLPFC	dorsolateral prefrontal cortex
EEG	electroencephalography
FEF	frontal eye fields
fMRI	functional magnetic resonance imaging
IFG	inferior frontal gyrus
IPL	intraparietal lobe
ITC	inter-trial coherence
LIP	lateral intraparietal area
MFG	middle frontal gyrus
MPC	medial premotor cortex
MT	middle temporal area
PFC	prefrontal cortex
PMC	premotor cortex
PPC	posterior parietal cortex
ROI	region of interest
S1	primary somatosensory cortex
S2	secondary somatosensory cortex
SFC	sequential frequency comparison
SFG	superior frontal gyrus
SSEP	steady-state evoked potential
VPC	ventral premotor cortex
WM	working memory

Abstract

To guide meaningful behavior in the environment, the human organism must rely on and incorporate sensory information to inform goal-directed actions. To study these processes, neuroscientists have experimentally established and tested a basic framework of the perception-action cycle by means of a vibrotactile sequential frequency comparison (SFC) task. In brief, two vibrotactile stimuli are subsequently applied to the finger of a subject. Subjects then have to decide whether the frequency of the second vibration was higher or lower than the first one. Based on this task, the neural processes underlying the sensory encoding of stimuli, the maintenance of the frequency of the first stimulus until the second stimulus is presented, as well as the comparison of the frequencies leading to the choice, have been extensively investigated in non-human primates as well as in humans.

In this thesis, the seminal work mentioned above was extended to study alterations in sensory encoding and maintenance in the psychiatric disorder of schizophrenia. In study 1, we provided novel evidence suggesting that in patients both of these processes are independently impaired. Study 2 focused on the decision process in this task and explored the *intentional framework* claiming that perceptual decisions are accomplished by the execution of action responses. Here, we showed that subjects' choices in this task were indeed represented in neural oscillations attributed to the frontal eye fields, an area involved in planning saccades, when they respond with eye-movements instead of button presses. In the last study, we demonstrated that when decision reports are instructed to be given after a delay, subjects still maintain stimulus information in parallel to the formation of decisions. Further, by manipulating the response characteristics we show that choices are generally represented in the context of their consequences.

Zusammenfassung

Menschliches Leben zeichnet sich durch eine ständige Interaktion des Organismus mit seiner Umwelt aus. Hierbei nimmt der Mensch sensorische Reize auf, um sie in kontextabhängige und zielgerichtete Handlungen umzusetzen. Um die neuronalen Prozesse, die diesem fundamentalen Verhalten zugrunde liegen, zu untersuchen, wurde die Charakterisierung einer basalen Wahrnehmungs-Handlungs-Schleife experimentell mit Hilfe der sequenziellen Frequenz-Vergleichs-Aufgabe etabliert. In diesem häufig verwendeten Paradigma bekommen Versuchspersonen zwei mechanische Vibrationen nacheinander am Finger präsentiert. Ihre Aufgabe ist nun, zu entscheiden, ob die zweite Vibration eine höhere oder eine niedrigere Frequenz hat, als die erste. Dieses einfache Paradigma hat viele Einsichten über die neuronale Enkodierung von somatosensorischen Reizen ermöglicht. Außerdem gibt es Aufschluss darüber, wie Informationen des ersten Reizes im Arbeitsgedächtnis aufrecht erhalten werden bevor der zweite Reiz appliziert wird und wie beide Reize verglichen werden, um schließlich eine Entscheidung zu fällen.

In der vorliegenden Dissertation wurde diese Aufgabe genutzt, um taktile Wahrnehmungsverarbeitung und Arbeitsgedächtnisprozesse in Patienten mit Schizophrenie zu untersuchen. Die Ergebnisse der Studie liefern neue Erkenntnisse darüber, dass diese beiden Prozesse in der klinischen Stichprobe unabhängig voneinander beeinträchtigt sind.

In der zweiten Studie, mit gesunden Versuchspersonen, stand die Entscheidungsphase der zuvor beschriebenen Aufgabe im Vordergrund. Hier war es das Ziel, die intentionale Theorie zur Entscheidungsfindung zu untersuchen, bei der angenommen wird, dass Entscheidungen weniger Vergleiche von Perzepten als vielmehr durch die Ausführung von Handlungen realisiert werden. Tatsächlich konnten wir mithilfe oszillatorischer Aktivität im Elektroenzephalogramm (EEG) zeigen, dass Entscheidungen in

denjenigen Hirnarealen prozessiert werden, die Augenbewegungen planen, mit denen die Versuchspersonen auch ihre Entscheidung mitteilten. Die dritte Studie verfolgte diese Theorie weiter. Hier konnten wir zum einen zeigen, dass die Frequenzinformation der einzelnen Vibrationen auch dann aufrechterhalten wird, wenn Entscheidungen schon getroffen wurden, die Antwort aber erst später mitgeteilt wurde. Zudem konnten wir zeigen, dass die neuronale Prozessierung von Entscheidungen davon abhängt, welche Konsequenzen diese hervorrufen.

List of original articles

This dissertation is based on the following articles:

Ludwig, S., Spitzer, B., Jacobs, A. M., Sekutowicz, M., Sterzer, P., & Blankenburg, F. (2016). Spectral EEG abnormalities during vibrotactile encoding and quantitative working memory processing in schizophrenia. *NeuroImage. Clinical*, *11*, 578–587. http://doi.org/10.1016/j.nicl.2016.04.004

Herding, J., **Ludwig, S.**, & Blankenburg, F. (2017). Response-Modality-Specific Encoding of Human Choices in Upper Beta Band Oscillations during Vibrotactile Comparisons. Frontiers in Human Neuroscience, 11. https://doi.org/10.3389/fnhum.2017.00118

Ludwig, S.*, Herding, J.*, & Blankenburg, F. (submitted). Oscillatory EEG-Signatures of Postponed Somatosensory Decisions and Different Response Modalities. *Cerebral Cortex*

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1 Introduction

A crucial feature that distinguishes us human beings from non-living objects is that we have the ability to act. Usually, we are not only passively at the mercy of our environment, but we can act on and react to it. Our lives are thus defined by a constant interaction with our environment. In this thesis, the focus is on the architecture of different aspects of this human-environment-interaction and what impact they can have on human live if they are dysfunctional.

One snapshot of the constant interplay between input from and output to our environment has also been called the perception-action cycle, describing the most basic processes that lead to human behavior (e.g., Fuster, 1990). Of course, this cycle does not implicitly start with action or perception, but rather resembles a typical chicken and egg problem. Actions are triggered by sensations of the environment and at the same time produce new sensations themselves. For a long time, these internal processes have been considered locked away from observation in a "black box" and the only approach to the human interior was through inference from the study of human behavior (Watson, 1913). Since the "opening" of this box by cognitivism in the 1950s, psychologists, biologists, and cognitive neuroscientists, among other disciplines, were increasingly interested in the vast amount of processes that fill the gap between external input to an organism and its consequent behavior. Conventionally, three major types of processes in the brain have been thought to bridge this gap from input to output: perception, cognition, and action. When a stimulus enters an organism through any kind of receptor, it is sensed through processing in primary sensory areas of the brain. Depending on our attention and intention (and many other influences such as emotions) we incorporate this percept as a more or less relevant feature to be considered in our goals. Thereupon, to achieve these goals, we plan

appropriate actions and shape our behavior. This is of course a very simplified description of what is nowadays considered to happen in the human brain. Especially the consecutiveness of these steps is challenged by a view in which there is a constant interplay between the mentioned processes on all levels of the cognitive hierarchy (Fuster, 1990; Friston, 2010). This is by no means an inherently new idea but finds its origins already in William James' *ideomotor theory* (James, 1890). He describes a *common code* of perception and action in order to provide a unification of these concepts rather than to separate them as two ends of a sequence of events. Today, this idea has regained attention in the work by Fuster (1990) as well as Cisek and Kalaska (2010), and is also a fundamental concept of the *Free Energy Principle,* a unifying theory of brain function by Friston (2010). Despite the development of this common understanding of highly interlinked processes within perception and action, this complexity needs to be simplified in order to approach an understanding of the bigger picture. An experimental paradigm, which has provided elementary insights into single parsimonious instances of the perception-action cycle, is operationalized through memory-based perceptual decisions. This task has been used extensively in the somatosensory domain in non-human primates (e.g., Romo et al., 1999; Hernández et al., 2010; for review see Romo and de Lafuente, 2013) and in humans (e.g., Preuschhof et al., 2006; Spitzer et al., 2010; for review see Pleger and Villringer, 2013). Here, two vibrotactile stimuli are presented one after the other, separated by a retention period, to the finger of the subject. The task is to report whether the frequency of the second stimulus was higher or lower than the first one. Hence, this task proves to be powerful by providing the possibility to study sensory encoding during the presentation of the stimuli, working memory (WM) mechanisms in the retention phase, and decision making as well as the mapping of decisions to a motor response, when subjects decide to respond in one or the other way. Furthermore, it can also

be used as a very informative tool to investigate these processes when they impact human life by dysfunctionality, for example in psychiatric disorders. We applied this task to specify cognitive impairments in schizophrenia as the cognitive processes mentioned above convey a central deficit in this disease. Further, we used this task to address questions derived from theories about the neural implementation of immediate and delayed decisions and action in the human brain.

In the following section, the specifics of the vibrotactile sequential frequency comparison (SFC) task will be introduced and related to already existing findings that motivated the studies of this thesis.

1.1 Sensory encoding and working memory in sequential frequency comparisons

1.1.1 Insights from studies in non-human primates

One of the most prominent and also most influential paradigms to study sensory and WM processes as essential parts of the perception-action cycle in the primate brain is the SFC task. Over 40 years ago, Mountcastle and colleagues started to train monkeys in this specific task and to record neural data during task performance (LaMotte and Mountcastle, 1975). During the task, the subject simply has to decide if the frequency of a second vibration (f2) was higher or lower compared to the frequency of a first vibration (f1), which was presented usually a couple of seconds before. Solving this basic task, however, induces a number of cognitive processes. Initially, f1 has to be perceived and then maintained in WM. Subsequently, f2 has to be encoded and to be compared to f1. The choice, as the result of this decision process, has then to be mapped to the adequate motor response. This action terminates the trial, or is sometimes followed by a reward or feedback depending on the correctness of the response. Starting with the encoding of the first stimulus, Salinas et al. (2000) found that neurons in the primary somatosensory cortex (S1), primarily align their

spiking activity to the periodicity of the stimulus. Some neurons, however, increase their firing rate parametrically with increasing stimulus frequency. Further, it was suggested that neurons encoding the stimulus frequency in their firing rate might be located on a hierarchically higher level within S1 than periodically firing neurons. These neurons (owning a rate code of stimulus frequency) are likely to be linked to higher order structures like the secondary somatosensory cortex (S2) or prefrontal areas to distribute this information (Burton et al., 1995). In fact, this purely sensory information is also represented in higher order areas such as the prefrontal cortex (PFC) and the medial and ventral premotor cortex (MPC/VPC; de Lafuente and Romo, 2006). Interestingly, these areas, in the same way as S2, include sets of neurons monotonically increasing and other sets showing a monotonic decrease of firing rates, together representing a dual code of the stimulus frequency (Romo and Salinas, 2003). Beyond triggering mere sensory processing, the aim of the task is to compare both stimuli. Therefore, the frequency information of f1 has to be maintained over time until the presentation of the second stimulus. Similar to the sensory encoding in modulated firing rates, some neurons in areas such as the PFC show a dual code by partly increasing and decreasing firing rates as a function of stimulus frequency also in the retention interval (Romo et al., 1999). Both kinds of populations of neurons firing during the retention interval can be found in S2, in the PFC, as well as in multiple parts within the premotor cortex, but not in S1 (Hernández et al., 2010). Analogue to the cortical hierarchy, S2 shows this pattern in the early phase of the retention interval. PFC and the VPC show sustained modulations during the whole maintenance phase and the dorsal premotor cortex (DPC), and MPC encode the stimulus frequency at the end of this interval (Hernandez et al., 2002; Romo et al., 2002, 2004).

1.1.2 Insights from studies in humans

Although single cell recordings in monkeys provide a spatially and temporally well-defined picture of the cognitive processes of interest in this task, a major question is whether this can be generalized to the human brain. These detailed reports from animal studies have thus motivated neuroscientists to study identical processes in human subjects with multiple neuroimaging techniques. In functional magnetic resonance imaging (fMRI), vibrotactile perception and WM have been investigated using similar paradigms (Burton et al., 2008; Kostopoulos et al., 2007; Preuschhof et al., 2006; Spitzer et al., 2010). These studies show distributed brain activity during WM maintenance of those stimuli. However, as a common feature the PFC seems to be consistently involved in this task, which is congruent with the previously presented animal work (e.g., Romo et al., 1999). More recently this vibrotactile SFC task has been used during Electroencephalography (EEG) recordings. In analogy to periodic firing of neurons in monkeys' S1 (Salinas et al., 2000) it was observed, that during vibrotactile stimulation, oscillatory power significantly increased in the time-frequency transformed EEG signal in the same frequency as generated for the vibrotactile stimulus applied to the index finger (i.e., vibrotactile stimulation at 20 Hz leads to an increase of evoked oscillatory power at 20 Hz; Giabbiconi et al., 2004; Spitzer et al., 2010). These so called steady-state evoked potentials (SSEPs) were significantly weaker in incorrect trials in the SFC task (Spitzer et al., 2010). This indicates a behavioral relevance of this measure and thus provides a justification for considering SSEPs as a correlate representing sensory stimulus encoding. Subsequently in the task, when subjects have to maintain f1 in the retention interval, the power of beta oscillations (20-25 Hz) in right prefrontal electrodes was shown to be parametrically modulated as a function of f1 (Spitzer at al., 2010). This effect has been replicated and extended in multiple following studies

(Spitzer and Blankenburg, 2011, 2012; Spitzer et al., 2014). Spitzer and Blankenburg (2011) reported that in a retro cue paradigm, the same modulatory effect of the cued and therefore maintained frequency on the power of beta oscillations in the right PFC was observed. Further, it was shown that this effect is the same also in an equivalent visual and auditory task, as well as when the duration or the intensity of the stimulus have to be maintained (Spitzer and Blankenburg, 2012; Spitzer et al., 2014). In sum, these studies provide a well-defined description of how quantitative WM might be represented in these oscillatory signals.

The paradigm and the according findings described in the previous sections, do not only provide essential insights into sensory and WM processes in the healthy human brain. They also create chances to investigate exactly these processes in cases when they are assumed to be disturbed. The following section will focus on highly prevalent cognitive impairments in schizophrenia and thereby motivate study 1.

1.1.3 Sensory encoding and working memory in schizophrenia

Schizophrenia is a psychiatric disorder with a prevalence rate in Germany of about 1% equally distributed among women and men. There is a broad spectrum of symptoms associated with schizophrenia. Usually, these symptoms are clustered into two kinds, positive and negative symptoms. Positive symptoms are hallucinations and delusions, and declared 'positive' because they describe sensory experiences (e.g., hearing voices) or beliefs (e.g., paranoia) that appear in addition to a person's usual state. Negative symptoms, in contrast, are disturbances of usually relatively stable systems as emotions or cognitive functions (e.g. depressiveness or cognitive impairment). Although schizophrenia is mostly noted for the positive symptoms, successful therapeutic treatment is often much more challenged by fundamental impairments through negative symptoms. Among others, the

impairment of WM is one of the most consistently reported cognitive deficit in schizophrenia (Goldman-Rakic, 1994). It is easy to imagine that disturbances in such a core function of human cognition, which is involved in nearly every daily task, can have a tremendous impact on the general quality of life. This is one reason why there has been a recent effort to study WM in schizophrenia by means of psychological and neuroscientific experiments. In a meta-analysis, Lee and Park (2005) show that patients with schizophrenia reliably display deficits in WM across different neuropsychological tasks in different modalities. Beyond behavioral evidence, neuroimaging studies have extended the picture by showing that alterations in, e.g., oscillatory activity (Haenschel et al., 2009) or parieto- and occipito-frontal connectivity (Bittner et al., 2015; Deserno et al., 2012) are involved in impaired WM function.

Besides these findings regarding WM deficits in schizophrenia, there is also a large body of research showing that very basic sensory processes can already be disturbed in patients (e.g., O'Donnell et al., 1996; Brenner et al., 2009). However, many of the above studies on WM impairments do not take these into account, although sensory functions are a prerequisite of proper WM performance (Pasternak and Greenlee, 2005). Hence, in the previous literature, there has been a controversy about the contribution of impaired sensory processes to WM deficits in schizophrenia (Hartman et al., 2003; Tek et al., 2002). For EEG recordings, the SFC task outlined in the previous sections provides an excellent temporal distinction between sensory encoding and WM maintenance as well as distinct neural correlates of these processes to be able to identify respective deficits. Thus, it appeared very suitable to investigate these processes in patients with schizophrenia.

1.2 Decision making in sequential frequency comparisons

1.2.1 Insights from studies in non-human primates

In the previous sections, the focus was on the sensory encoding of f1 and f2 and the WM maintenance of f1 in the SFC paradigm. Subsequently in the task, e.g., about three seconds after the presentation of f1, the second stimulus is presented and the two frequencies (f1 and f2) have to be compared, in order to decide if f2 was higher or lower than f1. This is thought to be implemented by a simple subtraction process of the currently presented stimulus frequency from the memory trace of f1. Romo et al. (2002) showed that by the end of the presentation of f2, portions of neurons in S2 already started to encode whether f2 was higher or lower compared to f1, respectively. The same is true for higher order cortical areas such as PFC and MPC (Hernández et al., 2010; Jun et al., 2010). Importantly, when monkeys knew already at the beginning of the trial which button to press, so that the comparison process became obsolete, these signals vanished, speaking against the hypothesis that they encode mere motor preparation (Romo et al., 2004). Surprisingly, going further along the lines of this comparison task towards the final response, besides coding merely the appropriate hand movement, some neurons in M1 also code for the comparison operation between f1 and f2 (Salinas and Romo, 1998). It is thus suggested, that through these different subpopulations M1 might convert the result of the sensory evaluation into the final motor response. Haegens et al. (2011) reported similar findings on a larger scale by analyzing spectral signals of local field potentials in MPC. The authors show that the power of beta band oscillations in MPC code for the monkey's choice, independent of the respective motor plan.

1.2.2 Insights from studies in humans

Besides the study of WM representations in the SFC task, other researchers have investigated the neural correlates of decision formation after the presentation of the second stimulus in humans. Pleger et al. (2006) conducted this task within an fMRI scanner. The authors report that the trial-by-trial difference between the first and the second stimulus was parametrically encoded in the left dorsolateral prefrontal cortex (DLPFC). Herding et al. (2016) investigated the decision phase of the SFC task using spectral analyses analogue to earlier studies focusing on the WM interval (e.g. Spitzer et al., 2010). Interestingly, they found that the power of frequencies in a similar frequency range (upper beta) over the premotor cortex (PMC) code for subjective choice, independent of mere motor preparation.

1.3 An intentional framework of decision making

While deriving a mere application of the SFC paradigm for study 1, we wanted to go beyond using the task as an explanatory tool, by developing it further and thereby deepen the understanding of perceptual decisions and action selection. In the previous animal studies, choice selective signals were reported in areas within MPC, VPC and even M1 (e.g., Romo et al., 2004). Since choice reportings always required specific actions (hand movement), the question arises, if these processes actually reflect perceptual decisions or rather the selection of an action. An attribution of choice selective activity in premotor areas to the planning of upcoming actions seems of course plausible (e.g. Cisek and Kalaska, 2005; Wise, 1985). However, the MPC, among other prefrontal association areas, also appears to play a role in the mere perceptual integration of stimuli. In the SFC task, this is indicated by a dual code in single neuron firing rates encoding f1 already slightly later than S2 (e.g., Hernández et al., 2010). Importantly, f1 is not predictive of any specific movement direction. These observations strengthen the view that activity in MPC might not have to be purely

action oriented (cf., Meyer, 2011). Anyway, previous animal research in the SFC task does not provide a sufficient answer to the question of choices in this task being coded in an effector-specific or an effector-independent way. Another very elaborate line of research in perceptual decision making is the work reviewed by Gold and Shadlen (2007). In these studies monkeys have to indicate the predominant visual motion direction in a cloud of randomly moving dots by an eye-movement to a previously known target location. Here, it is described that motion sensitive neurons in the middle temporal area (MT) code for the strength of perceived motion, whereas the lateral intraparietal area (LIP) accumulates this evidence and is predictive of the monkey's choice (Shadlen and Newsome, 1996). The authors argue that perceptual choices can be reduced to a mere selection of action alternatives. Mainly influenced by this assumption, Shadlen et al. (2008) proposed an *intentional framework of decision making* in which they underline the view of an effector-specific way to represent perceptual decisions. This framework was also fostered by authors as for example Cisek and Kalaska (2010), who argued that a large amount of neural data is difficult to explain with traditional views that describe brain processes as computations of abstract problem solving. These authors rather propose an ethologically inspired perspective, which encounters the fact that the human brain has developed in an environment in which real-time interactive behavior is required. Importantly, this view seems obvious in the light of the design characteristics of most of the underlying empirical studies (e.g., Shadlen and Newsome, 1996). There, as in most studies using the SFC task (e.g., Hernández et al., 2002), perceptual decisions are usually assigned to specific actions, making it hard to dissociate between a perceptual decision and action selection. A recent study, however, introduced a choice to target color mapping rather than a choice to saccade direction mapping in a visual random dot motion task (Bennur and Gold, 2011). Importantly,

in some trials the target color only appeared after the decision had been already made. Still, the authors found neurons in LIP coding for the perceptual decision, even though saccade direction was not known at this time of the trial. Until now, it remains to be understood how general or effector-specific the decision signals recorded from these different areas actually are. In studies 2 and 3 we developed different versions of the SFC task in order to address these open questions in this context.

1.4 The interplay of WM and decision making

The structure of the SFC task as described above was designed especially to dissociate the different cognitive processes (sensory encoding, WM maintenance, decision formation and action selection). In the experimental designs presented so far, subjects were always asked to respond immediately after the presentation of the second stimulus and their decision. If we consider decisions that we make every day, it is obvious that they are not always followed by an immediate overt action. For example, if you decide to take a left turn with your car behind the traffic light while waiting for it to turn green. This decision is not followed by an immediate overt action and might thus be processed very differently from deciding to turn left on an open road and being able to execute the appropriate action right away. Lemus et al. (2007) have implemented the former case of this example into the SFC task in monkeys by simply adding a short delay interval between the presentation of the second stimulus and the decision report. Here, it is interesting to see how decision and WM processes go hand in hand. The subject makes a decision that has then to be maintained in WM. Additionally, they have the opportunity to recapitulate the sensory information, i.e., the stimulus frequencies. Such maintenance of stimulus information would be very beneficial in natural behavior to preserve the possibility to flexibly change the action response if the question or the affordances change. Indeed, Lemus et al. (2007) report that

the frequency information of the stimuli (f1 and f2) is encoded in the firing rates of neurons in MPC in addition to choice selective signals. Can these findings be transferred to humans? This was the second question we operationalized in study 3. Therefore we used the same SFC task including a forced response delay.

1.5 Aim of this thesis

The overall aim of the present thesis was to apply, transfer, and continue to develop the paradigm and the respective results of the vibrotactile SFC task. The thesis was intended to test stimulus specific sensory and WM processes in patients with schizophrenia. Further, the thesis focused on the decision process within this task. First, it aimed to show if and how stimulus information and perceptual choices are maintained when reported at a later time. Second, the goal was to provide an answer to the question, if decisions in the SFC task are effector-specific and how decisions are represented if the according actions are unknown at the time of the decision.

2 Summary of the present studies

2.1 Study 1 "Spectral EEG abnormalities during vibrotactile encoding and quantitative working memory processing in schizophrenia" (Ludwig et al., 2016)

As described in the introduction, schizophrenia is associated with a number of positive and negative symptoms. Key negative symptoms are cognitive impairments such as deficient sensory processing as, for example, in form perception (Brenner et al., 2003) and visual context processing (Seymour et al., 2013) as well as higher-level impairments such as WM disturbances (Goldman-Rakic, 1994; Silver et al., 2003; for a meta-analysis see Lee and Park, 2005). While some studies suggest that higher-level cognitive impairments, e.g., in WM, could simply be a consequence of sensory dysfunctions (e.g., Hartman et al., 2003), other studies have provided evidence for WM deficits beyond sensory impairments (e.g., Tek et al., 2002; Haenschel et al., 2007; Haenschel and Linden, 2011). In particular, it remains

largely unclear how dysfunctions on these various levels of cortical processing contribute to alterations of stimulus-specific information representation. To investigate this issue in more detail, we tested nine patients with schizophrenia and nine matched healthy control subjects in the well-established sequential frequency comparison paradigm, in which subjects had to decide on whether the second of two serially presented vibrotactile stimuli had a higher or a lower frequency compared to the first stimulus that was presented three seconds before the second one. As described above (see section 1.1.1/1.2.1), this task was used intensively to record single cell data from monkeys describing the encoding of vibrotactile frequencies in primary somatosensory areas, the maintenance of this information in prefrontal and premotor regions and the formation of the decision in medial premotor regions (for a review see Romo and de Lafuente, 2013). While subjects performed the task we recorded scalp EEG to measure frequency-specific steady-state evoked potentials (SSEPs) and inter-trial (phase) coherence (ITC) over the primary somatosensory cortex (S1) (Tobimatsu et al., 1999; Teale et al., 2013) as a proxy of sensory encoding of the vibrotactile stimuli. Further, we investigated the maintenance of frequency information in working memory (WM) in terms of parametric power modulations of induced beta band EEG oscillations (Spitzer et al., 2010). Interestingly, we found that patients with schizophrenia and healthy control subjects performed equally well in discriminating the two stimuli. Even more interesting are the differences in the neurophysiological measures. Schizophrenic patients showed significantly less pronounced SSEPs and reduced ITC during vibrotactile stimulation than healthy controls. This finding is congruent with and complements to studies reporting general sensory or perceptual impairments in schizophrenia (Chen et al., 1999; Hartman et al., 2003; Javitt, 2009; Leitman et al., 2010; Seymour et al., 2013; Tek et al., 2002) and particularly to several studies consistently reporting reduced SSEPs and phase-locking (i.e. ITC) in response to similar

periodic stimulations in other modalities (i.e. visual flicker or auditory click trains) in schizophrenic patients (Krishnan et al., 2005; Kwon et al., 1999; Light et al., 2006; for a review see Brenner et al., 2009). Our study extends these previous results to the tactile domain and thus enriches the existing understanding of impaired neural synchronization in schizophrenia (see also Teale et al., 2013). Moreover, we analyzed the oscillatory correlates of WM content, i.e., of the stimulus frequency maintained during the retention interval (3 s). Healthy control subjects, as expected, showed a significant parametric increase of induced beta band oscillations (20-25 Hz) as a function of f1 stimulus frequency in our a priori selected electrodes. In contrast, for patients we found a reduced parametric power modulation by f1 in the same frequency band and electrodes. In earlier studies, this modulation of prefrontal beta oscillations was found to be a robust correlate representing a supramodal estimate of quantity (Spitzer and Blankenburg, 2012) independent of the stimulus feature of interest (Spitzer et al., 2014). Seemingly, patients do not form as strong abstract representations of the relevant stimulus information while still performing well in the task, probably by using different strategies. This appears reasonable in the light of evidence from behavioral studies showing reduced accuracies in patients performing stimulus feature abstraction tasks (Glahn et al., 2000; Weickert et al., 2014). In sum, beyond earlier reports of altered cortical activation during WM maintenance (Cannon et al., 2005; Perlstein et al., 2001; see also Manoach, 2003), we provide evidence that patients with schizophrenia show reduced sensory encoding of stimulus-specific information and altered neural representations of WM content during maintenance. Crucially, patients exhibited no general disturbances in attention, as inferred from the behavioral d2-test of attention and from the time courses of alpha-band event-related synchronization. A possible limitation of this study is the rather small sample size of nine patients and nine control subjects. Still,

power analyses speak in favor of the presented effects due to reasonable effect sizes. Together, our results provide novel evidence that patients with schizophrenia show altered neural correlates of stimulus-specific sensory encoding and WM maintenance, suggesting an early somatosensory impairment and alterations in the formation of abstract representations of task-relevant stimulus information.

2.2 Study 2 "Response-modality-specific encoding of human choices in upper beta band oscillations during vibrotactile comparisons" (Herding, Ludwig, & Blankenburg, 2017)

As outlined in section 1.1.1, one of the most complete pictures of the involved neural processes in memory-based perceptual decision making is based on seminal work in the somatosensory domain over the last years (see Romo and de Lafuente, 2013 for a comprehensive review). Romo and colleagues scrutinized neuronal activity in non-human primates during the vibrotactile SFC task. Decisions in this task (f2 > f1 or f2 < f1) were reported via button press after the presentation of f2. Electrophysiological recordings revealed that firing rates in somatosensory cortices (primary and secondary; S1 and S2) scaled with the stimulus frequencies during presentation (Hernández et al., 2000), whereas PFC firing rates mirrored f1 values during the WM period (Romo et al., 1999; see also Barak et al., 2010). Most importantly, firing rates in MPC and VPC encoded the upcoming choices of the monkeys before actual responses were given (Hernández et al., 2002; Romo et al., 2004). In a more recent study, Haegens et al. (2011) showed that the monkeys' choices were also reflected on a more global scale, namely by amplitude modulations of local field potentials (LFPs) in the beta band (~18 – 26 Hz) recorded from premotor areas. Applying the same vibrotactile SFC task in a human EEG study, Herding et al. (2016) found that this result also translates to beta band oscillations recorded at the scalp level. In particular, choices of "f2 > f1" were accompanied by higher amplitudes of upper beta band oscillations (~20 – 30

Hz) than “f2 < f1” choices, for correct and incorrect decisions. The most likely source of this effect was located in medial premotor cortex. Notably, these findings were in full agreement with the results of Haegens et al. (2011), and hence, complement the body of work by Romo and colleagues in non-human primates (see above).

However, the work in non-human primates, as well as this recent study, was limited to decision reports by button presses. In the visual domain on the other hand, a huge body of work focused on perceptual decisions reported by saccades (reviewed in Gold and Shadlen, 2007). The corresponding results present coherent evidence that oculomotor brain regions play a pivotal role for decision making in this context, (i.e. LIP; e.g. Shadlen and Newsome, 1996), frontal eye fields (FEF; e.g. Hanes and Schall, 1996), and superior colliculus (SC; e.g. Ratcliff et al., 2003). In order to be able to directly relate these findings to the work in the vibrotactile domain, in the current study, we combined the vibrotactile SFC task with saccade responses (as usually applied in the visual domain). That is, we examined whether the previously reported choice-selective upper beta band modulation (cf. Haegens et al., 2011; Herding et al., 2016) was domain general, or whether it will translate to the oculomotor system as predicted by the results from the visual domain (cf. Gold and Shadlen, 2007).

Therefore, we recorded EEG data of 24 participants completing the vibrotactile SFC task by performing a horizontal saccade to either side of a computer screen as decision report. To dissociate decisions from specific saccade-to-choice mappings, we counterbalanced the association between saccade direction and choices across participants. We contrasted the time-frequency (TF) transformed response-locked EEG data between both alternative choices (“f2 > f1” vs. “f2 < f1”) to reveal oscillatory signatures of the decision before responses were given.

We found that the amplitude of upper beta band oscillations (~24 – 32 Hz) in right frontal electrodes (FC2, FC4) was modulated by participants' choices before responses were given (-750 to -450 ms before saccades), regardless of whether choices were correct or incorrect, and independent of the specific saccade-to-choice mapping ($p_{cluster}$ = 0.034, family-wise error (FWE) corrected). In particular, "f2 > f1" choices were always associated with a higher beta band amplitude than "f2 < f1" choices. Importantly, this modulation pattern of beta band amplitude matches the previous studies (Haegens et al., 2011; Herding et al., 2016) that investigated oscillatory signatures of decision making in the same task, but used button press responses. In analogy to these studies, we also found in our study that premotor areas were implicated as the most likely source of the choice-selective signal, however, now with a focus on different, more lateral parts, including FEF.

Hence, we could show that the choice-selective modulation of upper beta band amplitude is present for different response modalities, and shows the same modulation pattern in a very similar frequency band. Moreover, the signal seems to be effector-specific, as the modulation of beta band amplitude was now most likely located in areas involved in saccade planning, i.e., the FEF. These findings are in line with the work in the vibrotactile domain (i.e., choice-related upper beta band modulation; cf. Haegens et al., 2011; Herding et al., 2016), as well as in accordance with the huge literature on perceptual decisions in the visual domain reported by saccades (i.e., activity in oculomotor regions reflect upcoming choices; cf., Gold and Shadlen, 2007).

On a conceptual level, the notion of an intentional framework of decision making (e.g., Cisek, 2007; Shadlen et al., 2008; Cisek and Kalaska, 2010) can be seen as the overarching theme that connects our findings to the results from research with non-human primates in the vibrotactile and the visual domain (respectively reviewed in Romo and de Lafuente,

2013; Gold and Shadlen, 2007). As the intentional framework of decision making proposes that decisions are expressed in form of intentions to act, neural correlates of decision formation should be found in brain areas that are responsible for motor planning in the according response modality. Accordingly, decision-related neuronal activity was found in MPC and VPC during the vibrotactile SFC task in which responses were reported by button presses (Hernández et al., 2002, 2010; Romo et al., 2004; Haegens et al., 2011). In the visual domain, neuronal activity in LIP, FEF, and SC have been shown analogously to encode ensuing choices when decisions were expressed by saccades (e.g., Shadlen and Newsome, 1996, 2001; Hanes and Schall, 1996; Kim and Shadlen, 1999; Ratcliff et al., 2003). Here, we could show for the first time that when the vibrotactile SFC task is combined with a different response modality than button presses (i.e., saccades), the choice-selective modulation of upper beta band amplitude is simply transferred to the corresponding new response modality. Hence, we could directly link the work of Romo and colleagues (vibrotactile SFC) with the work of Shadlen and colleagues (oculomotor responses), and show that their findings are united under the umbrella of an intentional framework of decision making.

2.3 Study 3 "Oscillatory EEG-Signatures of Postponed Somatosensory Decisions and Different Response Modalities" (Ludwig, Herding, & Blankenburg, submitted)

In study 3 our aim was to extend the line of research described in section 1.2.1 even further asking questions that go beyond the results of earlier research in monkeys. The classical SFC task allows the subjects to report their decision immediately after the presentation of the second stimulus. However, this task design is not able to explain scenarios in which we decide on an action to be carried out in the future. Lemus et al. (2007) studied these postponed decision reports in monkeys by introducing a short delay interval within the identical SFC task between the second stimulus and the decision report. They

recorded single cell activity from monkeys' MPC while they were performing the task. The authors reported that in the delay interval some of those neurons coded for subsequent decisions. In addition, other neurons showed sustained firing rates coding of f1 or f2. These findings show that even though a decision has already been computed with the difference between the two stimuli, stimulus information (f1 and f2) is still maintained in MPC. The first question we wanted to address in study 3 was whether we would find similar signals representing the maintenance of f1, f2 and f2-f1 when decision reports are delayed. We expected to find comparable oscillatory power modulations as has been also shown for WM maintenance of f1 (Spitzer et al., 2010; Spitzer and Blankenburg, 2011, 2012; see section 1.1.2). Secondly, we wanted to further investigate the influence of response characteristics in the task on the processing of decision signals in oscillatory EEG activity. It is still under debate whether decision signals found in PMC or FEF (Herding et al., 2016; study 2) are actually specific to the respective characteristics of the tasks (see section 1.3) or if these correlates are independent of the modality of the stimuli and the required response. Further, it remains to be understood how decisions are represented under conditions when the respective action to report the decision is still unknown and it has to be computed in an action independent space (see also Filimon et al., 2013). To address these questions we tested 73 subjects in the identical SFC task, including a forced response delay of 2.5 s after the offset of the second stimulus. The study itself contained four experiments (see Figure 1 in study 3). In each experiment subjects were instructed differently to report their decisions. In experiment 1 and 3 subjects provided their decisions with button presses, in experiment 2 and 4 with saccades. Moreover, in experiment 1 and 2 subjects were instructed with a direct assignment of their response to a specific action direction (right = higher, left = lower, or vice versa for the other half of the subjects). In contrast, in experiment 3 and 4, subjects were

instructed to saccade to or press on the side of a specifically colored target (blue/yellow) that appeared only after the response delay (i.e., the final action was unpredictable during the response delay). Target color was mapped to represent a specific response (e.g. blue = higher, yellow = lower, or vice versa for the other half of the subjects). EEG data were analyzed mainly in two ways. For the first research question, regarding the representation of stimulus information as well as the difference between both stimuli (f1, f2 & f2-f1) within in the delay interval, effects were analyzed for the whole sample (n = 73) in a region of interest (ROI) analysis motivated by earlier studies (e.g. Spitzer et al., 2010). The second question, testing the effects of response characteristics on the neural representation of choice ("f2 was higher/lower compared to f1") was analyzed separately for each of the experiments (n_1 = 17, n_2 = 17, n_3 = 18, n_4 = 21). For each effect we estimated a general linear model using a flexible factorial design with one regressor for each condition (e.g. f1 = 16/20/24/28 Hz) and a parametric contrast on the first level (e.g. [-1 -0.5 0.5 1]). Summary statistics were then tested on the group level using a cluster based permutation test. As a first result, we were able to replicate parametric modulations of the power of prefrontal beta oscillations in the retention interval (WM phase, between f1 and f2) as described earlier by Spitzer et al. (2010). Crucially, in the delay interval, after the presentation of f2, we found significant clusters in the same frequency range (15-35 Hz) for f1, f2, as well as for f2-f1 in our ROI, which were also mainly distributed over right prefrontal electrodes and source localized most consistently to the right inferior frontal gyrus (IFG) (Spitzer et al., 2010; Spitzer and Blankenburg, 2011). To regard the effect of choices in more detail, we looked at those contrasts in the single experiments, i.e. within different response conditions. In experiment 1 (side mapping; button press) we found a positive parametric effect, source localized to the superior frontal gyrus (SFG), most likely PMC. In experiment 2 (side mapping, saccade)

effects were weaker, but we still found a prominent positive cluster ($p < 0.05$, uncorrected) with sources also in the SFG and the middle frontal gyrus (MFG). In experiment 3 (color mapping; button press) we found a positive parametric modulation over parietal cortices (left intraparietal lobe; IPL). Similarly with respect to the topographical distribution and the according sources (left superior parietal cortex, intraparietal sulcus), in experiment 4 (color mapping; saccade) we found a negative parametric modulation in parietal cortices. All of the above effects, except from study 2, were significant on an alpha-level of $p = 0.05$ (FWE-corrected).

First, our results suggest that even though categorical decisions can be formed right after the presentation of the second stimulus, the stimulus information on which the decision was made is still encoded in prefrontal oscillatory power in addition to information about the difference between both stimuli (f2-f1). The frequency range as well as the topographical distribution of this modulation matches earlier findings, first reported by Spitzer et al. (2010), who interpret their results as reflecting quantitative WM content (Spitzer and Blankenburg, 2011). Our results are in line with an earlier study in monkeys, where they found parametric increases in firing rates as a function of f1, f2 and f2-f1, in different portions of neurons in the MPC (Hernández et al., 2010; Lemus et al., 2007). Secondly, we show that in direct choices the processing of subjective choices is mainly reflected in premotor areas, also responsible for planning the appropriate actions. In contrast, if a specific action is still unpredictable, choices seem to be encoded in parietal areas. This seems plausible in light of research suggesting that the posterior parietal cortex (PPC) incorporates visuo-spatial information, which is relevant for goal-directed actions. These results are in concordance with an intentional framework of decision making (section 1.3) but also suggest that decision information is represented in the space in which choices

were instructed to be relevant. This will be discussed again in the general discussion (section 3.3).

3 General discussion

In the course of the presented studies the perception-action cycle spans from the first entering of sensory information to the human organism acting by a button press or an eye movement. By means of the SFC task the studies of this thesis focused on basic sensory encoding, the maintenance and comparison of sensory information, as well as the resulting decision within these dynamically interacting processes. We could therefore enrich the understanding of disturbances within this cycle in schizophrenia as well as provide a link to the intentional organization of perceptual decision making.

In this thesis, a well-established SFC task (Figure 1, top) has been used to study different aspects of memory-based decisions. First, the paradigm was applied to study WM processes in the clinical population of schizophrenia. Further, we transferred findings from earlier animal research to humans and developed new versions of this particular task to advance the understanding of perceptual decisions and the according action selection.

In study 1 (Figure 1, blue box), by means of the vibrotactile SFC task that was extensively studied in non-human primates (for review, see Romo et al., 2013) and in humans (e.g. Spitzer et al., 2010), we investigated sensory encoding and WM maintenance in patients with schizophrenia as compared to healthy control subjects. We were able to show that patients with schizophrenia show impairments in vibrotactile encoding as revealed by measures of SSEPs and ITC during stimulus presentation. Further, while replicating earlier findings (Spitzer et al., 2010) in the control group, patients with schizophrenia showed weaker signals of WM maintenance reflected in a reduced parametric power modulation of

prefrontal beta oscillations in the retention interval. In study 2 (Figure 1, red box), we focused on the decision phase of the paradigm and extended findings from a study by Herding et al. (2016) who showed that subjective choices in this SFC task were represented in the premotor cortex if, as usual, subjects responded with button presses. In our study, subjects were instructed to indicate their responses with lateral saccadic eye-movements to test if the previous findings reflect decision processes specific to the response modality or a response independent decision signal. Our results show power modulations of oscillatory EEG activity coding for subjective choices in the FEF, suggesting that perceptual decisions reported by saccadic responses are represented in areas related to the planning of saccades. These results indicate that in general the computation of perceptual decisions depend largely on the response modality. In study 3 (Figure 1, green boxes), we introduced additional changes to the paradigm. First, we added a forced response delay after the presentation of the second stimulus to investigate the processing of stimulus and decision information in a case where the decision report is postponed. Second, in the four experiments within our study, participants reported their decisions in different ways. Here, we varied the response modality (saccade vs. button press) and the response mapping (direction vs. color) in all four possible combinations. As overall effects, we were able to show that in the response delay, frequency information about the first and the second stimulus, as well as about the difference of their frequencies were parametrically encoded in the power of right prefrontal oscillations in a frequency range between 15 and 35 Hz. Further, we found that choices, which were mapped directly to a specific action seem to be represented in premotor regions, whereas choices that were mapped to a color, thus if the

appropriate motor response was unpredictable, were encoded in different regions of the parietal cortex.

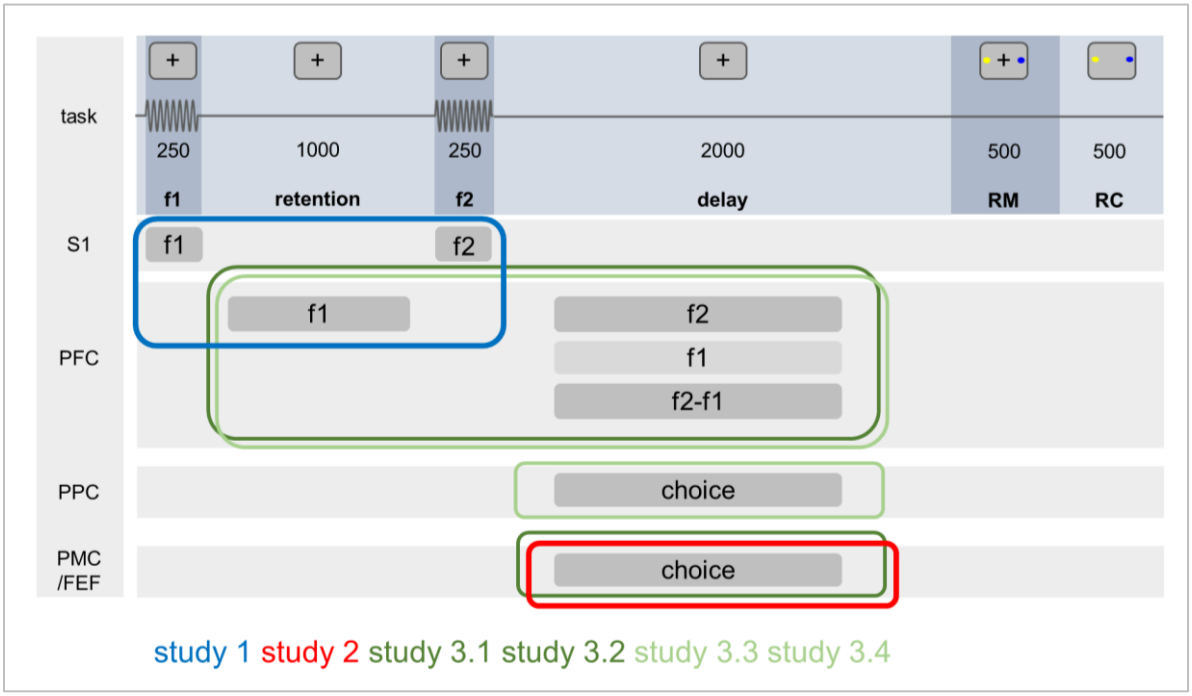

Figure 1. Graphical summary of studies 1 – 3. Left: areas where correlates of cognitive processes (center) were observed in the three studies (boxes).

3.1 Sensation

One of the core prerequisites for successful behavior within an environment is to sample reliable information about it. One might theoretically be able to solve the most difficult mathematical computations by mental calculation, but if the arithmetic problem is not properly visible, one will not be able to provide the right solution.

In the first study of this thesis we initially looked at very basic processes of sensory encoding in humans diagnosed with the psychiatric disorder of schizophrenia. It has been reported in many studies that these patients often show deficits in very rudimentary perceptual tasks (Chen et al., 1999; O'Donnel et al., 1996; Tek et al., 2002). As in these studies, behavioral tests are often challenged by the fact that in addition to perceptual elements, processes such as WM or decision making also play a role in executing the respective tasks. Here, neurophysiological recordings provide a unique opportunity to measure the direct representation of sensory stimuli in the brain. Previous studies made use

of such a method by presenting rapidly repeated stimuli such as visual flicker or auditory click trains to subjects with schizophrenia (Krishnan et al., 2005; Kwon et al., 1999; Light et al., 2006; for a review see Brenner et al., 2009). The authors of these studies were able to show that these stimuli were not represented as well in patients as compared to healthy control subjects in primary sensory areas. In study 1 we provide evidence that this observation is not specific to the visual and the auditory modality but generalizes also to the tactile domain (see also Teale et al., 2013). By adding a seemingly small detail to the overall picture of sensory stimulus representations in schizophrenia, this finding necessarily leads to the hypothesis that the observed effects do not reflect merely impaired sensory encoding but rather a general abnormality in neural functioning in these patients. Such complementary findings can therefore carry more explanatory value than just the observation that sensory stimuli are perceived less accurately. Associated to that, it has been discussed that disturbed oscillatory activity might play a general role in cognitive deficits in schizophrenia (Haenschel and Linden, 2011; Uhlhaas et al., 2008). From a broader perspective, together with the studies mentioned above, our results indicate fundamental differences in the neural representations of the outside world for patients with schizophrenia. It is hypothesized that these basic changes might even have the capability to lead to seemingly unrelated symptoms as e.g. delusions or hallucinations (Fletcher and Frith, 2009). In this paper, by means of a hierarchical Bayesian approach, the authors elaborate how aberrant percepts might lead to the formation of false beliefs or delusions. This framework is based on the *Free Energy Principle* of brain function described in detail by Friston (2010). There, it is assumed that the brain incorporates an internal model of the outside world, which is constantly updated by trying to minimize deviations between predicted and actual sensory inputs. Consequently, the current categorization of cognitive

deficits as a comorbid symptom resulting from the disorder of schizophrenia has to be questioned. In contrast, it should rather be considered that delusions could be a consequence of falsely perceived environmental information leading to an erroneous internal model of the world.

3.2 Working memory

A core cognitive module which combines currently maintained sensory input with prior knowledge, current intentions, or task sets is what we call the WM (Baddeley, 1992). The study of memory-based decisions is one of the simplest ways to investigate this natural behavior (Hayden and Pasternak, 2013). Here, perceptual tasks are not isolated but implemented within the natural process of combining current sensory with previously acquired information (see section 1). Since relevant information is usually not presented all at once but has to be accumulated over a time span or different time points in order to be combined with what we know from prior experience, WM is essential to create meaningful behavioral patterns. This combination of current sensory information with prior knowledge becomes evident for example in the time order effect (Karim et al., 2012; Preuschhof et al., 2006; Woodrow, 1935). This effect describes the fact that, e.g., in SFC tasks the frequency of the first stimulus is maintained as a weighted average of all frequency information that was perceived before and the current stimulus (Herding et al., 2016; Karim et al., 2012). Although this effect can have a significant impact on task performance in individual trials in the task, it might, from a broader conceptual perspective, even be beneficial by giving less weight to very unlikely events in an environment that we already know. While WM is a very powerful and inevitable tool for behavior, it is self-evident that dysfunctions in this cognitive procedure can cause tremendous consecutive problems in everyday life (Haenschel and Linden, 2011). As described above, patients with schizophrenia often show impairments in

WM function (see section 1.3). This impact can be very direct, indicated by a general impairment to solve daily tasks as a consequence of WM deficits. Additionally, cognitive behavioral therapeutic approaches profit from well-functioning WM processes in order to implement acquired coping strategies in daily life (Haenschel and Linden, 2011). For this reason, WM impairments have been considered a promising point of application for research to increase quality of life (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia, CNTRICS; Barch and Smith, 2008). As mentioned above there have been many measures and approaches in the neuroscience of schizophrenia showing impairments or abnormal activation patterns in various methods, such as fMRI or EEG. In study 1, we went beyond identifying differences in activation but focused on a correlate of WM content that was suggested to reflect a quantitative estimate of a relevant to be maintained stimulus feature (Spitzer and Blankenburg, 2011). In patients, the parametric relationship between the power of prefrontal beta oscillations and stimulus frequency was significantly weaker as compared to controls. This led us to conclude that patients might not form as strong abstract representations of this stimulus feature during WM maintenance. It should be mentioned that in this study, patients with schizophrenia showed no indications of attentional deficits that could explain our observations. Further, performance accuracies were indistinguishable in the SFC task between patients and controls. This poses the question whether patients actually showed impaired WM function. It can well be that patients form weaker abstract representations of the stimulus frequency in WM, but the amount to which they represent this information might still suffice the task demands. This would not automatically induce a ceiling effect of perfect performance accuracy because the comparison between frequencies is additionally challenging per se. Alternatively, patients might develop alternative strategies to solve such tasks, or in general to store quantitative

information that is not reflected in the same oscillatory code as in healthy subjects. This could also include a case in which they solve the task, for example, on a semantic or even a more sensory level. Besides that, equal performances in such clinical studies can be considered as an advantage because neurophysiological data become even more informative by not being confounded with mere performance differences.

In a broader context, our findings add to a line of research that shows that WM can, in different ways, be impaired in Schizophrenia (Haenschel and Linden, 2011; Lee and Park, 2005). As it is discussed above for sensory representations, WM also underlies multiple cognitive functions shaping successful behavior in one's environment. Here, even if information is encoded reliably by the senses, dysfunctional maintenance or erroneous combination of this information with prior knowledge can cause fundamental changes in the overall representation and the according behavior towards our environment. As further described by Fletcher and Frith (2009), delusional thoughts or false beliefs might be a consequence of unsuccessful updating of our internal model about the world. In consequence, this leads to false sensory predictions and hence to mismatches between expected and actual perceptual inputs, which will be surprising or even disturbing to experience. As a general message from our and the previous line of research, sensory and WM impairments should be further considered not as side effects of a disorder. On the contrary, they might even explain the progression of disease and be the cause of other more prominent symptoms. This is supported by studies showing that cognitive impairments as WM deficits are frequently observed in the schizophrenia prodrome (Simon et al., 2007). It would be interesting to systematically investigate the relationship of early cognitive deficits and the development of consecutive positive symptoms in future studies.

Besides the findings of study 1, it is furthermore an example of how basic research can also provide tools to study specific processes with respect to their dysfunctions in mental illnesses. In the recent years, there has been a promising trend in developing even an own field of computational psychiatry (e.g. Huys et al., 2016) that is devoted to combining the latest advances in data driven analyses with theory based approaches. This might lead to a new way to think about mental diseases informed by huge amounts of data, instead of traditional classification schemes.

3.3 Decision making

Perceiving a stimulus, extracting relevant information from it, and maintaining this information in WM, describes approximately half of the perception-action cycle. At this stage it can also be interrupted if the information is, for example, stored in long-term memory and only becomes relevant later in time. However, one could also argue that the decision about this information being irrelevant at this instant of time can also be considered an action. In this case the perception-action cycle would just continue with a covert, mental action instead of an overt motor response. However, recently acquired information can influence immediate subsequent decisions and actions, as also in the SFC task. Decisions are here defined as the comparison process per se. The outcome of this comparison we refer to as choice.

In study 3, we looked for representations of stimulus and decision information in the delay before the response. Here, we show that both types of information are encoded in the power of prefrontal beta oscillations. Our results provide an eclectic extension of the original findings by Spitzer et al. (2010). We show that the described power modulations in the beta band also code for dynamic combinations of quantitative estimates such as the signed difference between f2 and f1. Further, the maintenance of stimulus information in the

response delay is appealing from an ecological perspective, because time resources are exploited and the flexibility to adapt to changing affordances is preserved (Lemus et al., 2007).

In the field of perceptual decision making, mainly two hypotheses about the neural implementation of perceptual decisions evolved over the last decades. On the one hand, the intentional framework that views decisions as a selection within a limited set of affordances or intentions, processed in areas related to motor planning (Cisek and Kalaska 2010; Shadlen et al. 2008). This is opposed by the assumption of a modality transcending general decision module, proposed to be established by the DLPFC (Heekeren et al., 2008; Filimon et al., 2013).

The studies by Romo and colleagues are generally in line with an intentional interpretation of decision making. In these studies, monkeys report choices with button presses, and according choice selective firing is observed in MPC (e.g. Haegens et al., 2011; Hernández et al., 2002). Herding et al. (2016) found, in accordance to these findings, choice selective power signals in the upper beta band in the PMC as well. In study 2 of this thesis, we tested subjects in the classic SFC task but instructed them to respond with saccades. We found the same effect as Herding et al. (2016) but most likely originating from FEF. This indicates, that decisions seem to be reflected in an effector-specific way, corresponding to predictions of an intentional framework. However, in study 3 we show that irrespective of the response modality, under conditions when choices are mapped to a target color instead of to a specific action direction, we find choice selective signals in the power of beta oscillations over parietal areas. Here, subjects make a decision about f2 compared to f1, and map their decision outcome to a color. In consequence, subjects have to look for whether their color of choice is on the left or on the right when the response mapping is presented

and subsequently plan the appropriate saccade or button press. Importantly, subparts of monkeys' PPC (LIP for Saccades; PRR for reaching movements; AIP for grasping) have been shown to code visuo-spatial information, which is relevant to guide future actions (Andersen and Bueno, 2002). In our case, it is therefore not surprising that in the delay interval choice information is encoded in these areas which gather information about where or to which color to shift attention and inform the visuo-spatial context of the upcoming action. Taking study 2 and study 3 of this thesis together, it seems plausible to suggest that, in these experiments, neural correlates of choices are consistently found within those areas, which encode the consequence of the sensory decision outcome. These findings trigger some fundamental assumptions about perceptual decisions but also decision making in general. On one side of the spectrum of hypotheses in decision neuroscience stands the assumption that there is a general decision maker which forms abstract decisions that are then further mapped to the instructed response actions (Heekeren et al., 2008). On the other end of this spectrum we might place a purely intentional framework in which decisions are nothing else but the selection of actions. It seems that neither of both approaches provides a sufficient explanation. In light of earlier as well as the present studies it seems reasonable to assume that decisions are dynamic computations in the reference frame or feature space in which they are relevant with respect to their consequences. It appears improbable that a decision is one of several mental processes that are aligned one after another, executed in a serial way. This way to think about the organization of cognitive processes is likely a result of the way single trials were designed within psychological or neuroscientific experiments (Cisek and Kalaska, 2010). On the one hand these simplifications are of course necessary. On the other hand it is important to be aware of these simplifications and how they relate to natural behavior. Why are the theories of one decision maker as well as a purely intentional

framework not very likely? To have a single decision making module mediating between perception and action would be computationally very demanding (Massaro, 1990). Sensory information would always be required to be abstracted to consecutively being mapped to a motor response. This would be very inefficient, because different reference frames would always have to be mapped to each other (e.g. Massaro, 1990). Our data, and also many other studies mentioned above, suggest decisions to be much more action-oriented and also represented within the space of their affordances. Hence, it seems plausible to suggest that findings of our studies 2 and 3 (experiment 1 and 2) reflect intentional decisions. However, they were also instructed to be intentionally performed and the motor plan to report the decision was predictable throughout the delay period. In experiments 3 and 4 of study 3 in contrast, decisions are relevant to spatial and feature based attention, processed in PPC. In this case affordances are defined within a space, which one could call more abstract.

In sum, we provide novel evidence suggesting that neural representations of perceptual choices highly depend on the subsequent behavioral or cognitive consequences that are informed by the decision. This can be well explained In terms of the perception-action cycle. There, decisions can be implemented in the direct connection from the sensory hierarchy to the lowest level possible within the motor hierarchy (Fuster, 1990).

3.4 Challenges and Outlook

As already argued in the beginning, there have been multiple attempts to develop a model of brain function to incorporate the direct links between perception and action (Friston, 2010; Fuster, 1990). This thesis underlines this necessity. We show that in patients with schizophrenia, fundamental cognitive processes that can shape human behavior are disturbed. It is discussed how these alterations might lead to even more drastic impacts on daily life, for example in delusions. Further, we provide a direct link between basic

perceptual processes that are implemented in a set of affordances concerning either direct consecutive actions or higher cognitive processes such as feature based attention. In the course of the studies it appeared obvious that it is necessary to study these single processes and to be aware of their impact from being interlinked with many other brain functions. On the other hand, these dense interactions between seemingly different processes in the brain demand unifying models of brain function and therefore of the basis of human behavior.

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Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt,

- dass ich die vorliegende Arbeit eigenständig und ohne unerlaubte Hilfe verfasst habe,
- dass Ideen und Gedanken aus Arbeiten anderer entsprechend zitiert wurden,
- dass ich mich nicht bereits anderwärts um einen Doktorgrad beworben habe und keinen Doktorgrad in dem Promotionsfach Psychologie besitze und
- dass ich die zugrundeliegende Promotionsordnung vom 02.12.2008 anerkenne.

Berlin, den 17.02.2017 Simon Ludwig

Original Publications

Study 1

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Spectral EEG abnormalities during vibrotactile encoding and quantitative working memory processing in schizophrenia

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ABSTRACT

Schizophrenia is associated with a number of cognitive impairments such as deficient sensory encoding or working memory processing. However, it is largely unclear how dysfunctions on these various levels of cortical processing contribute to alterations of stimulus-specific information representation. To test this, we used a well-established sequential frequency comparison paradigm, in which sensory encoding of vibrotactile stimuli can be assessed via frequency-specific steady-state evoked potentials (SSEPs) over primary somatosensory cortex (S1). Further, we investigated the maintenance of frequency information in working memory (WM) in terms of parametric power modulations of induced beta-band EEG oscillations. In the present study schizophrenic patients showed significantly less pronounced SSEPs during vibrotactile stimulation than healthy controls. In particular, inter-trial phase coherence was reduced. While maintaining vibrotactile frequencies in WM, patients showed a significantly weaker prefrontal beta-power modulation compared to healthy controls. Crucially, patients exhibited no general disturbances in attention, as inferred from a behavioral test and from alpha-band event-related synchronization. Together, our results provide novel evidence that patients with schizophrenia show altered neural correlates of stimulus-specific sensory encoding and WM maintenance, suggesting an early somatosensory impairment as well as alterations in the formation of abstract representations of task-relevant stimulus information.

1. Introduction

Schizophrenia is a psychiatric disorder associated with a number of positive and negative symptoms. One core negative symptom is cognitive impairment, which may affect various levels of cognitive processing. On the lowest level, this can manifest in early sensory deficits. For example, patients diagnosed with schizophrenia show impairments in object- or visuospatial discrimination (O'Donnell et al., 1996; Tek et al., 2002), motion- (Chen et al., 1999) or form perception (Brenner et al., 2003), visual context processing (Seymour et al., 2013; Tibber et al., 2013; Yang et al., 2013), as well as slowed visual encoding (Hartman et al., 2003; see also Javitt, 2009). These early sensory deficits have been substantiated by reports of lowered amplitudes in steady-state evoked potentials (SSEPs, i.e., rapidly repeating stimuli such as visual flicker, auditory click trains or tactile flutter evoke a frequency-specific neural entrainment in early sensory cortices; e.g., Regan, 1966; Mäkelä and Hari, 1987; Kelly et al., 1997) or differences in inter-trial coherence (ITC, i.e., a measure of phase-locking of a particular frequency over trials; e.g. Makeig et al., 2004) using electroencephalography (EEG). In patients with schizophrenia, SSEPs (Kwon et al., 1999) as well as ITC (Light et al., 2006) were significantly reduced in response to auditory click trains or visual flicker (Krishnan et al., 2005; for a review see Brenner et al., 2009) as compared to healthy controls. (See Table 1.)

Beyond early sensory deficits, cognitive impairments in schizophrenia also include higher-level processes such as working memory (WM) (Goldman-Rakic, 1994; Silver et al., 2003; for a meta-analysis see Lee and Park, 2005). WM subserves the short-term maintenance of internal and external action-related information (Baddeley, 1992). While some behavioral and neurophysiological studies suggest that such higher-level impairments are possibly caused by aforementioned sensory dysfunctions (Tek et al., 2002; Hartman et al., 2003; Haenschel et al., 2007), other studies have provided evidence that beyond early sensory impairments, schizophrenic patients also show deficits in WM processing per

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se (e.g., Tek et al., 2002; Haenschel et al., 2007; Haenschel and Linden, 2011). Together, these studies imply that schizophrenia is associated with a symptomatology of altered WM-related cognitive processing as a result of cortical hypo- and hyperactivity (Haenschel et al., 2009) as well as disturbed occipital to frontal (Bittner et al., 2015) and frontal to parietal connectivity (Deserno et al., 2012). However, from these studies it remains largely unclear how stimulus-specific information is perturbed during sensory encoding and WM maintenance in patients with schizophrenia.

Sensory encoding and WM maintenance of such intrinsic stimulus features (e.g. the frequency of a vibration on the skin) have been studied in a vibrotactile sequential frequency comparison (SFC) task in non-human primates (Romo et al., 1999; Romo and Salinas, 2003) and in humans (Spitzer et al., 2010; Spitzer and Blankenburg, 2011, 2012). During the SFC task, the frequency of a first stimulus (f1) has to be encoded and maintained in WM during the retention interval until it is compared to the frequency of a second stimulus (f2) in order to decide whether the f2-frequency was higher or lower than the f1-frequency. Romo et al. (1999) recorded single cell activity from neurons in primary somatosensory (S1) and prefrontal cortices (PFC) of monkeys performing this task. S1 neurons showed periodic spike trains in synchrony with the vibrotactile stimulation, as well as parametrically increasing firing rates with higher stimulus frequencies. In the retention interval, the firing rate of PFC neurons parametrically in- or decreased as a function of the f1-frequency maintained in WM. Spitzer et al. (2010) transferred this paradigm to humans by investigating evoked (i.e. phase-locked) and induced (i.e. ongoing or non-phase-locked) oscillatory power evolutions in the EEG signal during a similar vibrotactile frequency comparison task. The authors observed SSEPs over S1 during stimulation. In the retention interval, in contrast, induced beta-power (20–25 Hz) over right frontal electrodes was parametrically increased as a function of f1-frequency. Additional studies showed that, beyond encoding vibrotactile stimulus frequencies, this prefrontal power modulation during WM maintenance can be generalized to other sensory modalities (vision and audition; Spitzer and Blankenburg, 2012) and other quantitative stimulus properties (intensity and duration; Spitzer et al., 2014) and therefore might indicate a prefrontal correlate of abstract (i.e. unspecific with regard to the stimulus feature or modality) quantity information in human WM (Spitzer et al., 2014).

Studying vibrotactile frequency processing in patients with schizophrenia may generalize and complement previous findings in at least two ways. First, tactile vibrations can be regarded as a somatosensory equivalent to visual flicker or auditory click trains, which were previously used to assess deficits in early sensory encoding in schizophrenia (Krishnan et al., 2005; Kwon et al., 1999; Light et al., 2006; for review see Brenner et al., 2009). Thus far, there have been no studies in schizophrenic patients investigating analogous neural responses to vibrotactile stimuli across multiple frequencies (cf. Teale et al., 2013). Second, it was previously shown that patients with schizophrenia show deficits in deducing abstract stimulus categories from visual stimuli (Glahn et al., 2000). However, the neural processing of such abstract stimulus features (e.g. stimulus frequency; cf. Spitzer et al., 2010, 2014) in WM has not yet been studied in patients.

In the present study, patients with schizophrenia and healthy control subjects performed a vibrotactile SFC task while EEG was recorded. Somatosensory SSEPs and ITC were measured during the presentation of the stimuli as a proxy for tactile sensory encoding. On the basis of previous studies, we hypothesized that patients with schizophrenia would show reduced SSEPs and ITC. Furthermore, the power of induced beta-band oscillations was analyzed in the retention interval (during maintenance of the first stimulus). We hypothesized that if patients suffer from impairments in WM maintenance, they should show a relatively weaker parametric modulation of prefrontal beta-oscillations. Lastly, we analyzed the power evolution of overall induced alpha-activity as an indicator for the extent to which subjects attend to the task (Haegens et al., 2010; Spitzer and Blankenburg, 2012).

2. Materials and methods

2.1. Participants

Twelve patients diagnosed with schizophrenia (11 male, 25–37 years old, mean $age_{patients} = 31$) and nine healthy control subjects (mean $age_{controls} = 32$) matched in age, gender, and level of formal education took part in the study (for participant details, see Table 1). Three patients were excluded from the analysis, two due to poor task performance (<50% correct responses), and one because of insufficient EEG signal quality. Informed consent was obtained from every participant prior to the experiment and the study was approved by the local ethics committee at the Charité University Hospital, Berlin.

Patients with paranoid schizophrenia (ICD10: F20.0; World Health Organization) were recruited at the outpatient clinic of the Psychiatry Department of the Charité University Hospital, Berlin. The *Positive and Negative Syndrome Scale* (PANSS) (Kay et al., 1987) was used to assess the patients' current clinical symptoms. Patients with acute psychosis or any signs of an upcoming psychotic episode were not included in the study. At the time of the study, all but one patient were on stable doses of atypical antipsychotic medication (Olanzapine, 3; Risperidone, 1; Aripiprazole, 1; Amisulpride, 2; Quetiapine, 2). One patient also received a selective serotonin reuptake inhibitor and Methimazole, another patient received Pregabalin.

Healthy control subjects were recruited via online advertisements and telephone interviews. Exclusion criteria for control participants were any previous diagnosis of a psychiatric disorder or any psychopharmacological medication. Exclusion criteria in both groups were neurological disorders and drug abuse up to seven days before testing.

2.2. Task and procedure

Prior to the main experiment, subjects performed a standard computerized n-back task (Kirchner, 1958) in order to assess each participant's performance in a traditional WM task. The task included two conditions, the '0-back' and the '2-back' condition. In both conditions, a stream of serially presented numbers with an inter-stimulus interval of 900 ms was displayed in the center of the screen. In the '0-back' condition subjects were asked to only identify the target number '0'. In the '2-back' condition, targets were defined as those numbers that had appeared already two numbers earlier in the stream. Subjects

Table 1
Sample characteristics. Subject, group (SCZ: patients with schizophrenia; HC: healthy control subjects), Gender (m: male; f: female), education (HSD: high school diploma; CVT: completed vocational training; TD: technical diploma; GQUE: general qualification for university entrance; BA: Bachelor of Arts), PANSS (Pos: positive symptom scale; Neg: negative symptom scale; GPS: general psychopathology scale).

Subject	Group	Age	Gender	Education	PANSS		
					Pos	Neg	GPS
1	SCZ	26	m	HSD	12	9	16
2	SCZ	30	m	CVT	21	14	34
3	SCZ	29	m	HSD	7	9	16
5	SCZ	29	m	HSD	14	8	22
6	SCZ	25	m	HSD	14	7	18
9	SCZ	36	m	GQUE	–	–	–
10	SCZ	37	m	TD	7	7	16
11	SCZ	33	m	HSD	7	19	18
12	SCZ	30	m	GQUE	17	15	25
13	HC	32	m	CVT			
14	HC	38	m	TD			
15	HC	35	m	HSD			
16	HC	25	m	HSD			
17	HC	28	m	BA	–		
18	HC	32	m	HSD			
19	HC	28	m	HSD			
20	HC	37	m	TD			
21	HC	31	m	GQUE			

responded by pressing the 'space' bar of a computer keyboard. Each run contained six targets. Participants completed three runs per condition.

Subsequently, subjects performed the SFC task during EEG recording. Vibrotactile stimuli were presented at the left index finger using a 16-dot piezoelectric Braille display (4 × 4 quadratic matrix; 2.5 mm spacing) controlled by a programmable stimulator (Piezostimulator; Quaerosys). The stimulus set for the first vibrotactile frequency (f1) contained six different frequencies in the flutter range (i.e., 16, 19, 22, 25, 28, and 31 Hz); the second frequency (f2) was always 3 Hz higher or lower than f1. The driving signals of the stimuli were generated by fixed sinusoidal amplitude modulation of a constant carrier frequency of 133 Hz in order to reduce EEG artifacts in the frequency spectrum of interest. Importantly, subjects perceive the trial-specific modulating frequency which corresponds to the envelope curve of the stimulus function (Tobimatsu et al., 1999). The sound of the braille display was masked by white noise (~90 dB), which was constantly presented through loudspeakers during the whole experiment.

After a variable inter-stimulus interval (1500–2000 ms) the first vibrotactile stimulus (base frequency, f1, 500 ms) was presented. Following a 3000 ms retention interval, the second stimulus (comparison frequency, f2, 500 ms) was applied. Subjects were asked to respond within 2000 ms after f2 offset whether the second stimulus had a lower or higher frequency compared to the first one. Participants pressed the 'space' bar once for "f1 > f2" or twice for "f2 > f1" (cf. Spitzer et al., 2010). Visual feedback in the form of '+' symbols for correct responses or '−' symbols for incorrect responses was displayed left and right of the fixation cross. To avoid eye movement artifacts in the EEG, participants were asked to fixate a black cross presented in the center of the screen during the entire duration of the trial. In each experimental block, each of the twelve possible stimulus pairs occurred six times in total and in a random order. Overall, there were six blocks, resulting in a total number of 12 (stimulus pairs) × 6 (repetitions per block) × 6 (blocks) = 432 trials. The whole session including EEG preparation lasted for 2.5 h. After the experiment, participants' general ability to attend to a task was assessed using the '*d2 test of attention*' (Brickenkamp, 1962; for validity measures see Bates and Lemay, 2004).

2.3. EEG recording

EEG was recorded using a 64-channel active electrode system (ActiveTwo; BioSemi) with electrodes placed according to the extended 10–20 system. Four additional electrodes were used to record blinks and eye movements. Single electrode locations were registered using a stereotactic electrode positioning system (Zebris Medical).

2.4. Behavioral analysis

Performance in the n-back task was assessed using sensitivity measure *d-prime* (Swets, 1964). In the d2 test we computed the GZ-f value, a measure of overall performance, representing the total number of treated items corrected for number of mistakes.

Behavioral group differences in the n-back and the d2 task were tested for significance using two-tailed two sample *t*-tests for independent measures. To test for group differences and a potential frequency-specific effect on performance accuracy or reaction times in the SFC-task we computed, for each dependent variable, a two-factorial (2 [groups, between subject factor] × 6 [frequencies, within subject factor]) ANOVA. As an additional behavioral measure we computed the performance accuracy across ratios of stimulus frequency-difference to the frequency of f1 (i.e., [f2 − f1] / f1). This ratio represents a corrected estimate of the stimulus frequency difference with respect to Weber's law (Fechner, 1966), which would predict an increasing discrimination difficulty with increasing stimulus frequency.

2.5. EEG analysis

EEG analyses were performed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK; www.fil.ion.ucl.ac.uk/spm/) and custom MATLAB code (The MathWorks).

2.5.1. Preprocessing

Preprocessing included co-registration of the channels to the individual electrode positions, rejection of noisy channels, average referencing, adaptive spatial filtering to correct for eye-blink artifacts, as well as high- (0.5 Hz) and low-pass (45 Hz) filtering. The continuous recordings were segmented into epochs from 1000 ms before f1-onset to 1000 ms after f2-offset. Epochs with amplitudes greater than 80 mV were rejected. Remaining artifacts were excluded after careful visual inspection.

2.5.2. Steady-state evoked potentials (SSEPs)

For evoked responses, epochs were averaged for each f1 condition. These data were transformed into the time–frequency domain using Morlet wavelet-transformation (seven cycles, 5–45 Hz). Baseline correction of the time–frequency data was done with respect to a 500 ms pre-stimulus interval (−600 ms to −100 ms). For SSEP analysis, we extracted for each subject the narrowband power in the frequency of stimulation for each f1 and the same f2 conditions. We averaged these signals over all f1 and f2 conditions, respectively.

2.5.3. Inter-trial coherence (ITC)

To analyze the coherence of the EEG signal phase in the stimulation frequency over trials (phase locking), we again used a Morlet wavelet-transformation (seven cycles, 5–45 Hz) but applied it on every single trial epoch. We calculated the circular average of the phases for each f1 and corresponding f2 conditions, respectively. For each condition we extracted the ITC at the frequency of stimulation and averaged those values over conditions to get a grand mean estimate for each subject.

2.5.4. Parametric induced responses

To examine induced, i.e. non-phase locked responses, the mean event-related potential (ERP) associated with each condition was subtracted from every trial before Morlet wavelet-transformation was performed on a single trials basis. Changes in spectral power in certain frequency bands are reported as event-related (de)synchronization (ERD/ERS; Pfurtscheller and Aranibar, 1977). Thus, values are in percentage signal change compared to a pre-stimulus baseline (−600 ms to −100 ms). To reduce inter-trial variability, time frequency data were convolved using a 3 (Hz) × 500 (ms) Gaussian smoothing kernel (Kilner et al., 2005). The single trial power spectra were then averaged for each f1 frequency. For parametric effects of the stimulus frequency (f1) on the induced beta-power during the maintenance period, we first computed the average ERS for every f1 over the whole retention interval. We fitted a linear trend for the power of the ERS over the six f1 conditions using a least-squares algorithm. Slopes of the linear regression line were used as a measure of the strength of the parametric effect.

2.5.5. Overall induced responses

Overall changes in the induced spectral power were computed by averaging the time frequency data across all conditions. In particular, as described above, we focused on potential changes in the alpha-band (8–12 Hz).

2.5.6. Statistical analysis

First, electrodes that showed SSEP signals ($p < 0.05$, uncorrected) for both, patients and controls, were identified. Group differences for the SSEP and ITC were then calculated by the average of this subset of electrodes (i.e., Fz, F2, F4, FC2, FC4, C6, CP6, P2, P4 and P6). For SSEPs, two-sample *t*-tests for independent measures were performed for every

time point during f1 and f2. For statistical analysis of ITC values, we used the Wilcoxon rank sum test to account for non-normal distributed data. For overall induced alpha-power we identified electrodes which showed an ERS in patients as well as in controls (Pz and POz). To test for group differences, we computed two-sample *t*-tests for independent measures for every time point of the whole trial. Based on previous work, statistical tests for a parametric effect was performed for a priori selected electrodes (i.e., F2, FC2, F4 and FC4) and frequencies of interest (i.e., beta-band: 20–25 Hz; Spitzer et al., 2010). To test if parametric effects in induced beta-band responses were significantly different from zero, we computed a one-sample *t*-test over the individual slopes for each of the a priori selected electrodes and each group. Group differences in the parametric modulation of prefrontal beta-power in each electrode of interest were then compared using two-sample *t*-tests for independent measures. All of the above *t*-tests were one-tailed given the strong a priori hypotheses that controls show higher values for measures of SSEPs, ITC as well as the parametric beta-modulation compared to patients. To correct for multiple comparisons for each of the above analyses, the respective p-values were adjusted by false discovery rate (FDR) correction (Benjamini and Hochberg, 1995). Given the small sample size of this study and to increase the interpretability of the data, we determined effect sizes and conducted formal power analyses (G*Power; Faul et al., 2007) for the central statistical tests within our study. Hence, we can estimate the probability to which our observations describe true positive effects.

To test for the impact of SSEPs and the parametric modulation on behavioral performance we additionally analyzed both of these measures for incorrect trials. Within-group comparisons of correct vs. incorrect trials were computed by two-sample *t*-tests for dependent measures.

2.5.7. Source reconstruction

For supplementary source modeling, we used the source reconstruction techniques as implemented in SPM8 (Friston et al., 2006). A forward model was constructed for each participant using a template cortical mesh of 8196 points, incorporating the participant's individual electrode positions. The lead field of this forward model was computed using the three-shell BEM EEG head model (Phillips et al., 2007). Before model inversion, the data were band-pass filtered in the respective frequency band of interest. Using multiple sparse priors (Friston et al., 2008) the locations of condition-specific sources were estimated under group constraints (Litvak and Friston, 2008). 3D images were computed for each subject to summarize oscillatory source power for a given frequency at a given time. On the group level effects were estimated in a flexible factorial design.

3. Results

3.1. Behavioral results

3.1.1. N-back

For the group statistics of the n-back task one of the control subjects was excluded because of an extreme response strategy producing an immense false alarm (FA) — rate of 22.22% ($mean_{FA}$ = 5.24%; 95% CI_{FA} [2.78, 7.69]). Control subjects performed the task with an average sensitivity of $d' = 2.41$ (standard error of the mean (SEM) = 0.33) and patients with a sensitivity of $d' = 2.34$ (SEM = 0.12). These values were statistically indistinguishable ($t(15) = -0.29$, n.s.).

3.1.2. d2 test of attention

In the d2 test control subjects performed with an average GZ-f value of mean = 454 (SEM = 39.3). This value did not differ significantly from the average performance (m = 443; SEM = 20.3) of patients with schizophrenia ($t(16) = 0.25$, n.s.).

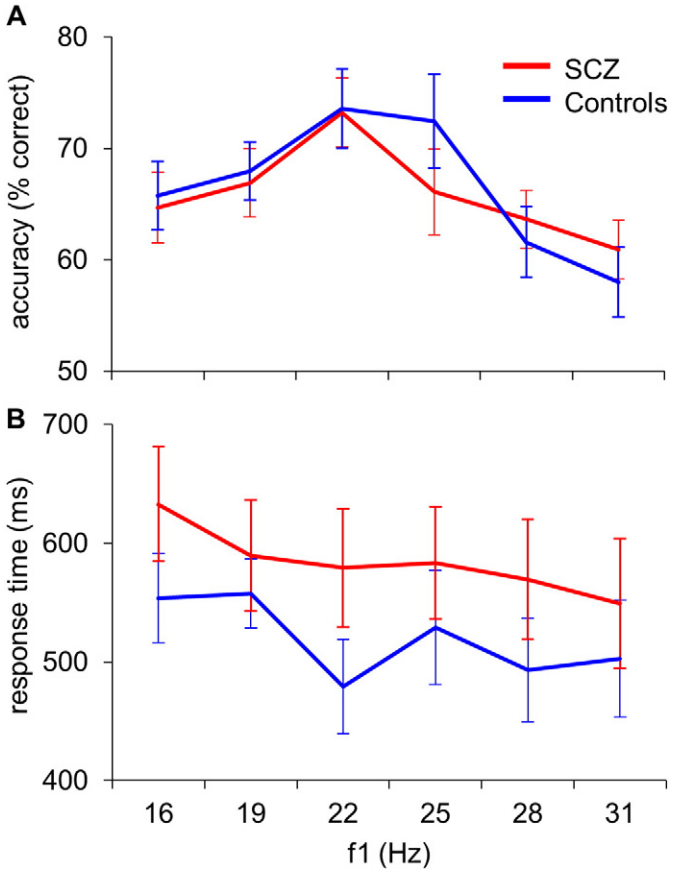

Fig. 1. Performance measures in the sequential frequency comparison (SFC) task. Subjects had to indicate whether the second stimulus (f2) had a higher or a lower frequency compared to the first stimulus (f1). The stimulus set consisted of six frequencies for f1. F2 was 3 Hz higher or lower compared to f1. Average accuracies (A) and response times (B) of healthy controls (blue) and patients with schizophrenia (Scz, red) sorted by f1-frequency. Error bars indicate standard errors of the mean.

3.1.3. Vibrotactile SFC task

Fig. 1 shows the accuracies and response times for individual f1 frequencies for both groups. On average, control subjects responded correctly in 66.55% (SEM = 7) and patients with schizophrenia in 65.9% (SEM = 8) of the trials. This difference was not significant ($F(1, 16) = 0.33$, n.s.). The ANOVA revealed only a significant main effect for the within-subject factor *f1 frequency* ($F(5, 80) = 10.08$, $p < 0.01$). On average, subjects tend to perform better at medium f1 frequencies (22 and 25 Hz). For higher and lower f1 frequencies performance levels decreased in both groups. Control subjects responded on average 536 ms, (SEM = 49 ms) and patients 584 ms (SEM = 42 ms) after the offset of f2. In the response time analysis, only the main effect of f1-frequency was significant ($F(5, 80) = 3.49$, $p < 0.01$). Patients did not respond significantly slower than controls ($F(1, 16) = 0.12$), but on average, subjects tended to respond faster for higher f1 frequencies. The interaction *group × f1 frequency* was not statistically significant ($F(5, 80) = 0.8$, n.s.). Response accuracy tended to decrease with decreasing f2–f1 to f1 ratio in healthy controls (slope = 0.65) as well as in patients (slope = 0.34). However, a linear trend analysis revealed no significant effect for neither group ($p_{controls} = 0.15$; $p_{patients} = 0.42$).

Performance in the n-back task and performance in the vibrotactile FC task were significantly positively correlated, $r = 0.87$ ($p < 0.01$) for healthy controls, and positively but insignificantly correlated, $r = 0.4$ ($p = 0.4$) for patients. Patients' measures of negative symptoms

surveyed with the PANSS showed no significant correlation with task performances (all $p > 0.3$).

3.2. EEG results

3.2.1. SSEPs

Fig. 2 B shows average f1- and f2-SSEPs for patients and control subjects, respectively. Frequency-following steady-state evoked responses were prominent in both groups and were source-localized to the right primary somatosensory cortex S1 (Fig. 2 D, source cluster includes Brodmann areas 3a, 3b, 1 and 2 both in patients and control subjects, illustrated at a level of $p < 0.05$ FWE-corrected for multiple comparisons). For f1-SSEPs control subjects showed a significantly higher ($p < 0.05$, $d = 1.14$; one-tailed; FDR-corrected) change in evoked power between 88 and 283 ms after f1-stimulus onset. For f2-SSEPs control subjects showed a significantly higher ($p < 0.05$, $d = 1.27$; one-tailed, FDR-corrected) change in evoked power between 104 and 201 ms after f2-stimulus onset.

3.2.2. ITC

Average f1- and f2-ITCs are shown in Fig. 2 C for patients and control subjects, respectively. For f1 there was a trend for higher ITC values for controls compared to patients ($p = 0.09$, $d = 0.96$; one-tailed; FDR-corrected) from 137–234 ms after f1-stimulus onset. During f2 ITC was significantly higher ($p < 0.05$, $d = 1.42$; one-tailed; FDR-corrected) in controls than in patients from 104 to 201 ms and at 299 ms after f2-stimulus onset.

3.2.3. Parametric induced responses

Parametric modulations of spectral activity during the retention interval are displayed in Fig. 3. Statistical tests of the linear relationship of average induced power changes in the beta-band (20–25 Hz) revealed a significant parametric effect for control subjects ($p < 0.05$; one-tailed; FDR-corrected) in electrodes F4, FC4 and FC2 but not in F2. For patients with schizophrenia there was no significant effect at any electrode. The parametric effects measured by the slopes of the linear fit were significantly different ($p < 0.05$; $d = 1.01$; one-tailed; FDR-corrected) between patients and controls in electrodes F4 and FC4. There was a trend of a difference in FC2 ($p = 0.069$; $d = .85$; one-tailed; FDR-corrected). Importantly, overall baseline beta-band activity was equally variable in patients compared to controls. Thus, unspecific group differences in overall beta-band activity appear unlikely to explain this effect.

3.2.4. Overall induced responses

Time–frequency maps of induced spectral power changes are shown in Fig. 4. To illustrate the most prominent (post-central to occipital) effects, we show time–frequency maps of the EEG signal in electrode Pz. For both groups, a prominent increase in oscillatory power in the alpha-band (8–12 Hz) was observed, starting during f1 stimulation and most pronounced during the retention interval. Source reconstruction analyses yielded the largest source cluster in early visual areas (BA 17, 18) for both groups illustrated at a level of $p < 0.05$ uncorrected. Controls seem to have a slightly steeper increase of alpha-power during the first 500 ms of the retention interval (Fig. 4 B), but all group differences

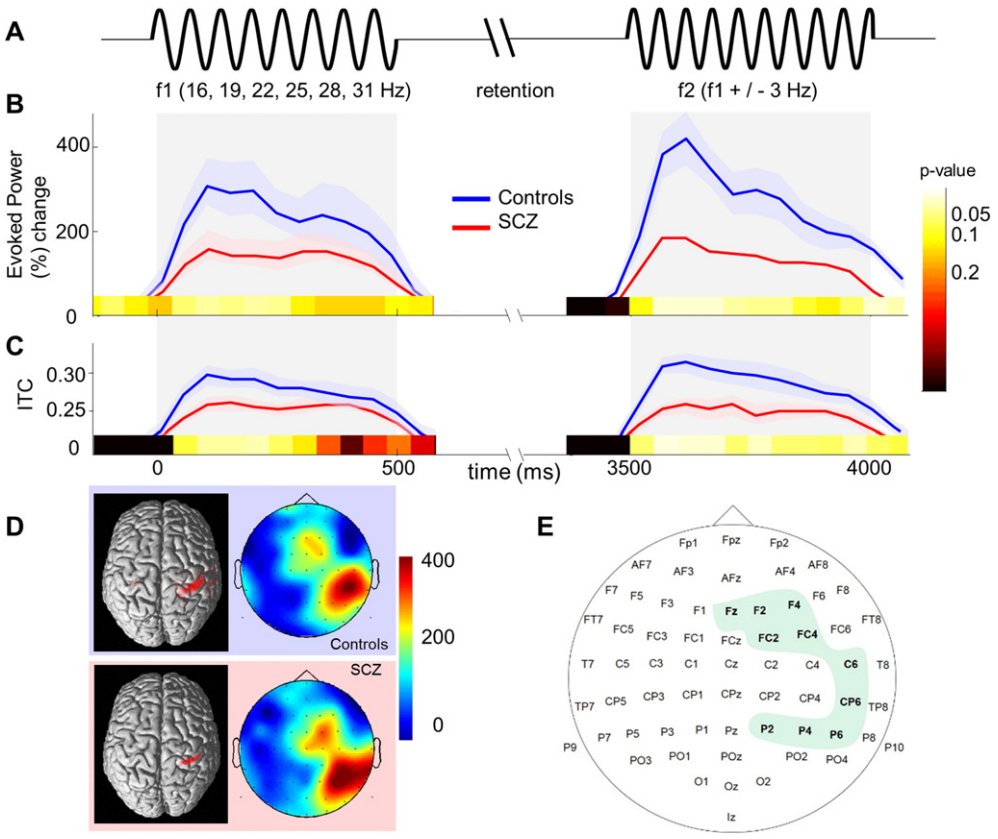

Fig. 2. Trial design, steady-state evoked potentials (SSEP) and inter-trial coherence (ITC). Grey shadings indicate the stimulus presentation time. *A*, Exemplary trial, starting with 500 ms of vibrotactile stimulation (f1) in one of six frequencies (16, 19, 22, 25, 28, and 31 Hz). Followed by a 3 s retention interval, and subsequently a second 500 ms stimulation (f2) 3 Hz higher or lower compared f1. *B*, Left graph: Mean evoked frequency-specific power changes for healthy control subjects (blue) and patients with schizophrenia (red) averaged across all f1 conditions and over representative electrodes (see E). Right graph: same as in the left graph, for the f2 conditions (16, 19, 22, 25, 28, and 31 Hz). *C*, Left graph: mean values of inter trial coherence (ITC) for healthy control subjects (blue) and patients with schizophrenia (SCZ, red) averaged over all f1-frequencies and over representative electrodes (see E). Right graph: same as in the left graph, for f2 conditions (16, 19, 22, 25, 28, and 31 Hz). *D*, Left, SPM source reconstruction and right, scalp topographies of the steady-state response over all f1 conditions. Blue background for healthy controls, red background for patients with schizophrenia. E, Subset of electrodes used for the analysis of SSEPs and ITC (see Section 2).

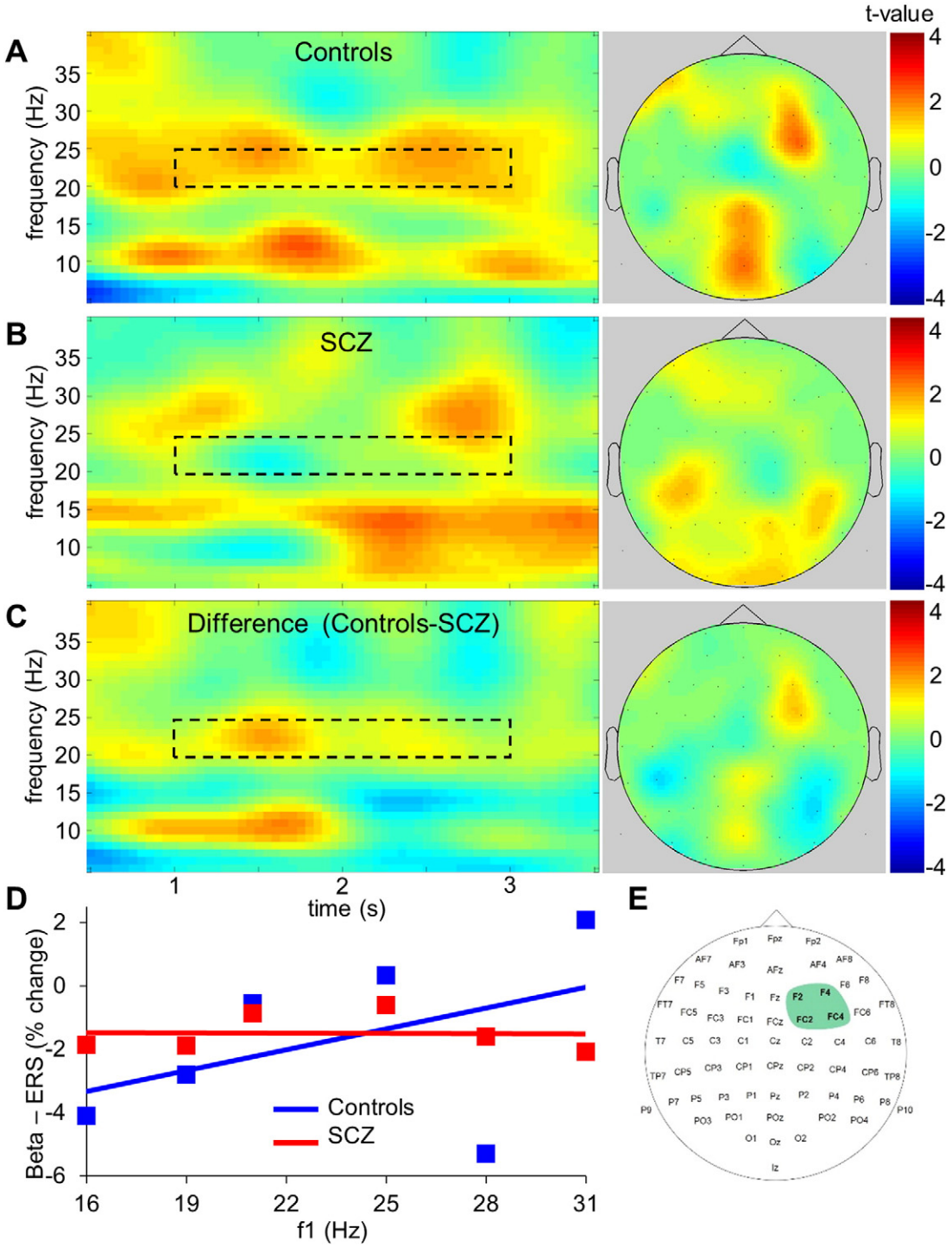

Fig. 3. Parametric modulations of induced power. *A*, Strength of the parametric relationship between induced power and f1 stimulation frequency control subjects averaged over electrodes of interest F2, F4, FC2 and FC4. Right panel: Scalp topographies of the parametric power modulation for time–frequency windows indicated by the dashed rectangle. *B*, Same as *A*, for patients with schizophrenia. *C*, Difference contrast of the parametric effect (Control subjects − patients with schizophrenia). *D*, Induced ERS in the time–frequency window of interest (1000–3000 ms retention interval; 20–25 Hz) for each of the six f1 conditions in both groups. Lines show the linear fit using a least-squares method. *E*, A priori selected set of electrodes for the parametric analysis.

in alpha-power during the whole trial were far from significant (all $p > 0.38$). During f1 presentation, a slight decrease in spectral activity in the beta-band (15–25 Hz) was evident, with a characteristic topographical distribution over bilateral sensorimotor areas. At the end of the trial average power in a broad frequency range (5–30 Hz) decreased, mostly over sensorimotor areas.

3.2.5. Correct vs. incorrect trials

Control subjects' SSEPs showed a significantly higher evoked power in correct trials than in incorrect trials during f1 ($t(8) = 2.74$, $p < 0.05$) and f2 ($t(8) = 4.13$, $p < 0.01$). For patients with schizophrenia this difference was only significant for f1-SSEPs ($t(8) = 2.34$, $p < 0.05$). Mean slopes of the linear fit were significantly different for correct versus

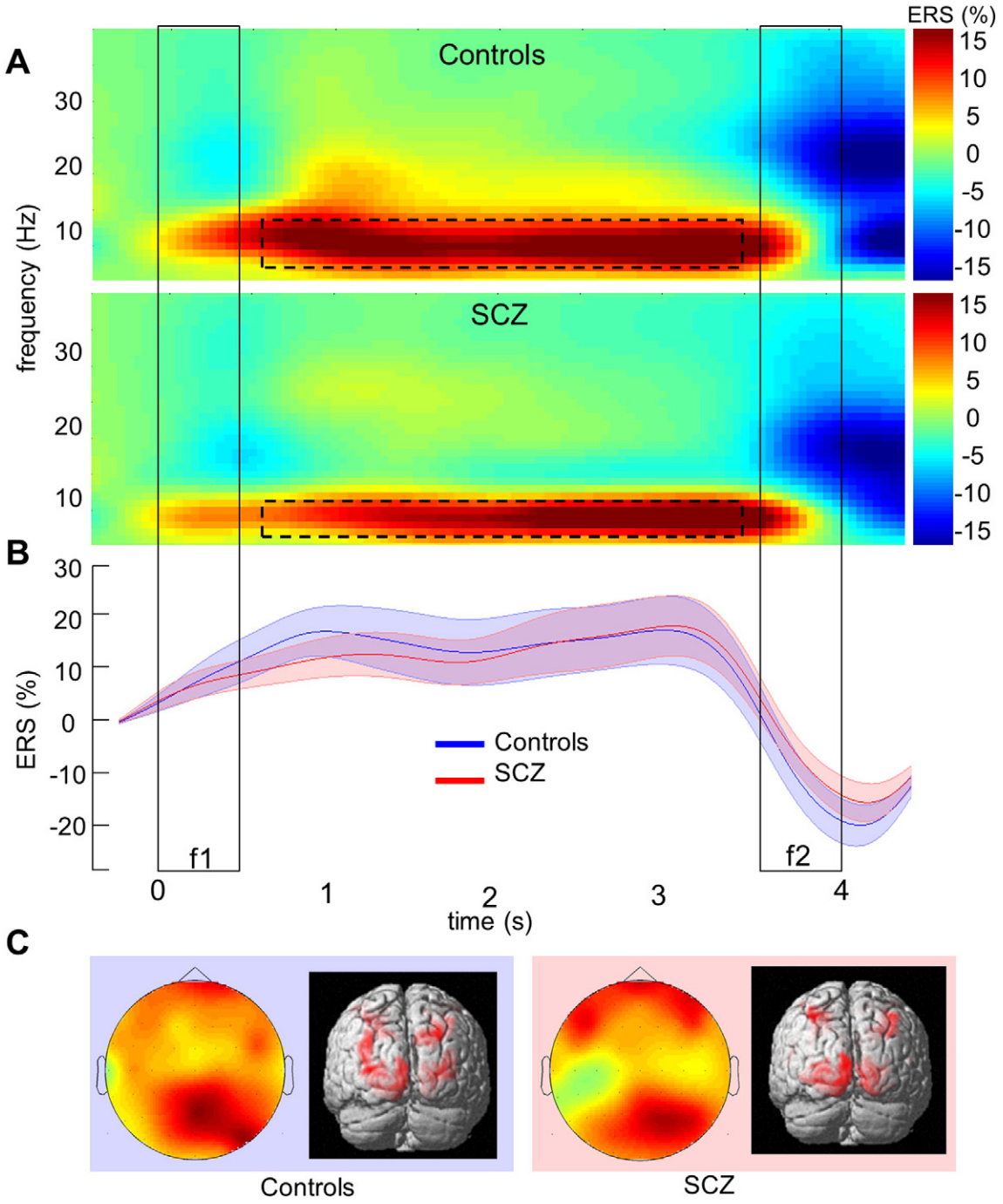

Fig. 4. Overall induced power changes. *A*, Time–frequency plots of induced power changes (ERS) for healthy controls (upper panel) and patients with schizophrenia (lower panel) averaged over all conditions (data from a representative electrode Pz). *B*, Mean alpha-ERS (8–12 Hz) for healthy controls (blue) and patients with schizophrenia (SCZ, red). Colored shadings show the standard error of the mean. *C*, Scalp topography (color scale as in A) plots and SPM source reconstruction of the time–frequency windows delineated in A. Blue background is for healthy controls, red background is for patients with schizophrenia.

incorrect trials in the control group ($t(8) = 2.36$, $p < 0.05$). No significant difference was observed in patients.

3.3. Correlational results

Across the patient sample, scores from the negative symptom scale of the PANSS correlated negatively with the peak steady-state evoked response ($r = -.81$, $p = 0.018$). There was no significant correlation of the scores in the negative symptom scale and measures of ITC ($r = -0.32$, n.s.). Peak SSEPs showed no significant correlation with behavioral performance either in control subjects ($r = 0.44$, n.s.) or in patients ($r = -.40$, n.s.). In healthy controls the linear trend (slope) of accuracy across ratios of f2–f1 to f1 showed a slightly positive correlation ($r = 0.31$, n.s.) with individual slopes in prefrontal beta-power across f1 frequencies, which was, however, not significant. For patients there was a significant negative correlation between these measures ($r = -.78$; $p = 0.013$).

4. Discussion

We studied patients with schizophrenia and healthy control subjects in a well-established (Romo and Salinas, 2003; Spitzer et al., 2010)

vibrotactile sequential frequency comparison (SFC) task to assess vibrotactile sensory encoding and parametric WM. Somatosensory steady-state evoked potentials (SSEPs) during f1 and f2 as well as inter-trial coherence (ITC) during f2 and by trend during f1, in response to periodic tactile stimuli were significantly reduced in patients. Further, compared to healthy control subjects, patients showed a significantly reduced parametric modulation of prefrontal beta-oscillations by the stimulus frequency. Interestingly, patients with schizophrenia and healthy controls differed neither in behavioral task performance nor in behavioral or electrophysiological measures of attention allocation.

More specifically, we evaluated the primary somatosensory encoding of stimulus frequencies by means of the power of the somatosensory SSEPs and more specifically ITC of these frequencies in the primary somatosensory cortex. We found significantly weaker SSEPs during f1 and f2 presentation as well as a significant reduction of ITC during f2 in patients compared to control subjects. Our results indicate that patients with schizophrenia have an impaired sensory representation of the applied stimuli. This finding is well in line with other behavioral and neurophysiological studies reporting general sensory or perceptual impairments in schizophrenia (Chen et al., 1999; Hartman et al., 2003; Javitt, 2009; Leitman et al., 2010; Seymour et al., 2013; Tek et al., 2002). Additionally, steady-state evoked responses to visual or auditory periodic stimulations were previously studied to examine sensory functioning in patients with schizophrenia. Several studies consistently found reduced SSEPs as well as reduced phase-locking (i.e. ITC) in schizophrenic patients (Krishnan et al., 2005; Kwon et al., 1999; Light et al., 2006; for a review see Brenner et al., 2009). Our study extends these previous results to the tactile domain by reporting similar findings (reduced SSEPs and ITC in schizophrenic patients) with respect to vibrotactile stimulation at multiple frequencies, and thus enriches the existing understanding of impaired neural synchronization in schizophrenia (see also Teale et al., 2013). Currently, alterations in gamma-aminobutyric-acid (GABA) inter-neuronal networks in association with glutamatergic input are discussed as a potential explanation for these impairments in neural entrainment (e.g. Uhlhaas and Singer, 2010). Due to minimal task demands and its replicability across modalities, a reduction of neural responses to periodic stimulations has already been considered as a potential biomarker that might be relevant for diagnosis of this disease in the future (Brenner et al., 2009).

We moreover analyzed the oscillatory correlates of WM content, i.e. of the stimulus frequency, maintained during the retention interval. Healthy control subjects, as expected, showed a significant parametric increase of induced beta-band (20–25 Hz) ERS as a function of f1 stimulus frequency in our a priori selected electrodes (Fig. 3). For patients, in contrast, we found a reduced parametric power modulation by f1 frequency in the same frequency band and electrodes. Monotonic increases in neural firing rates varying with the concurrently maintained frequency of a previously presented stimulus were originally found in monkey PFC (Romo et al., 1999). The authors argued that these neurons encode an analogue measure of a continuous quantity, i.e. in this case the stimulus frequency (high firing rates for high stimulus frequencies and low firing rates for low stimulus frequencies). In humans, by analyzing time–frequency transformed EEG responses, recorded during the same task, an equivalent of this effect was reported in form of a parametric power modulation in the beta-band (Spitzer et al., 2010). This modulation indicated an internal top-down WM updating modulated by the stimulus frequency (Spitzer and Blankenburg, 2011) and has been further generalized to periodic stimuli in the visual and auditory modality (Spitzer and Blankenburg, 2012) as well as to different stimulus features such as intensity and duration of tactile stimuli (Spitzer et al., 2014). Thus, the modulation of prefrontal beta-oscillations is likely to reflect an abstract representation of quantity information about the relevant stimulus attribute (Spitzer et al., 2014). In line with these reports control subjects in the present study showed a significant parametric effect which was significantly reduced in patients. Further, in the control group, but not in patients, the parametric effect was stronger for correct than for incorrect trials. Although this points to the behavioral relevance of the prefrontal beta-modulation by stimulus frequency, patients showed no such parametric effect in the beta-power despite a sustained level of behavioral performance. Together, these findings indicate that parametric beta-modulations can manifest as a result of an abstract quantity representation during WM updating, but might not be essential for solving the task. Our results indicate that patients do not form as strong abstract representations of stimulus information (i.e. less parametric modulation in the beta-band by the stimulus frequency) as healthy controls, but might instead use a different strategy that still allows for a similar level of discrimination accuracy. This appears reasonable in the light of evidence from behavioral studies investigating stimulus feature abstraction (Glahn et al., 2000; Weickert et al., 2014). In these studies, results indicated that patients with schizophrenia show impaired capabilities in inferring a stimulus category on the basis of low-level stimulus features. Interestingly, individual slopes of the linear trend of decreasing accuracy with decreasing Weber-adjusted stimulus differences were negatively correlated with the slopes of prefrontal beta-band modulation in patients. That is, they show a reduced dependency of prefrontal beta-power modulation if they are actually sensitive to changes within the task. As before, this might hint to the conclusion that patients use different strategies in order to solve the task while avoiding higher-level abstract representations of WM content. However, as discussed later, this alternative explanation remains speculative due to the limited sample size of this study. In sum, our results complement former studies with schizophrenic patients which reported, e.g., hyperactivity during WM maintenance as apparent by high power of gamma oscillations in a visual DMTS-task (e.g. Haenschel et al., 2009) as well as other studies showing alterations of neural activity specifically during WM maintenance and mostly in areas within the prefrontal cortex (Cannon et al., 2005; Perlstein et al., 2001; see also Manoach, 2003). Beyond these reports of altered cortical activation, we provide evidence that patients with schizophrenia show reduced sensory encoding of stimulus-specific information as well as altered neural representations of WM content during maintenance.

To interpret our results, however, it is crucial to consider the effect of potential attentional impairments which are prevalent in schizophrenic patients (Heinrichs and Zakzanis, 1998; Nuechterlein et al., 2004). Fundamental attentional deficits in patients could influence the cognitive processes in demand for the present task. However, our different control analyses speak against this objection: First, we consider overall changes in induced oscillatory power (see Fig. 4) which were mainly expressed in a parietal to occipital ERS in the alpha-band (8–12 Hz). Importantly, patients showed similar ERS as control subjects. This increase in alpha activity might be largely explained by a general top-town focus favoring internal over external processing, as potential external input might interfere with ongoing WM processing (Klimesch et al., 2007; Spitzer and Blankenburg, 2012). Moreover, since visual input is irrelevant in this specific vibrotactile task, a modality-specific inhibitory effect of alpha-activity on task-irrelevant brain areas, as here on the visual cortex, might add to this global effect (Haegens et al., 2010; Spitzer and Blankenburg, 2012; Tuladhar et al., 2007; see Klimesch et al., 2007 for a review). In this regard, patients in our study do not seem to display obvious disturbances (see also Gold et al., 2006). Second, Giabbiconi et al. (2004) investigated the effect of attention on the power and on phase-locking of stimulus-following frequencies in the EEG in response to periodic tactile stimuli. Importantly, attended compared to unattended tactile vibrations elicited an increased amplitude of the stimulation frequency in the EEG. In contrast, ITC was not affected by different levels of attention. This is noteworthy, because the power of averaged EEG signals (ERP or SSEP), depends on the amplitude of this specific frequency in the single trial epochs as well as on the amount of phase-locking or inter-trial (phase) coherence of this frequency across trials (Makeig et al., 2004). Thus, SSEP and ITC are by no means independent measures. Rather, ITC represents one factor which

influences the power of an SSEP. Our results indicate a reduction in the power of the overall SSEPs and in particular reduced ITC for patients compared to control subjects. Thus, we assume that patients with schizophrenia indeed show impairments in the neural entrainment of the stimulation frequency beyond potential attentional deficits. Third, both groups did not show significant performance differences in the n-back task or the d2 test of attention. Hence, the reported findings are very likely to reflect differences in the specific neurophysiological basis underlying the considered sensory and cognitive processes, and not mere attentional effects. We are aware of the fact that similar levels in measures of attention in both groups cannot be interpreted as a significant null-effect. However, given that multiple tests and analyses (n-back, d2-test of attention, accuracy in the SFC-task & alpha-activity) show not even trends in differences between groups, major confounding factors like, e.g., differences in the level of attention or impaired task performance are rather unlikely to explain the findings.

Finally, the relatively small sample size should be mentioned as a potential limitation of the present study, which led us to restrict our analysis to a priori specified effects of interest, rather than performing explorative analyses of potential other effects that might have occurred in the patient group only. Further, our observed effects showing significant differences between patients and controls achieve a statistical power between 64 and 90%. These values describe the probability to which our observed test results can be considered true effects. This appears reasonable given that a power of 80% has been suggested as a sensible value in the behavioral sciences (Cohen, 1988). Furthermore, many studies in the neurosciences show a much lower level of statistical power (median = 21%; Button et al., 2013).

To summarize, we studied patients with schizophrenia and healthy control subjects in a WM task, which enables researchers to examine primary somatosensory encoding of vibrotactile stimuli as well as abstract representations of stimulus features during WM maintenance. Our results provide evidence that the neural entrainment of vibrotactile stimuli in primary somatosensory cortex is impaired in schizophrenic patients. Furthermore, neural oscillatory correlates of abstract stimulus information were reduced in patients during WM maintenance. Our study for the first time provides evidence for altered neural responses of stimulus-specific information during sensory encoding as well as WM maintenance, and thus contributes to the overall understanding of altered oscillatory signals in schizophrenia.

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Study 2

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Response-Modality-Specific Encoding of Human Choices in Upper Beta Band Oscillations during Vibrotactile Comparisons

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Perceptual decisions based on the comparison of two vibrotactile frequencies have been extensively studied in non-human primates. Recently, we obtained corresponding findings from human oscillatory electroencephalography (EEG) activity in the form of choice-selective modulations of upper beta band amplitude in medial premotor areas. However, the research in non-human primates as well as its human counterpart was so far limited to decisions reported by button presses. Thus, here we investigated whether the observed human beta band modulation is specific to the response modality. We recorded EEG activity from participants who compared two sequentially presented vibrotactile frequencies (f1 and f2), and decided whether f2 > f1 or f2 < f1, by performing a horizontal saccade to either side of a computer screen. Contrasting time-frequency transformed EEG data between both choices revealed that upper beta band amplitude (~24–32 Hz) was modulated by participants' choices before actual responses were given. In particular, "f2 > f1" choices were always associated with higher beta band amplitude than "f2 < f1" choices, irrespective of whether the choice was correct or not, and independent of the specific association between saccade direction and choice. The observed pattern of beta band modulation was virtually identical to our previous results when participants responded with button presses. In line with an intentional framework of decision making, the most likely sources of the beta band modulation were now, however, located in lateral as compared to medial premotor areas including the frontal eye fields. Hence, we could show that the choice-selective modulation of upper beta band amplitude is on the one hand consistent across different response modalities (i.e., same modulation pattern in similar frequency band), and on the other hand effector specific (i.e., modulation originating from areas involved in planning and executing saccades).

Keywords: beta band, EEG, decision making, vibrotactile, saccade

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INTRODUCTION

One of the most complete pictures of neural processes involved in perceptual decision making emerges from the seminal work that has been done in the somatosensory domain over the last years (see Romo and de Lafuente, 2013 for a comprehensive review). Romo and colleagues scrutinized neuronal activity in non-human primates during all stages of a vibrotactile two-alternative forced

choice (2AFC) task. In this task, monkeys had to compare two frequencies (f1 and f2) that were presented one after another, separated by a short working memory (WM) period. Decisions about whether f2 > f1 or f2 < f1 had to be reported via button press after the presentation of f2. Electrophysiological recordings revealed that firing rates in somatosensory cortices (primary and secondary; SI and SII) scaled with the stimulus frequency during presentation (Hernández et al., 2000), whereas prefrontal cortex (PFC) firing rates mirrored f1 (i.e., the frequency) during the WM period (Romo et al., 1999; see also Barak et al., 2010). Most importantly, firing rates in medial and ventral premotor cortex (mPMC and vPMC) encoded the upcoming choices of the monkeys for correct and incorrect decisions (Hernández et al., 2002; Romo et al., 2004).

More recently, Haegens et al. (2011) showed that the monkeys' choices in the vibrotactile 2AFC task were also reflected by amplitude modulations of beta band oscillations (∼18–26 Hz) in premotor local field potentials (LFPs). Applying the same task in a human electroencephalography (EEG) study, we found that this result also translates into beta band oscillations recorded at the scalp (Herding et al., 2016). In particular, the amplitude of upper beta band oscillations (∼20–30 Hz), most likely originating from medial premotor areas, was higher when participants chose "f2 > f1" as compared to "f2 < f1," for correct and for incorrect decisions. These findings match the results of Haegens et al. (2011), and hence, nicely complement the body of work by Romo and colleagues in non-human primates (see above).

According to the notion of an intentional framework of decision making, neural correlates of decisions should be found in brain areas that are involved in the planning and execution of the ensuing motor response (e.g., Cisek, 2007; Shadlen et al., 2008; Cisek and Kalaska, 2010). The work in non-human primates, as well as our recent study, required choices to be reported by a button press. Thus, observing choice-specific neural activity in premotor areas, for planning and informing an ensuing button press, is in line with an intentional framework of decision making. The importance of the intentional framework has been fostered in particular by the extensive body of work compiled by Shadlen and co-workers (reviewed in Gold and Shadlen, 2007). In the visual domain, perceptual decisions that are expressed by saccades, involve those brain areas that are responsible for saccade planning/execution, i.e., lateral intraparietal area (LIP; e.g., Shadlen and Newsome, 1996), frontal eye fields (FEF; e.g., Kim and Shadlen, 1999), and superior colliculus (SC; e.g., Ratcliff et al., 2003).

Taken together, each of the two major lines of research on perceptual decision making in non-human primates (cf. Gold and Shadlen, 2007; Romo and de Lafuente, 2013) appears to converge towards the notion of an intentional framework of decision making. However, the findings from both approaches (vibrotactile button press decisions and visual saccade decisions) have not yet been linked, and thus it is still unclear whether the respective results are directly transferable. In the present study, we aimed to bridge the gap between these two lines of research. We used the vibrotactile 2AFC task typically utilized by Romo and colleagues combined with saccade responses as applied in most of the work by Shadlen and colleagues. In particular, we investigated whether the choice-specific beta band modulation that we observed in our recent study (Herding et al., 2016) would still be present when participants were asked to respond with saccades instead of button presses. If so, can such a modulation be attributed to a brain area that is involved in the planning and execution of saccades as predicted by an intentional framework of decision making? To address these questions, we recorded EEG data of human participants during the vibrotactile 2AFC task, where choices were indicated by horizontal saccades. We contrasted the time-frequency (TF) transformed response-locked EEG data between both alternative choices ("f2 > f1" vs. "f2 < f1") to reveal oscillatory signatures of decision making before responses were given. In line with the results from our previous study with button press responses (Herding et al., 2016), we found again a choice-selective modulation of upper beta band oscillations (∼24–32 Hz) in frontal electrodes. However, source localization of the choice signal suggested more lateral premotor areas as compared to medial premotor areas for the button press responses, importantly, including FEF.

MATERIALS AND METHODS

Participants

Twenty four healthy, right-handed volunteers (20–36 years; nine males) participated in the experiment after giving written informed consent in accordance with the Declaration of Helsinki. The study was approved by the local ethics committee at the Freie Universität Berlin. Two participants (both female) were excluded from the analysis due to near chance-level behavioral performance (<60% correct answers), resulting in 22 data sets for further analysis.

Stimuli and Behavioral Task

Supra-threshold vibrotactile stimuli with constant peak amplitude were applied to the left index finger using a piezoelectric Braille stimulator (QuaeroSys, Schotten, Germany). The stimuli consisted of amplitude-modulated sinusoids with a fixed carrier frequency of 137 Hz. The amplitude-modulation of this carrier signal with frequencies 12–32 Hz created the sensation of tactile 'flutter' (see Talbot et al., 1968; Romo and Salinas, 2003), while the spectrum of the physical driving signal was limited to frequencies above 100 Hz (e.g., Tobimatsu et al., 1999). Thus, the risk of physical artifacts in the EEG analysis range of interest (<100 Hz) was minimized. The sound of the stimulator was masked by white noise of ∼80 dB that was played throughout the experiment (e.g., Spitzer et al., 2010; Spitzer and Blankenburg, 2011). Participants were comfortably seated ∼60 cm in front of a TFT monitor. A fixation cross was displayed at the center of the screen to minimize eye movements. On each trial, two flutter stimuli were successively presented for 250 ms each (with frequencies f1 and f2), interleaved by a retention interval of 1000 ms (see **Figure 1A**). The values of f1 were randomly drawn from 16, 20, 24, or 28 Hz, whereas f2 differed from f1 by ±2 or 4 Hz (**Figure 1B**). After presentation of the second stimulus the central fixation cross vanished and two target dots (diameter of ∼0.5° visual angle) appeared on the left

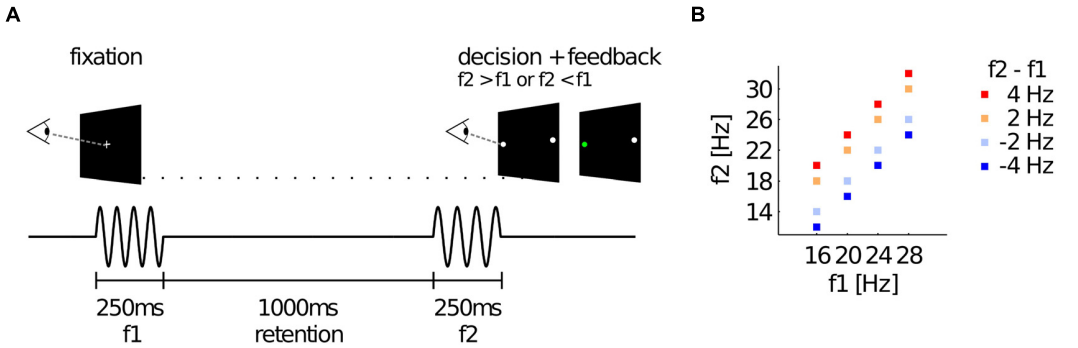

FIGURE 1 | Experimental paradigm and stimulus set. (A) Illustration of a single trial. Participants were presented with two vibrotactile stimuli (with frequencies f1 and f2) at the left index finger, while holding central fixation until the offset of the second stimulus. Afterwards, they decided whether f2 > f1 or f2 < f1 by means of a horizontal saccade. Online feedback was provided immediately after the decision via color change of the selected dot (green for correct, red for incorrect trials). **(B)** The set of all possible frequency combinations of f1 and f2 that were applied in this study. Color-coded squares each indicate one stimulus pair with according f1 and f2 values.

and on the right side of the screen (∼12° visual angle off-center). Participants indicated whether f2 > f1 or f2 < f1 by making a saccade to the right or to the left target, respectively. Importantly, the response assignment of saccade directions was reversed for half of the participants, such that the mapping of choices onto specific saccades (which might have been associated with specific motor preparatory signals) was fully counterbalanced across participants. Responses were registered as soon as participants fixated one of the targets for 200 ms. According choices were evaluated online to provide immediate (with a latency of 20 ms) performance feedback by changing the color of the selected target dot for 200 ms (green for correct, red for incorrect choices). After the feedback, the central fixation cross reappeared and replaced the target dots to indicate the beginning of a new trial. Participants had to fixate the central cross to start the new trial. After a variable time interval (1500–2000 ms) a new stimulus pair was presented. Participants completed seven blocks of 160 f1-vs-f2 comparisons (each block lasted ∼15 min including eye-tracker calibration), for a total of 1120 trials. Before the experiment started, participants performed ∼50 practice trials.

Eye-Tracking

A Tobii T60 eye-tracker was used to record participants' eye movements during each trial (binocular sampling at 60 Hz). The T60 is integrated into a 17″ TFT monitor, and is able to track participants that are comfortably seated in front of the monitor (i.e., no chin rest required). Online evaluation of the participants' gaze directions was implemented with custom code using the Tobii toolbox for MATLAB. Thus, we could check whether participants kept the gaze on the central fixation cross during each trial (with tolerance of ∼3° visual angle), and displayed a warning message if this was not the case ("Please keep fixation throughout the trial"). Additionally, we could read out participants' choices (200 ms fixation on target dot with tolerance of ∼3° visual angle) and provide performance feedback online. To maintain a high tracking accuracy, the eye-tracker was calibrated before the beginning of each block using a standard 5-dot calibration procedure.

Behavioral Analysis Using Bayesian Modeling

We estimated subjectively perceived frequency differences (SPFDs) based on the observation that participants do not compare f2 with the physical value of f1 (cf. Hellström, 1985, 2003), but rather with a value slightly shifted toward the mean of all presented stimulus frequencies (cf. Preuschhof et al., 2010; Ashourian and Loewenstein, 2011; Karim et al., 2012; Sanchez, 2014). Using the framework of Bayesian inference, we introduced this shifted version of f1, which we call f1′, as the expected value of the posterior distribution of f1 when using a Gaussian prior centered over all presented frequencies. Three free parameters (the variance of the likelihood distribution of f1, the variance of the prior distribution, and an overall response bias) were estimated in this model based on each participant's choices (further details in Herding et al., 2016). The SPFDs are then defined as the differences f2–f1′ for each stimulus pair. To assess the quality of the SPFD model, we computed Bayes factors (BFs) comparing the model with a "null" model (based on the physical frequency differences f2–f1) while accounting for differences in model complexities (e.g., Kass and Raftery, 1995).

EEG Recording and Analysis

EEG (ActiveTwo; BioSemi) was recorded at 2048 Hz (offline down-sampled to 512 Hz) from 64 electrodes positioned in an elastic cap according to the extended 10–20 system. Individual electrode locations for each participant were obtained prior to the experiment using a stereotactic electrode-positioning system (Zebris Medical GmbH, Isny, Germany). Four additional electrodes were used to register the horizontal and vertical electrooculogram (hEOG and vEOG). For preprocessing, EEG data were first re-referenced to a common average montage, and then high- and low-pass filtered (with cut-off frequencies of 0.5 and 48 Hz, respectively). Eye blink artefacts in the EEG data were corrected using adaptive spatial filtering based on individual calibration data informed by the vEOG signal (see Ille et al., 2002). The artefact-free EEG data were segmented into

epochs from −2500 to 1000 ms relative to the time of saccade onset (based on the hEOG signal) in order to examine EEG oscillations before choices were reported (i.e., response-locked analysis). Based on visual inspection, noisy trials were excluded from further investigations (10.5% of trials on average). To get a time-resolved representation of spectral power in the EEG signal, Morlet wavelet transforms of short segments of EEG data were computed every 50 ms. The lengths of these segments depended on the frequency of the applied wavelet (i.e., 4–48 Hz resolved with 1 Hz), and always spanned seven cycles (e.g., 700 ms for 10 Hz, 350 ms for 20 Hz). The resulting TF representations of the EEG data were hence resolved at 50 ms and 1 Hz (i.e., TF bin = 50 ms × 1 Hz). All analyses were done in MATLAB (The MathWorks) using the SPM12 toolbox (Wellcome Department of Cognitive Neurology, London[1]), including the FieldTrip toolbox for EEG/MEG data (Radboud University Nijmegen, Donders Institute [2]).

Statistical Analysis

The response-locked single-trial TF data were square root transformed (yielding spectral amplitudes) to approximate normally distributed data (see Kiebel et al., 2005). Additionally, TF data were smoothed with a 3 Hz × 300 ms FWHM (full width at half maximum) Gaussian kernel to decrease inter-subject variability (e.g., Kilner et al., 2005; Litvak et al., 2011). For each participant, we used the smooth TF images of all trials to estimate the average TF maps for either choice category (i.e., f2 < f1 and f2 > f1 trials) separately for correct and incorrect decisions. That is, we implemented a general linear model (GLM) with 2x2 factorial design (factors: "f2 < f1/f2 > f1"; "correct/incorrect"), and estimated the interaction terms. We contrasted the average TF maps within each participant to identify interaction effects between both factors (i.e., between "f2 < f1/f2 > f1" and "correct/incorrect"; contrast vector = [−1 1 1 −1]), as this resulted in contrasting the actual choices of participants disregarding whether choices were correct or incorrect (i.e., chose "f2 > f1" vs. chose "f2 < f1"). The resulting contrast images hence showed the difference in spectral amplitude for each TF bin between both choices (i.e., "f2 > f1" choices minus "f2 < f1" choices) considering correct and incorrect trials. To identify time, frequencies, and channels for which this contrast was consistently different from zero across participants, we used cluster-based permutation testing (Maris and Oostenveld, 2007). We compared the summary statistics of the observed data (one-sample *t*-test across contrast images of all participants in each TF bin) with a distribution of summary statistics obtained from 500 randomly sign-flipped permutations. Consistent with our previous work focusing on strong and focal effects (Herding et al., 2016), a cluster was defined as a group of adjacent TF bins that all exceeded a cluster-defining threshold of $p_{\text{threshold}} < 0.001$ (uncorrected). Clusters that exceeded a family-wise error (FWE) corrected threshold of $p_{\text{cluster}} < 0.05$ (corrected for time, frequency, and channels) were considered to be statistically significant. Additionally, we probed whether a significant modulation by choice was observed individually for correct and incorrect trials within the identified TF cluster. Hence, we computed a conjunction analysis of the choice modulation between correct and incorrect trials (i.e., conjunction of contrasts: [−1 1 0 0] AND [0 0 1 −1]; cf. Friston et al., 2005; Nichols et al., 2005). As described above, we identified significant TF clusters using cluster-based permutation testing separately for correct and incorrect trials, and inspected whether the resulting clusters overlapped. For this analysis, we used a cluster-defining threshold of $p_{\text{threshold}} = 0.01$ (uncorrected), and only corrected for channels that displayed a choice-modulation in the previous analysis of interaction effects.

Source Reconstruction

The cortical sources of choice-modulated beta band activity observed on the scalp-level were localized using the 3D source reconstruction routines provided by SPM12 (Friston et al., 2006). Based on the individually recorded electrode positions for each participant, a forward model was constructed using an 8196-point cortical mesh of distributed dipoles perpendicular to the cortical surface of a template brain (cf. Friston et al., 2006). The lead field of the forward model was computed using the three-shell Boundary Elements Method (BEM) EEG head model available in SPM12. The forward model was inverted using a smoothness prior (called 'COH' in SPM; cf. Litvak et al., 2011), which is similar to the LORETA approach (Pascual-Marqui et al., 1994). That is, the inverse solution preferred source activity with only proximal sources showing correlated activity while the total energy of source activity was minimized. Additionally, we applied group constraints for the model inversion, which effectively restricted the inverse solution to explain individual data using the same set of sources across participants (cf. Litvak and Friston, 2008). Preprocessed response-locked single-trial EEG data before TF transformation (i.e., in the time-domain) were used to invert the forward model. Before model inversion, the single-trial data were additionally tailored to the time interval of the choice modulation identified on the scalp level (i.e., −750 to −450 ms before responses were given). According to the interaction terms of the 2x2 factorial design (see above), the results of the model inversion were summarized in four 3D images that reflected average spectral source power in a representative TF window (i.e., 24–32 Hz; −700 to −500 ms from saccade onset). These images were obtained by computing wavelet transforms of single-trial source activity, and then averaging the source power across trials for each condition of interest. The 3D images were then used to contrast source power between choices for each participant, analogously to the conjunction analysis in sensor space (i.e., conjunction of contrasts: [−1 1 0 0] AND [1 −1 0 0]). The conjunction analysis yielded only sources that exhibited significantly higher beta band power for "f2 > f1" choices than for "f2 < f1" choices in both correct and incorrect trials (i.e., testing the conjunction null; cf. Friston et al., 2005; Nichols et al., 2005). The results of this mass-univariate statistical test are displayed at a significance level of $p < 0.001$ (uncorrected) indicating the most probable sources of the effect observed at the sensor-level. Anatomical reference for source estimates was established on the

[1] http://www.fil.ion.ucl.ac.uk/spm

[2] http://www.fieldtriptoolbox.org

basis of the SPM anatomy toolbox (Eickhoff et al., 2005) where possible.

Time Courses

To get further insights into the effects obtained from the TF analysis, we extracted underlying time courses from the statistically significant TF cluster separately for correct and incorrect trials. For correct trials, we computed the time courses individually for different levels of SPFDs. Based on all observed SPFD values (differences of log-transformed frequency values), we defined six levels of SPFD (i.e., [< -0.18]; [-0.18 to -0.09]; [-0.09 to 0]; [0 to 0.09]; [0.09 to 0.17]; [> 0.17]). We specified the levels symmetrically around a SPFD of zero (corresponding to chance-level performance), and in such a way that each participant had at least one stimulus pair for each level. Based on the identified TF cluster, we computed the grand average time courses of upper beta band amplitude (24–32 Hz) for each level of SPFD. For incorrect trials, we separated the trials only into two classes (due to low trial numbers for some levels of SPFD) with SPFD < 0 and SPFD > 0, i.e., f2 $<$ f1 and f2 $>$ f1, and computed the grand average time courses.

RESULTS

Behavioral Results

On average, participants made correct choices on 74.4% of all stimulus pairs. We performed a within-subject analysis of variance (ANOVA) with the factors "difficulty" (± 4 vs. ± 2 Hz stimulus differences) and "sign" (positive vs. negative stimulus differences) on proportions of correct responses (PCRs), using a logit-transform to account for non-normality of the residuals. The analysis revealed significant main effects of the factors difficulty ($p < 0.001$) and sign ($p = 0.001$), and a significant interaction of the two factors ($p < 0.001$). As expected, a larger proportion of trials were judged correctly when the physical f2–f1 frequency difference was ± 4 Hz (80.9% correct) compared with trials where the difference was only ± 2 Hz (67.8%; $p < 0.001$; paired t-test; see difficulty effect **Table 1**). We also observed more correct responses for positive (78.1% correct) compared with negative frequency differences (70.6%; $p = 0.006$ paired t-test; see sign effect **Table 1**), which indicates an overall response bias toward "f2 $>$ f1" choices (mean criterion shift: 0.12; $p = 0.003$; one-sample t-test).

An ANOVA (2x2x2 repeated measures design with factors "correct/incorrect," "difficulty," and "sign") of the median response times (RTs) showed a significant main effect for the factor "correct/incorrect" ($p < 0.001$), and two significant interactions ("correct/incorrect" $\times$ "sign", $p = 0.001$ and "correct/incorrect" $\times$ "difficulty", $p = 0.004$). More precisely, the median RT with respect to f2 stimulus onset was on average shorter for correct trials (570.4 ms) than for incorrect trials (620.5 ms; $p < 0.001$; paired t-test). For correct trials, RTs were faster for trials with f2 $>$ f1 (548.1 ms) as compared to f2 $<$ f1 (599.1 ms; $p = 0.001$; paired t-test), whereas for incorrect trials the pattern was reversed (665.1 ms when f2 $>$ f1, and 604.9 ms when f2 $<$ f1; $p = 0.002$; paired t-test; all patterns of interaction effects in the RT data are detailed in **Table 1**). Thus, participants were in general faster when choosing "f2 $>$ f1," no matter whether this choice was correct or incorrect. This is in line with the overall response bias toward "f2 $>$ f1" choices (see above). Accordingly, when computing criterion shifts separately for fast and slow trials of each participant (i.e., median split of RTs), fast responses displayed a much stronger bias toward "f2 $>$ f1" choices than slow responses ($p < 0.001$, paired t-test). In fact, whereas participants clearly favored "f2 $>$ f1" choices in fast trials (mean criterion shift: 0.31; $p < 0.001$, one sample t-test), in slow trials the bias was actually reversed (mean criterion shift: -0.11; $p = 0.009$, one sample t-test).

Upper Beta Band Oscillations in Right Frontal Electrodes Encode Choices before Responding

To test if choices were reflected in oscillatory EEG activity before a response was given, we compared average TF maps of f2 $<$ f1 and f2 $>$ f1 trials in response-locked data, while considering that any possible effect of choice should switch sign between correct and incorrect trials (i.e, we checked for an interaction effect of the factors "f2 $<$ f1/f2 $>$ f1" and "correct/incorrect"). The analysis revealed that upper beta band amplitude ($\sim$24–32 Hz) in right frontal electrodes (FC2, FC4; inset **Figure 2A**) was significantly higher for "f2 $>$ f1" choices well before responses were given (-750 to -450 ms from response; $p_{\text{cluster}} = 0.034$, FWE corrected; **Figure 2A**, dashed

TABLE 1 | Behavioral data.

	Frequency difference of stimuli (f2–f1) in Hz					
	−4	−2	2	4	Difficulty effect	Sign effect
PCR (%)	75.9 ± 4.4	65.3 ± 3.5	70.5 ± 4.3	86.1 ± 3.7	n/a ($p < 0.001$)*	n/a ($p = 0.002$)*
RT correct (ms)	590.2 ± 44.8	608.0 ± 48.3	554.5 ± 47.1	541.6 ± 44.7	−15.4 ± 9.0 ($p = 0.002$)*	−51.1 ± 28.6 ($p = 0.001$)*
RT incorrect (ms)	615.9 ± 64.9	593.9 ± 60.7	651.5 ± 58.1	678.6 ± 68.2	24.5 ± 19.0 ($p = 0.014$)*	60.2 ± 34.8 ($p = 0.002$)*

Proportion of correct responses (PCRs) and response times (RTs) as a function of the physical frequency difference f2–f1. Mean values ± 95% confidence interval (CI) are shown. 'Difficulty effect' compares easy (±4 Hz) and difficult (±2 Hz) trials in a paired t-test. 'Sign effect' compares between trials with positive (2 and 4 Hz) and negative (−2 and −4 Hz) frequency differences in a paired t-test. PCRs and RTs showed significant effects of difficulty and sign. RTs showed both effects for correct and incorrect trials, however, in opposing directions (cf. interactions in ANOVA of RTs). PCRs were logit-transformed before testing, due to non-normally distributed residuals. We omitted average differences of logit-transformed PCRs for both effects to avoid confusion (indicated by n/a). Asterisks indicate statistically significant results.

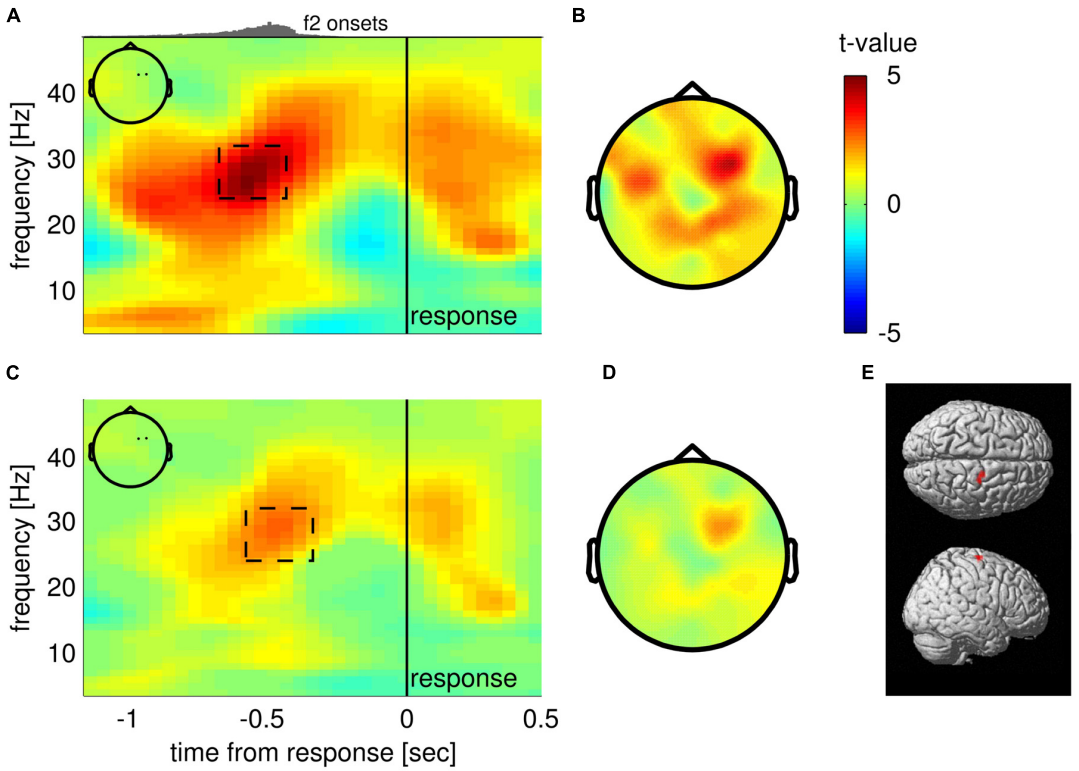

FIGURE 2 | Choice-selective modulation of upper beta band amplitude. (A) Time-frequency (TF) map displaying *t*-values from group analysis of interaction effect ("f2 < f1/f2 > f1" × "correct/incorrect"), averaged over electrodes FC2 and FC4 (see inset) spanning a statistically significant cluster. Histogram on top indicates the distribution of stimulus onset times of the second stimulus. **(B)** Scalp topography of TF window centered on significant cluster as indicated in **(A)**. **(C)** Results of the conjunction analysis between correct and incorrect trials averaged over electrodes FC2 and FC4 (inset). The TF map displays the minimum of *t*-values when combining choice-selective modulation computed separately for correct and incorrect trials. **(D)** Scalp topography corresponding to the TF window indicated in **(C)**. **(E)** Most likely source location of the choice-selective beta band modulation.

rectangle). The scalp topography of the TF cluster shows that the effect also spreads to parietal electrodes and displays a second, weaker peak in left frontal electrodes (**Figure 2B**; the cluster extended to both sites for a lower cluster-defining threshold of $p_{\text{threshold}} = 0.01$). Notably, steady-state evoked potentials (SSEPs) of vibrotactile stimuli are known to lead to a narrow-band power increase in the EEG signal at frequencies corresponding to the stimulus frequency in electrodes contralateral to stimulation (e.g., Tobimatsu et al., 1999). For f2 > f1 trials, f2 was generally higher (25 Hz on average) than for f2 < f1 trials (19 Hz on average). Hence, correct choices of "f2 > f1" were primarily accompanied by SSEPs in the upper beta band, whereas correct choices of "f2 < f1" were mainly associated with SSEPs in lower frequencies. Given that the reported effect partly overlapped with the presentation of f2, we were concerned whether the alleged choice-selective modulation of upper beta band amplitude was driven by the systematic differences in SSEPs between choices. Importantly however, the systematic relationship between SSEPs and choices can only compromise our findings for correct trials. Therefore, we computed a conjunction analysis between correct and incorrect trials to probe whether the observed beta band modulation was the same for both correct and incorrect trials. Indeed, we found overlapping significant TF clusters in the upper beta band (∼25–30 Hz) approximately 500 ms before responses were given in previously identified electrodes FC2 and FC4 (correct: −600 to −400 ms; 26–35 Hz; $p_{\text{cluster}} = 0.044$; incorrect: −1000 to −400 ms; 20–33 Hz; $p_{\text{cluster}} = 0.004$; cf. **Figure 2C**). Remarkably, the effect was even stronger for incorrect trials than for correct trials. Displaying the minimum *t* statistics between correct and incorrect trials reveals that only right frontal electrodes show the choice-selective modulation of upper beta band amplitude consistently for correct and incorrect trials (**Figures 2C,D**). Accordingly, the most probable source of the effect was found in the right precentral gyrus including FEF (MNI coordinates of cluster peak: 18, −12, 70; $p < 0.001$, uncorrected; **Figure 2E**). Taken together, we can largely rule out a major contribution of SSEPs to the observed beta band modulation.

Next, we looked at the choice-selective beta band modulation independently for correct and incorrect choices by separately computing the according grand mean time courses of upper beta band amplitude (24–32 Hz; **Figure 3**). The time courses for correct trials show that beta band amplitudes separate categorically according to choices (**Figure 3**; correct trials). That is, the according choice category modulated upper beta band amplitude, but not the specific values of the SPFD. Notably, the SPFDs described participants' choices more accurately than

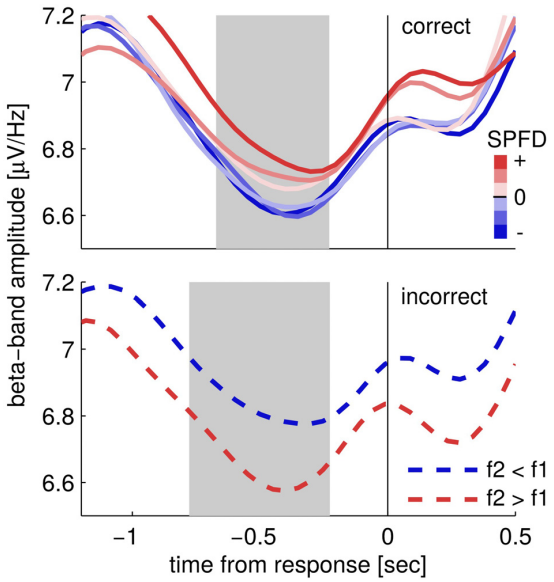

FIGURE 3 | Time courses of upper beta band amplitude (24–32 Hz) separately for correct (upper) and incorrect trials (lower). Correct trials are split into six levels of subjectively perceived frequency differences (SPFDs) as inferred from a Bayesian inference model that describes choice behavior in this task better than physical differences (see text for details). Despite this fine-grained partitioning, time courses are separated solely according to choice categories. Incorrect trials were split only into two classes (according to f2 > f1 and f2 < f1, due to low trial numbers) and still showed a higher beta band amplitude for (incorrect) "f2 > f1" choices (i.e., f2 < f1, blue line) than for "f2 < f1" choices (i.e., f2 > f1, red line). Shaded areas denote the time interval in which the second stimulus was typically presented (central 50%).

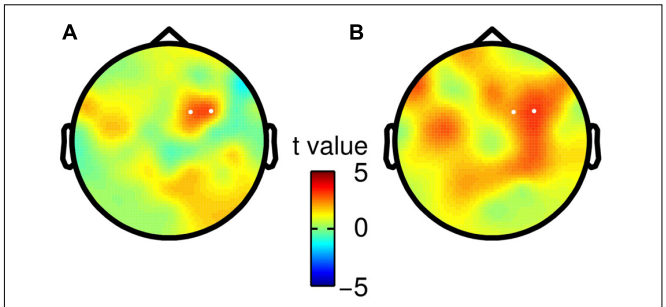

FIGURE 4 | Scalp topographies of choice-selective beta band modulation for both saccade-to-choice mappings. White dots correspond to electrodes spanning the significant TF cluster in the main analysis based on all participants. **(A)** Choices of "f2 > f1" were associated with a rightward saccade, whereas "f2 < f1" choices required a leftward saccade. **(B)** Opposite mapping as described in **(A)**.

the physical differences in each trial (strong evidence in favor of our model, i.e., BFs > 20, for 20/22 participants). For incorrect trials, we only distinguished between SPFD > 0 and SPFD < 0 (i.e., f2 > f1 and f2 < f1), and found that upper beta band amplitude was still higher for (incorrect) choices of "f2 > f1" (**Figure 3**; incorrect trials). Reiterating the results of our conjunction analysis, the identified modulation of beta band amplitude by choices was neither driven solely by correct trials nor solely by incorrect trials. Interestingly, for incorrect trials beta band amplitude was separated according to choices already well before the presentation of the second stimulus. Such a pre-stimulus difference might possibly explain why participants made erroneous choices in according trials (i.e., as the result of a bias), and would foster the interpretation of upper beta band amplitude as a precursor of the ensuing decision report.

In a control analysis, we examined whether the observed modulation of upper beta band amplitude was possibly related to the present variations in RTs according to choices. In particular, RTs for "f2 > f1" choices were always faster as for "f2 < f1" choices, for both correct and incorrect trials. That is, the same interaction as in the EEG data was also present in RTs (see **Table 1**). Thus, if faster RTs were associated with higher beta band amplitude in electrodes FC2 and FC4, the RT variations would be an alternative explanation of the observed modulation in beta band amplitude. We computed correlations between single-trial RTs and beta band amplitude for each participant, however, the obtained correlation coefficients scattered randomly around zero across participants (one sample *t*-test of correlation coefficients; mean $\rho = -0.021$, $p = 0.245$). Additionally, we checked for the same correlation within each choice category, but again, did not find any connection (one sample *t*-test of correlation coefficients; "f2 > f1" choices: mean $\rho = -0.013$, $p = 0.463$; "f2 < f1" choices: mean $\rho = -0.018$, $p = 0.408$). Hence, we can largely rule out that the reported modulation of beta band amplitude can be attributed to systematic RT variations. We also probed whether the overall response bias toward "f2 > f1" choices could explain the observed modulation in the beta band. To this end, we repeated the main analysis only using data from participants showing no such bias, or even a bias in the opposite direction (criterion shift < 0.1, 10 participants). These participants did also not show systematic differences in RTs between choices (i.e., "f2 > f1" vs. "f2 < f1" choices) neither for correct nor for incorrect trials (paired *t*-test between choices, $p = 0.224$ and $p = 0.352$). Despite the markedly reduced sample size, we observed the same pattern of upper beta band amplitude being higher for "f2 > f1" choices than for "f2 < f1" choices.

Finally, we tested whether the observed choice-selective modulation in the beta band was consistent for both specific mappings of choices onto saccade directions. Hence, we split participants according to their response mapping (i.e., right saccade = "f2 > f1" or right saccade = "f2 < f1"), and repeated the analysis of TF data separately for both groups ($N = 11$). We did not find any statistically significant differences between both groups (independent two-sample *t*-test, no clusters with $p < p_{\text{threshold}}$ before saccade onset), but rather found a considerable agreement in the topography of the choice-selective beta band modulation (**Figure 4**).

DISCUSSION

In the current study we investigated oscillatory EEG signatures of perceptual decisions based on the comparison between two sequentially presented vibrotactile frequencies f1 and f2.

Participants decided whether f2 > f1 or f2 < f1 by performing a horizontal saccade, where the association between saccade direction and choice was counterbalanced across participants. We found that the amplitude of upper beta band oscillations (∼24–32 Hz) in right frontal electrodes was modulated by participants' choices before responses were given, regardless of whether choices were correct or incorrect, and independent of the specific saccade-to-choice mapping. In particular, "f2 > f1" choices were always associated with a higher beta band amplitude than "f2 < f1" choices. Notably, the same modulation pattern of beta band amplitude was recently shown when participants (non-human primates and humans) completed the same task, but reported choices by button presses (Haegens et al., 2011; Herding et al., 2016). In analogy to these studies, we found in the current data that premotor areas were implicated as the most likely source of the choice-selective signal, however, now with a focus on distinct lateral parts, including FEF.

The crucial role of premotor cortex in decision formation during the vibrotactile 2AFC task was established by the seminal work of Romo and colleagues with non-human primates (reviewed in Romo and de Lafuente, 2013). Electrophysiological recordings in mPMC and vPMC showed choice-selective differences in premotor firing rates before actual responses were given by button presses (Hernández et al., 2002, 2010; Romo et al., 2004). Similar to the current data, this modulation was observed as early as during the presentation of the second stimulus (Hernández et al., 2002, 2010; Romo et al., 2004), and was shown to be behaviorally relevant, as the modulation was inverted for incorrect choices (Hernández et al., 2002). Conversely, the choice-selective differences in firing rates disappeared when no comparison of f1 and f2 was necessary in order to respond (i.e., a visual cue guided action), dissociating the finding from mere motor preparation (Hernández et al., 2002, 2010; Romo et al., 2004). To dissociate specific left/right saccade preparation (i.e., lateralized parietal alpha/beta band decrease; see Carl et al., 2016) from choices in the current study, we counterbalanced the mapping from saccade direction to choice across participants. We found that both mappings led to very similar results when according data were analyzed separately (i.e., for either half of the participants). Hence, the reported choice-selective modulation of beta band amplitude is most likely independent of specific saccade preparation. Moreover, we did not find any additional lateralized choice effects (i.e., for neither half of the participants) as a consequence of a consistent mapping between saccade direction and choice (cf. lateralized beta band decrease before decision reports by button presses, e.g., Donner et al., 2009).

Typically, beta band oscillations (∼15–25 Hz) are associated with sensorimotor processing. That is, beta band amplitude is known to decrease over somatosensory areas in anticipation and during the presentation of tactile stimuli, as well as to rebound afterwards (e.g., Jasper and Andrews, 1938; Pfurtscheller, 1981; Bauer et al., 2006; van Ede et al., 2011). In preparation for and during voluntary hand movements like button presses, the same pattern of beta band decrease followed by a rebound over contralateral motor areas is also reliably observed (e.g., Jasper and Penfield, 1949; Pfurtscheller, 1981). Likewise, several studies suggest that a decrease in beta band amplitude over contralateral posterior parietal areas accompanies the execution of saccades (e.g., Pesaran et al., 2002; Brignani et al., 2007; Carl et al., 2016). Moreover, Jo et al. (2016) recently reported a negative correlation between the level of beta band amplitude over motor areas before initiating voluntary button presses and according RTs. Given that in the current study RTs varied systematically in the same way as the (upper) beta band was modulated by choice (i.e., faster responses for "f2 > f1" than for "f2 < f1" choices for correct and incorrect trials), we carefully examined whether the observed beta band modulation could be attributed to these RT variations. However, RTs were not correlated with upper beta band amplitude, neither over all trials, nor within the separate choice categories (i.e., "f2 > f1" or "f2 < f1"). More likely, the variations in RTs are related to the observed response bias toward "f2 > f1" choices, i.e., the preferred choice is also accompanied by faster responses. In favor of this interpretation, fast trials exhibited a stronger bias than slower trials. Moreover, the bias disappears when introducing a response delay to the task (unpublished observation), suggesting that the tendency for choosing "f2 > f1" might be confined to decisions under time pressure. To rule out that the response bias itself accounts for the observed beta band modulation, we additionally analyzed EEG data separately for participants that showed no substantial bias (or even a bias in the opposite direction) and no systematic RT differences between choices. Despite the reduced sample size, we still found the same tendency of "f2 > f1" choices being accompanied by higher beta band amplitude than "f2 < f1" choices, for correct and incorrect trials. Taken together, the reported modulation of upper beta band amplitude by participants' choices is unlikely to be related to systematic shifts of sensorimotor beta band effects due to RT variations or an overall response bias.

Rather, our finding aligns well with previous work that established a link between prefrontal upper beta band oscillations and WM content in the same task (i.e., f1 values; see Spitzer et al., 2010; Spitzer and Blankenburg, 2011), and thus further supports the notion of upper beta band oscillations encoding different task-relevant entities at according processing stages of the vibrotactile 2AFC task (cf. Herding et al., 2016). In the context of decision making, given location (i.e., premotor areas) and characteristics (i.e., representation of content on which choice is based, independent of specific motor response) of the observed effect, we propose that this entity might reflect the input to the (pre)motor system which is in charge of the subsequent response. In particular, beta band amplitude might signal the decision outcome which in turn informs the ensuing action that is planned in effector-specific brain areas. How the beta band modulation might be implemented in detail, however, remains an open question. A recently proposed biophysically principled computational model was able to reproduce beta bursts in human MEG and animal LFPs (monkey and mouse) in great detail (Sherman et al., 2016). Interestingly, the model predicts modulations of the burst amplitudes by changes in the firing rates of some neurons in the network. Hence, this model might provide a new angle on how the firing rate code revealed by Romo and colleagues (e.g., see Romo and de Lafuente, 2013 for review) might be directly translated into

amplitude modulations in the beta band as reported here, and in previous work (Haegens et al., 2011; Herding et al., 2016).

Besides the considerable agreement between our current results and previous work in the vibrotactile 2AFC task, the findings presented here are notably the first ones based on decisions with saccade responses in this paradigm. In the visual domain, however, extensive research has investigated perceptual decision making utilizing saccades for responding in non-human primates (reviewed in Glimcher, 2003; Gold and Shadlen, 2007). The large body of work compiled by Shadlen and colleagues presents coherent evidence that choices, which are expressed by saccades, are reflected in the firing rates of various oculomotor brain areas, i.e., LIP (e.g., Shadlen and Newsome, 1996), FEF (e.g., Hanes and Schall, 1996; Kim and Shadlen, 1999), and SC (e.g., Ratcliff et al., 2003). More precisely, in the random dot motion (RDM) task, LIP activity was shown to reflect the accumulated evidence (i.e., motion information) provided by visual area MT (e.g., Ditterich et al., 2003; Hanks et al., 2006) peaking at RT (e.g., Shadlen and Newsome, 2001). A similar accumulation-to-bound signal was found in FEF (Hanes and Schall, 1996) and SC (Ratcliff et al., 2003) using a visual search task. In general, LIP, FEF, and SC seem to play similar roles in saccade target selection and spatial attention by implementing salience or relevance maps with gradually less abstract representations of the visual field (see e.g., Colby and Goldberg, 1999; Andersen and Buneo, 2002; Fecteau and Munoz, 2006; Schall, 2015). In the visual RDM task, however, Katz et al. (2016) recently questioned the causal role of LIP for decision making by showing that a pharmacological inactivation had no effect on task performance, whereas area MT (i.e., the momentary evidence) proved to be indispensable. Notably, the source reconstruction of the present choice-selective modulation of upper beta band modulation suggested areas in the precentral gyrus including FEF as likely sources. Hence, our findings are remarkably consistent with the work in non-human primates investigating decisions reported by saccades (cf. Hanes and Schall, 1996; Kim and Shadlen, 1999). Contrasting the results from the current study with our previous work, in which participants completed the same task but responded with button presses, reveals that the signal (i.e., choice-selective modulation of upper beta band amplitude) remained the same, however, the topography and the suggested source locations differ considerably. In particular, whereas button press responses implied medial premotor areas as a putative source of the choice signal, saccade responses hinted at source locations including FEF. Hence, both studies observed the same choice-selective signal, however, found sources that are associated with the planning of respective motor responses in an effector specific way.

In line with the aforementioned studies, our findings thus support the notion of an intentional framework of decision making (e.g., Cisek, 2007; Shadlen et al., 2008; Cisek and Kalaska, 2010), which proposes that decisions are expressed in form of intentions to act. As a consequence, neural correlates of decision making should be found in brain areas that are involved in the planning/preparation of the action that is used to express the choice, independent of the specific task at hand. In this light, also the work of Romo and colleagues is in agreement with an intentional framework of decision making. Choices in the vibrotactile 2AFC task were always reported by button presses, and choice-selective neuronal activity was found in mPMC and vPMC (Hernández et al., 2002, 2010; Romo et al., 2004; Haegens et al., 2011). Here, we provide novel evidence that a combination of the vibrotactile 2AFC task with another response modality (i.e., saccades) translates the choice-selective signal to corresponding effector-specific brain areas. Hence, we could effectively bridge the gap between the work of Romo and colleagues (vibrotactile 2AFC) and the work of Shadlen and colleagues (oculomotor responses), and show that their findings are transferable within an intentional framework of decision making.

AUTHOR CONTRIBUTIONS

JH, SL, and FB designed the study. JH and SL collected the data. JH, SL, and FB analyzed the data, interpreted the results, and wrote the manuscript. All authors approved the final version of the manuscript for submission.

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Study 3

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Oscillatory EEG-Signatures of Postponed Somatosensory Decisions and Different Response Modalities

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Running title: Postponed Somatosensory Decision Reports

Abstract

The conversion from sensations to actions has been extensively studied in non-human primates by means of a vibrotactile frequency comparison task. More recently, this task using a predictable response mapping and immediate decision reports has also been applied to study oscillatory signatures of working memory processes and decision making in humans. However, for delayed decisions and unpredictable response contexts, corresponding findings are lacking. Here, we investigated oscillatory EEG signatures in four experiments (73 subjects) using postponed decision reports in the vibrotactile frequency comparison task, while systematically varying response modality (saccade vs. button press), and response mapping (action mapping vs. color mapping). In all experiments, induced power of beta oscillations in right prefrontal cortex coded for stimulus and decision information in the response delay. Subjects' choices with unknown subsequent actions were represented in the beta power over parietal cortices, whereas choices with a known action mapping were encoded in premotor cortices. Hence, our data support an intentional framework of decision making suggesting that choices are encoded in areas that implement the required covert or overt action consequences. Additionally, they indicate that the more abstract these action consequences are, the further up in the sensorimotor hierarchy the perceptual decision variables are processed.

Keywords

beta band, decision making, response context, vibrotactile,

Introduction

The key question of perceptual decision making concerns the functional role of sensory, higher association, and motor cortices in the mapping of sensory information onto motor actions (Gold and Shadlen, 2007). Besides the highly influential studies on perceptual decisions in visual tasks, such as the random-dot motion (RDM) paradigm (for reviews see Hayden and Pasternak, 2013; Heekeren et al., 2008), there has been a whole line of research on sensory processing, working memory, and perceptual decisions in the *somatosensory* modality (for review see Romo and de Lafuente, 2013). Romo and colleagues used a vibrotactile sequential frequency comparison (SFC) task, in which monkeys decided whether the second of two serially presented vibrations had a higher or a lower frequency than the first one. During vibrotactile stimulation, single neurons in the primary somatosensory cortex were shown to encode the frequency of the first stimulus (f1) by monotonically increasing firing rates for higher stimulus frequencies (Salinas et al., 2000). In the retention interval, during WM maintenance, neurons in prefrontal and premotor cortices showed a sustained parametric increase or decrease of firing rates as a function of f1 (Brody et al., 2003; Romo et al., 1999). Additionally, the decision process was extensively studied for this task, where it has been observed that neurons in the secondary somatosensory cortex (S2; Romo et al., 2002), in the prefrontal cortex (Hernández et al., 2010), as well as in the medial premotor cortex (MPC; Hernández et al., 2002) encode the signed frequency difference between both stimuli during and after the second stimulus was presented. This information is subsequently mapped onto a specific motor response in the primary motor cortex (M1; Mountcastle et al., 1992, Salinas and Romo, 1998). Further research targeted the processing of stimulus information (i.e. stimulus frequencies, f1 and f2) and the signed difference (i.e. f2-f1) if the decision report was postponed by a forced delay (Lemus et al., 2007). Here, it was shown that

these signals could be identified in neuronal activity within MPC up to the response of the monkeys.

This work in animals has been more recently extended to humans in multiple Electroencephalography (EEG) studies (Spitzer et al., 2010, 2012; Spitzer and Blankenburg, 2011, 214). Here, it was shown that the power of prefrontal beta oscillations (20 – 25 Hz) during the retention interval parametrically increased with increasing f1 that was maintained in WM. This prefrontal graded activity of oscillatory power in the beta band has also been evident for other sensory modalities as well as different stimulus properties (Spitzer et al., 2012; 2014), thus suggesting to play a general role in representing WM content of quantitative stimulus information. In a recent study, Herding et al. (2016) have shown that the power of upper beta band oscillations in the human premotor cortex (PMC), encodes also the subjective choice whether subjects felt f2 to be higher or lower as compared to f1.

Even though these previous studies have investigated sensory encoding, WM maintenance, as well as decision making in humans performing this particular task, several open questions remain: (i) does stimulus information vanish once a decision has been made or do humans recapitulate the sensory evidence during the delay period until the decision has to be reported, as suggested by monkey data? (ii) Does the decision making process of the SFC task depend on the response modality, e.g. saccades vs. button presses, as suggested by the intentional framework (Shadlen et al., 2008)? (iii) To go even further, how are perceptual decisions processed if there is no one-to-one mapping of the choice to motor intention, i.e., if subjects cannot prepare a specific action as a consequence of their decision but have to decide in a more abstract space?

The aim of the present paper was to address these issues by means of four EEG experiments using the well-established SFC paradigm. We introduced a response delay of 2.5 seconds between the offset of the second stimulus and the actual decision report in all

experiments. In addition, using always the identical sequential frequency comparison task, we varied over experiments the way subjects reported and were able to prepare their decisions. In two of the four experiments subjects responded with button presses, in the other two with saccades. In one of each of those two experiments, the mapping of choice ("f2 is higher/lower compared to f1") to action direction (right vs. left) was fixed. In the other two experiments it was flexible by mapping choice to a target color which was only presented after the response delay.

Based on prior work in animals (e.g., Romo et al., 1999) and in humans (Spitzer et al., 2010), we hypothesized that the stimulus frequency of the first stimulus (f1) in the retention interval, and the frequency of both stimuli and their signed difference (f1, f2, and f2-f1) in the response delay, would be encoded in parametric power modulations (most likely in frequency bands of 15-35Hz) in prefrontal cortex (PFC; e.g., Spitzer et al., 2010; Spitzer and Blankenburg, 2011). Further, we expected a choice related signal in premotor areas, i.e., in the PMC (Herding et al., 2016) and the frontal eye fields (FEF), respectively, when decisions were directly assigned to a certain motor response (saccade or button press). In contrast, for the experiments in which decisions were assigned to a color, we expected a choice signal in a more abstract space with candidate areas in the PFC (e.g., Filimon et al., 2013) or the posterior parietal cortex (PPC; e.g. Bennur and Gold, 2011).

Materials & Methods

Participants

We tested a total of 73 (47 female; 21 – 40 years old) right-handed participants in the delayed SFC task (see figure 1) during EEG recording. Informed consent was obtained from every participant prior to the experiment and the study was approved by the local ethics committee at the Freie Universität Berlin.

Stimuli & Task

All four experiments included the same SFC task but varied in the way subjects reported their decisions (see Figure 1). The experiment design was implemented in Matlab (The MathWorks), using the Psychophysics Toolbox extensions (Brainard, 1997; Kleiner et al, 2007) and custom Matlab code. Vibrotactile stimuli were presented at the left index finger using a 16-dot piezoelectric Braille display (4x4 quadratic matrix; 2.5 mm spacing) controlled by a programmable stimulator (Piezostimulator; Quaerosys). The driving signals of the stimuli were generated by a fixed sinusoidal amplitude modulation of a constant carrier frequency of 133 Hz in order to reduce EEG artifacts in the frequency spectrum of interest. Importantly, subjects perceive the trial-specific modulating frequency which corresponds to the envelope curve of the stimulus function (Tobimatsu et al., 1999). The sound of the braille display was masked by white noise (~ 90 dB), which was constantly presented through loudspeakers during the whole experiment.

Figure 1

Two vibrotactile stimuli (f1 and f2; 250ms each) were sequentially presented to the subjects' left index finger, separated by a retention period (1 s). The first stimulus (f1) contained one of four frequencies (16, 20, 24 and 28 Hz, randomly varied). The frequency of the second stimulus (f2) was always 2 or 4 Hz higher or lower as compared to f1. In general, subjects had to respond whether they felt f2 as having a higher or a lower frequency than f1. In all experiments, 2 s after the offset of f2, two colored targets (diameter of 1° visual angle) were presented 12° of visual angle to the left and to the right of the fixation cross. One of the targets was blue, the other one was yellow. In experiments 1 and 2, subjects choice was directly assigned to a button press of the left arrow key with the right index finger or the right

arrow key with the right middle finger (experiment 1) or to a saccade to the left or the right target (experiment 2). In experiments 3 and 4, choices were assigned to the target color (yellow/blue). In experiment 3, subjects pressed the left arrow key (right index finger) or the right arrow key (right middle finger) depending on where their color of choice was located. In experiment 4, subjects responded with a saccade to the respective colored target. In experiments 1 and 2, the colored targets were also present but irrelevant to the subjects. Importantly, for all experiments the assignments of choice to the specific direction or color were counterbalanced over subjects. After another 500 ms after the fixation cross had disappeared, subjects were allowed to report their decision by the appropriate action. Please note, that also in experiments 1 and 3 (button press responses) subjects held eye fixation in the middle of the screen during the whole trial and also during the response. This was ensured by careful visual inspection of the raw EEG-signal where trials with saccades were excluded from the analysis. After a short training of 20 trials, subjects performed eight full experimental blocks, each containing 128 trials.

EEG recording

EEG was recorded using a 64-channel active electrode system (ActiveTwo; BioSemi) with electrodes placed according to the extended 10-20 system. Three additional electrodes were used to record eye-blinks and horizontal eye-movements. Single electrode locations were registered using a stereotactic electrode positioning system (Zebris Medical).

Eye tracking

In experiments 2 and 4 saccadic responses as well as other eye movements were recorded during each trial (monocular sampling at 500 Hz) using an EyeLink 1000 Desktop Mount (SR Research). Online evaluation of the participants' gaze directions was

implemented with Matlab, using the Psychophysics Toolbox extensions (Brainard, 1997; Kleiner et al, 2007). Thus, it was monitored whether participants kept the gaze on the central fixation cross during the whole trial (within a 6° rectangular region centered on the fixation cross), and displayed a warning message if this was not the case ("Please keep fixation throughout the trial"). Additionally, the participants' choices (200 ms fixation after a saccade within a 6° circular region centered on a target dot) was evaluated online. A 9-point eye calibration was performed before each of the experimental blocks to facilitate reliable tracking of the eyes.

Behavioral analysis

Performance accuracies were analyzed using a two factorial 4 x 4 ANOVA including the within-subject factor *f1-frequency* (4 levels) and the between-subject factor *experiment* (4 levels). We used Greenhouse-Geisser correction to correct degrees of freedom and hence p-values for violated assumptions of sphericity.

EEG analysis

EEG analyses were performed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK; www.fil.ion.ucl.ac.uk/spm/), FieldTrip (Oostenveld et al., 2011) and custom Matlab code.

Preprocessing included co-registration of the channels to the individual electrode positions, rejection of noisy channels, average referencing, adaptive spatial filtering to correct for eye-blink artifacts, as well as high-pass filtering (0.5 Hz). The continuous recordings were segmented into epochs from 2250ms before f2-onset (i.e. 1000 ms before f1-onset) to 500ms after the response cue. Artifact rejection was done by careful visual inspection of the whole EEG-data in addition to automatically marking epochs with amplitudes greater than 150 μV.

Induced Activity: To examine induced, i.e. non-phase locked responses, the mean event-related potential (ERP) of each stimulus pair was subtracted from every trial before Morlet

wavelet-transformation (seven cycles, 5 – 45Hz) was performed on a single trials basis. Changes in spectral power in certain frequency bands are reported as event-related (de)synchronization (ERD/ERS) (Pfurtscheller and Aranibar, 1977). Thereby, values provide the percentage in power change relative to a pre-stimulus (f2) baseline (-2000 ms to -1300 ms, for parametric effects by f1; -1000 ms to 0 ms, for parametric effects of f2, f2 – f1, & choice). To reduce inter-trial variability, time frequency data were convolved using a 3 (Hz) x 300 (ms) Gaussian smoothing kernel (Kilner et al., 2005).

Statistical analysis For each factor of interest (f1, f2, f2-f1), we estimated for the different experiments a single-trial factorial design for repeated measures and weighted the according beta-images with specific contrast weights. For parametric effects of f1, we used one factor with four levels for the four f1 conditions (16, 20, 24, and 28 Hz) and a parametric contrast (f1-contrast: [-0.75 -0.25 0.25 0.75]). For parametric effects of f2, we used one factor with five levels for the five f2 conditions (18, 20, 22, 24 and 26 Hz) but only for a subset of trials, in which f2 and f2-f1 are uncorrelated. In the present stimulus set where f2 is 2 or 4 Hz higher compared to f1, factors f2 and f2-f1 are correlated. Analyzing this subset prevents us from confounding the signed differences (f2-f1) with f2-stimulus information and vice versa. As a parametric f2-contrast we used: [-1 -0.5 0 0.5 1]. For the effects of the difference between f2 and f1 (f2-f1), we used one factor with four levels for the four f2-f1 conditions and a parametric contrast (difference-contrast: [-1 -0.5 0.5 1]). Up to this point, analyses were calculated on correct trails only. For the effects of choice we used a 2 x 4 flexible factorial design with one factor (two levels) for correct and incorrect responses and another factor (four levels) for the four f2-f1 conditions and estimated the interaction term. Focusing on the subjective judgment which was assumed to be inverted in incorrect trials as compared to correct choices, we applied the choice-interaction-contrast: [-1 -1 1 1 1 1 -1 -1]. Contrast images were then tested for significant effects using a cluster based permutation test (Maris

and Oostenveld, 2007). For effects of f1, f2, and f2-f1 we compared the summary statistics of the observed data (one-sample t-test pooling across participants from all four experiments; n = 73) with a distribution of summary statistics obtained from 500 randomly sign-flipped permutations. For choice effects we followed the same procedure but computed the respective tests for each experiment individually. A cluster was defined as a group of adjacent TF bins that all exceeded a cluster-defining threshold of $p_{threshold} < .005$ (uncorrected). Clusters that exceeded a family-wise error (FWE)-corrected threshold of $p_{cluster} < .05$ (corrected for time, frequency, and channels) were considered to be statistically significant. Due to strong a priori assumptions on the topographircal distribution of signals encoding quantity information (Spitzer et al., 2010, Spitzer and Blankenburg 2011), for parametric effects of f1, f2 and f2-f1 we corrected only for right frontal electrodes (AF4, AFz, Fz, F2, F4, F6, FC6, FC4, FC2, FCz).

Source reconstruction The cortical sources of amplitude modulations observed on the scalp level were localized using the 3-D source reconstruction routines provided by SPM8 (Friston et al., 2006). On the basis of the individually recorded electrode positions for each participant, a forward model was constructed using an 8196-point cortical mesh of distributed dipoles perpendicular to the cortical surface of a template brain (cf. Friston et al., 2008). The lead field of the forward model was computed using the three-shell boundary elements method EEG head model available in SPM8. Conventional minimum norm priors under group constraints (Litvak and Friston, 2008) were used to invert the forward model. For each condition, the results of model inversion were summarized in a 3-D image that reflected spectral source amplitude in the TF window of interest. Relevant contrasts of these 3-D images served as an estimate for subject-specific source locations and were used for group level statistical analysis (see Litvak et al., 2011). The signal was localized using the preprocessed stimulus-locked EEG data (i.e., in the time domain). Additionally, the data were

bandpass filtered in the frequency range of the TF cluster identified on the scalp level (±1 Hz to ensure that no information is lost at the cluster borders). The 3-D images summarizing each condition were computed over a representative TF window. To identify cortical sources in which the respective amplitude was modulated by f1, f2, f2-f1, or by choice, the 3-D images were weighted by a contrast vector analogously to the sensor space analysis. Source estimates were statistically analyzed on the group level using conventional t-tests and displayed at a threshold of $p < .05$ (uncorrected). Anatomical reference for source estimates was established on the basis of the SPM anatomy toolbox (Eickhoff et al., 2005) where possible.

Results

Behavior

Table 1 shows the performance accuracies across f1-frequencies for the four experiments and an overall average. There was no main effect for the factor *experiment* ($F(3, 69) = 0.518$, $p = 0.67$), but a significant main effect for *f1-frequency* ($F(2.09, 207) = 16.65$, $p < 0.001$). Within-subject contrasts revealed that performance accuracy was significantly lower for f1 = 16 Hz compared to every single other condition, and that for f1 = 28 Hz accuracy was significantly lower compared to f1 = 20 and 24 Hz. There was no interaction between both factors ($F(6.28, 207) = 0.7$, $p = 0.66$).

Table 1

EEG

Parametric effects of f1 Figure 2 shows parametric effects of f1 during the retention interval and the response delay pooled over all four experiments. Here, we identified two significant

clusters. First, in the retention interval after the offset of f1 and before the onset of f2, there was a significant parametric increase in a frequency range from 15 to 20 Hz from -800 to -400 ms ($p_{cluster}$ = 0.02, FWE-corrected over a priori defined set of electrodes). In the response delay, we found an additional significant cluster ($p_{cluster}$ = 0.02, FWE-corrected over a priori defined set of electrodes) also in the frequency range from 15 to 20 Hz, 600 to 1200 ms after the onset of f2. The topographical distributions (extracted from the marked time-frequency windows) show that mostly right frontal electrodes carry the signal showing this parametric effect. Source reconstruction revealed no effect over the display threshold for the first cluster of the modulation by f1. The second cluster, however, was attributed to middle frontal gyrus (MFG) and inferior frontal gyrus (IFG), area 45 of the right and the left PFC.

Parametric effects of f2 Figure 2 C shows parametric effects of f2 during the response delay for correct and incorrect responses pooled over all four experiments. We identified one significant cluster ($p_{cluster}$ = 0.02, FWE-corrected over a priori defined set of electrodes) in the response delay in the frequency range from 30 to 35 Hz, 1400 to 1950 ms after the onset of f2. Source reconstruction localizes the modulation by f2 within right IFG, area 45. We found in line with Spitzer et al. (2010) for parametric effects of f1 and of f2 that within the time-frequency windows of the three above mentioned significant clusters, modulations are tendentially weaker (two-sample t-tests, p_{f1_1} = 0.08; p_{f1_2} = 0.14; p_{f2} = 0.09) for incorrect trials than for correct trials

Parametric effects of f2-f1 Figure 2 G shows the effects of the difference between f2 and f1 (f2-f1) pooled over all four experiments. We identified one significant cluster ($p_{cluster} < 0.05$, FWE-corrected over a priori defined set of electrodes) in the response delay in the frequency range from 20 to 40 Hz, 650 to 1250 ms after the offset of f2.

Figure 2

Choice Effects Figure 3 shows the effects of choices irrespective of whether they were correct or incorrect. That is, the time-frequency maps display the group statistics of the interaction contrast between the sign of the frequency difference (f2<f1/f2>f1) and correct/incorrect decisions.

In *experiment 1* there was one significant cluster ($p_{cluster}$ = 0.03, FWE-corrected) in frequencies from 30 to 40 Hz at a time around 750 to 1150 ms after the onset of f2. Source reconstruction localizes this modulation to the superior frontal gyrus (SFG) anterior to M1.

Experiment 2 did not contain any significant effect on a FWE-corrected level. Still there is a cluster which shows a dominant effect ($p_{cluster}$ < 0.05, uncorrected). This cluster ranges from 15 to 40 Hz at a time around 1050 and 1450 ms after the onset of f2. Source localization attributed this modulation to the (SFG) and the medial frontal gyrus (MFG) in both hemispheres most dominantly anterior to M1. Posterior borders of this cluster also range into small parts of M1.

In *experiment 3* we found one significant cluster ($p_{cluster}$ = 0.04, FWE-corrected) with positive effects (higher amplitude for response "higher"). This cluster was evident in a frequency range between 25 to 35 Hz around 1150 to 1550 ms after the offset of f2. Source reconstruction localized the modulation by choice to the intra parietal lobe (IPL) in the left hemisphere.

Experiment 4 revealed one significant cluster ($p_{cluster}$ = 0.04, FWE-corrected) showing a negative relationship (lower amplitudes for responses "higher") in frequencies from 15 to 20 Hz, 250 to 500 ms after the offset of f2. Source localization attributed this modulatory effect of choice to the superior parietal lobe (SPL) and the intra parietal sulcus (IPS) predominantly in the left, but also to the right hemisphere.

Figure 3

Discussion

In the present study we investigated oscillatory correlates of stimulus information in postponed decision reports using the SFC task. Further, we focused on the oscillatory signatures of subjects' choices in four different response contexts (see Figure 1).

We found during the retention interval, i.e. during WM maintenance, a parametric modulation of the power in right prefrontal beta band oscillations (15 - 25 Hz) by the frequency of the first stimulus (f1). During the ensuing response delay, parametric power modulations by f1, f2, as well as f2-f1 were also evident in right prefrontal electrodes spanning similar frequencies (15 – 35 Hz). In each of the four experiments, we additionally found different cortical sources to explain choice-selective power modulations in frequencies between 15 and 40 Hz. These sources indicate that choices which were mapped to a specific action (experiments 1 and 2) were represented in premotor areas. In contrast, choices that were associated with the color of the response target (experiments 3 and 4) were processed in parietal areas. Notably, all observed choice-related power modulations were inverted for incorrect trials, underpinning the behavioral relevance of the respective signals.

Maintenance of stimulus information throughout the task

Memory based perceptual decisions entail the comparison of an active representation of sensory information with previously presented sensory information maintained in WM (Hayden and Pasternak, 2013). For memory based decisions in the somatosensory domain, a vibrotactile SFC task was used to study the underlying processes (e.g. sensory encoding, WM maintenance, decision making, and action selection) extensively in monkeys (Romo et al., 1999; Hernández et al., 2010; for review see Romo and de Lafuente, 2013) and in humans (Li

Hegner et al., 2010; Pleger et al., 2006; Spitzer et al., 2010; 2012; Spitzer and Blankenburg, 2011; 2014).

We found that the power of beta band oscillations during the retention interval in prefrontal electrodes depended on the frequency that was maintained in WM. This is in accordance with animal work (Romo et al., 1999) and replicates several earlier human studies (Spitzer et al., 2010; Spitzer and Blankenburg, 2011). Other studies generalized this effect to visual and auditory WM (Spitzer and Blankenburg, 2012), as well as to different analogue stimulus features (Spitzer et al., 2014). Taken together, these findings propose that the large scale oscillatory beta band effect in human EEG might reflect an internal estimate of an abstract quantity ascribed to the relevant stimulus feature held in WM (Spitzer et al., 2011; Spitzer and Blankenburg, 2014). In the previous studies, subjects usually reported their decision right after the presentation of the second stimulus. Only a few studies investigated how stimulus information and decision evidence are further processed in cases where the decision report is delayed, i.e. when the decision has to be stored in WM (e.g., Lemus et al., 2007; Hernández et al., 2010; Haegens et al., 2011). Here, an interesting question is whether only information about the decision is maintained in WM or if stimulus information, on the basis of which the decision was made, is also stored, e.g., to reevaluate the decision. If such stimulus information would be retained in WM during the decision delay one could expect it in a similar form as the maintenance of f1 during the WM period of the same task, which was observed as a parametric modulation of beta power by f1 (see above, and e.g., Spitzer et al., 2010). Indeed, we observed a parametric modulation of prefrontal beta oscillations as a function of f2 and f1 after the presentation of the second stimulus, i.e. in the response delay. In line with the WM effect during retention (e.g., Spitzer et al., 2010), we found this modulation in the right PFC. Further, a ROI based analysis indicated that also decisional evidence in form of the signed difference (f2-f1) was represented in right prefrontal beta

oscillations. The present findings, thus, complement and support earlier studies of the delayed SFC task, in which firing rates in monkeys' medial premotor cortex (MPC) showed monotonic increases either dependent on f1 or f2 (Lemus et al., 2007) as well as increases and decreases of firing rates as a function of f2-f1 in MPC (Lemus et al., 2007) and PFC (Hernández et al., 2010). Our results further extend the original findings by Spitzer et al. (2010) in multiple ways. We show that the maintenance of f2 and a reactivation of f1 during the forced delay induce the same parametric modulations of beta band power as f1 in the retention interval. This modulation was also evident for dynamic combinations of quantitative estimates such as the signed difference between f2 and f1. Hence, the processing of stimulus and decision information do not seem to be organized serially, but to be maintained and computed in parallel (see also Hernández et al., 2010; Lemus et al., 2007). This appeals from an ecological perspective because time resources are exploited and the flexibility to adapt to changing affordances is preserved (Lemus et al., 2007).

Choice signals for postponed decisions reports for two distinct response modalities

In the field of perceptual decision making, mainly two hypotheses about the neural implementation of decision formation evolved over the last decades. On the one hand, the intentional framework, viewing decision making as a selection between a limited set of affordances or intentions, processed in areas related to motor planning (Cisek and Kalaska 2010; Shadlen et al. 2008). And on the other hand, the assumption of a modality transcending general decision module, proposedly located in the dorsolateral prefrontal cortex (Heekeren et al., 2008). Curiously, the findings obtained in the vibrotactile SFC paradigm (reviewed in Romo and de Lafuente, 2013) have rarely been linked to either of the two conceptual frameworks, possibly, because most of the work with the SFC task focused their research exclusively on decision reports by button presses. In the context of button press responses,

however, the available results appear to be in favor of an intentional framework of decision making. Choice-selective signals were consistently reported in recordings from premotor areas (e.g., Hernández et al., 2002, 2010; Romo et al., 2004; Haegens et al., 2011) that are known to be involved in the preparation of motor responses (e.g., Wise, 1985; Cisek and Kalaska, 2005). At the same time, also firing rates in PFC were shown to reflect upcoming choices (Jun et al. 2010; Hernández et al., 2010), which might be related to a general decision module. Results from our experiments 1 and 2, however, further corroborate the notion of an intentional framework of decision making.

In experiment 1, where subjects were asked to indicate choices by button presses, we found a choice-selective power modulation in the upper beta band over SFG, including premotor cortices (see Figure 3 A). This finding is in general agreement with the work by Romo and colleagues who consistently reported choice-related signals in premotor areas when responses were given by button presses (e.g., Hernández et al., 2002, 2010; Romo et al., 2004; Haegens et al., 2011). In particular, the present results extend previous work that reported the same pattern of beta band modulation in similar premotor areas, however, without a forced response delay (Herding et al., 2016). Hence, we could show that, in line with previous animal studies (Lemus et al., 2007; Haegens et al., 2011) choice information is also maintained in premotor areas throughout a forced delay period. Furthermore, a recent study in rats substantiated a causal role of frontal motor cortices for the maintenance of choice information (Goard et al., 2016). In a memory-guided visual decision task, the authors showed that after optogenetic inhibition of frontal motor cortices, but not of parietal or sensory areas, maintenance of choice information was disrupted.

In experiment 2, subjects were required to express choices by saccades, whereas the rest of the task was identical to experiment 1. Analogously to the findings of experiment 1, we found the same modulation of upper beta band power by subjects' choices. However, in accordance

with the relatively weak effect on the scalp-level, the most likely locations of reconstructed sources were not very specific. Nevertheless, it is worth mentioning that the bulk of suggested sources lie in premotor and prefrontal areas, including FEF. Importantly, neuronal firing rates in FEF were found to encode upcoming decisions that were reported by saccades in different visual decision making paradigms (Hanes & Schall, 1996; Kim and Shadlen, 1999; Yang and Heinen, 2015). In more general terms, FEF is known to be involved in saccade target selection and covert attention (e.g., Schall, 2015). Taken together, experiment 1 and 2 both utilized a fixed mapping of choices onto known motor responses, only differing with respect to the response modalities. For both button presses and saccades, choice-related signals were found in premotor areas that are known to be involved in the planning and preparation of the respective response. Hence, both studies provide evidence in favor of an intentional framework of decision making, complementing and extending previous work in the vibrotactile SFC task to the oculomotor response modality (cf. Hernández et al., 2002, 2010; Romo et al., 2004; Lemus et al., 2007; Haegens et al., 2011; Herding et al., 2016).

Choice signals for postponed decisions without specific motor consequence for two distinct response modalities

Evidence in favor of an intentional framework of decision making stems largely from research on perceptual decisionss making in the visual domain, where responses were mainly reported by saccades (for review see Shadlen and Gold, 2007). In particular, the seminal work by Shadlen and colleagues provides coherent evidence that choices, which are expressed by saccades, are encoded in the firing rates of different oculomotor brain regions, i.e., LIP (e.g., Shadlen & Newsome, 1996), FEF (e.g., Hanes & Schall, 1996; Kim and Shadlen, 1999), and SC (e.g., Ratcliff et al., 2003). More precisely, in the RDM task, activity in these areas was shown to reflect the accumulated evidence (i.e., motion information)

provided by visual area MT (e.g., Ditterich et al., 2003, Hanks et al., 2006) with a peak tightly locked to the response time (e.g., Shadlen & Newsome, 2001). Conversely, when decisions were expressed by reaching to a target, firing rates in medial intraparietal area (MIP), which is known to be involved in reach preparation, encoded upcoming choices in a similar way (e.g., de LaFuente et al., 2015).

However, the exact relationship between the similar signals in frontal (i.e., FEF) and parietal areas (i.e., LIP) remains unclear. In a recent study, Gold and Shadlen (2003) probed the specific role of FEF in decision making by applying microstimulations during different variants of the RDM task. In two versions of the task, a specific motor mapping was known to the non-human subjects, whereas in the third version a color mapping informed about the subsequent action, thus, preventing a specific saccade preparation. Microstimulation of FEF reliably evoked an involuntary saccade of the subjects before they could indicate their choices. Importantly, this evoked saccade was deflected towards the response targets that subjects wanted to select, only if the specific motor response associated with the choice was known in advance. Hence, these results suggest that FEF accumulates evidence for upcoming decisions only if the ensuing choice is associated with a specific motor response. At the same time, Katz et al. (2016) questioned the causal role of LIP for decisions under these circumstances. The authors showed that a pharmacological inactivation of LIP had no effect on task performance, whereas area MT (i.e., the momentary evidence) proved to be indispensable. Hence, LIP activity seems to be largely redundant for a decision when a specific motor response is known in advance (Katz et al., 2016). Conversely, FEF appears to encode choices solely under these conditions (Gold and Shadlen, 2003). Taken together, these results suggest that premotor areas (i.e., FEF) and PPC (i.e., LIP) play distinct roles in decision making, dissociated by the level of abstractness of the resulting action consequence. This interpretation is in line with the principal role of both brain areas, i.e., saccade target

selection in FEF (e.g., Hanes and Schall, 1995) and the encoding of intentions in PPC (e.g., Andersen and Bueno, 2002).

In line with the predictions derived from the work in non-human primates (Katz et al., 2016; Gold and Shadlen, 2003), we found in experiments 3 and 4 that abstract decisions, which are not associated with a specific motor response but with a color mapping, display choice-related signals in parietal brain areas. In particular, we found for both response modalities (i.e., button presses and saccades) that oscillatory power in the beta band was modulated by participants' choices during the forced delay. These findings nicely complement a recent study in non-human primates using the RDM task with a similar color mapping, which was, however, randomly presented at different stages of the task (Bennur and Gold, 2011). Hence, monkeys obtained full information about which specific action was necessary to report the desired choice at different times of the task. Importantly, the authors found that neurons in LIP encoded decisional evidence (i.e., net motion direction) for the ensuing choice before the specific motor response was known, no matter when this information was revealed. After the motor mapping was clear, firing rates in LIP started to encode the direction of the subsequent saccade that was performed to indicate the choice (Bennur and Gold, 2011).

To conclude, we systematically investigated the influence of different response modalities (button presses vs. saccades) and response mappings (motor mapping vs. color mapping) in postponed decisions based on vibrotactile frequency comparisons. We found that for all combinations of response modality and response mapping, stimulus information, decisional evidence, and choices were represented in beta band power throughout the task. Additionally, we found that across response modalities choices which can be mapped to specific motor responses are encoded in premotor areas that are concerned with the planning and preparation of the according response. At the same time, choices that are not associated with a specific motor response are encoded in posterior parietal regions. In sum, these findings are in line

with an intentional framework of decision making, and nicely complement the current understanding on perceptual decision making derived from the somatosensory and visual domain.

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Tables

Table 1

Behavioral Results

Accuracy (%)

f1 (Hz)	16	20	24	28
experiment 1	64.4	72.0	72.1	68.4
experiment 2	67.2	73.7	72.1	72.8
experiment 3	68.5	75.1	74.7	70.9
experiment 4	66.9	71.2	71.9	70.7
mean	66.8	73.0	72.7	70.7

Note: Discrimination perfromance for each f1 condition in experiments 1-4.

Captions to figures

- Figure 1

Schematic of the task and the overall experimental design. A F1 was presented for 250 ms, followed by a retention interval of 1000 ms. Subsequently, f2 was presented for 250 ms, followed by a 2000 ms response delay. Thereafter, the response mapping (RM) in form of two colored targets was presented lateral to the fixations cross. Note, that the response mapping was only relevant in experiments 3 and 4. In experiments 1 and 2 the dots were also presented to ensure consistency over the experiments. After another 500 ms the fixation cross disappeared (response cue; RC) and the subject reported their decision. B Distribution of sample sizes across the four experiments with according response conditions.

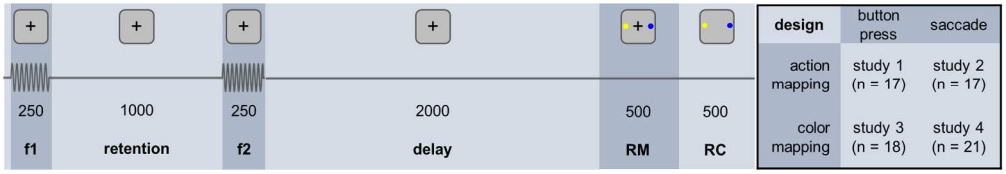
- Figure 2

Induced parametric activity as a function of f1 and f2 stimulus frequency. **A** Statistical parametric map of the effect of oscillatory power as a function of f1 averaged over a priori defined electrodes. The significant clusters ($p_{retention}$ = 0.02; p_{delay} = 0.02; FWE-corrected over a priori defined set of right frontal electrodes) are marked by dashed rectangles. **B** Time-courses of oscillatory power in a frequency range from 15 Hz to 20 Hz for the four f1 stimulus frequencies (16, 20, 24, and 28 Hz) averaged over electrodes showing a significant effect. **C** Upper part: Topographical scalp distributions of the two marked time-frequency windows in the retention interval and the delay (dashed rectangles). Lower Part: 3D source localization for the parametric modulation by f1 for the indicated time-frequency window (dashed rectangle). **D** Same as **A** for effects as a function of f2 ($p_{cluster}$ = 0.02; FEW-corrected over a priori defined right frontal electrodes). **E** Time-courses of oscillatory power in a frequency range between 30 Hz and 35 Hz for the five f2 stimulus frequencies of the orthogonal subset (18, 20, 22, 24, and 16 Hz) **F** Same as **C** for effects of f2. **G** Same as **A** for effects as a function of f2-f1 ($p_{cluster}$ < 0.05; FEW-corrected over a priori defined right frontal electrodes). **H** Time-courses of oscillatory power in a frequency range between 20 Hz and 40

Hz for the four f2-f1 stimulus frequency differences (-4, -2, 2, and 4 Hz) **I** Same as **C** for effects of f2-f1.

- Figure 3

Statistical parametric maps, topographical distributions, and estimated sources of the choice contrast and the significant clusters in experiments 1 – 4. **A** Significant cluster for choices in a direct mapping to button presses ($p_{cluster}$ = 0.03, FWE-corrected) **B** Significant cluster for choices in a direct mapping to saccades ($p_{cluster}$ < 0.05, uncorrected) **C** Significant cluster for choices being mapped to target color with subsequent button presses ($p_{cluster}$ = 0.04, FWE-corrected) **D** Significant cluster being mapped to target color with subsequent saccades ($p_{cluster}$ = 0.04, FWE-corrected) **E – H** Left part: Topographical scalp distributions of the marked time-frequency windows for experiments 1 – 4 (dashed rectangles). Right part: 3D source reconstructions of the modulations by choice for the respective experiments.



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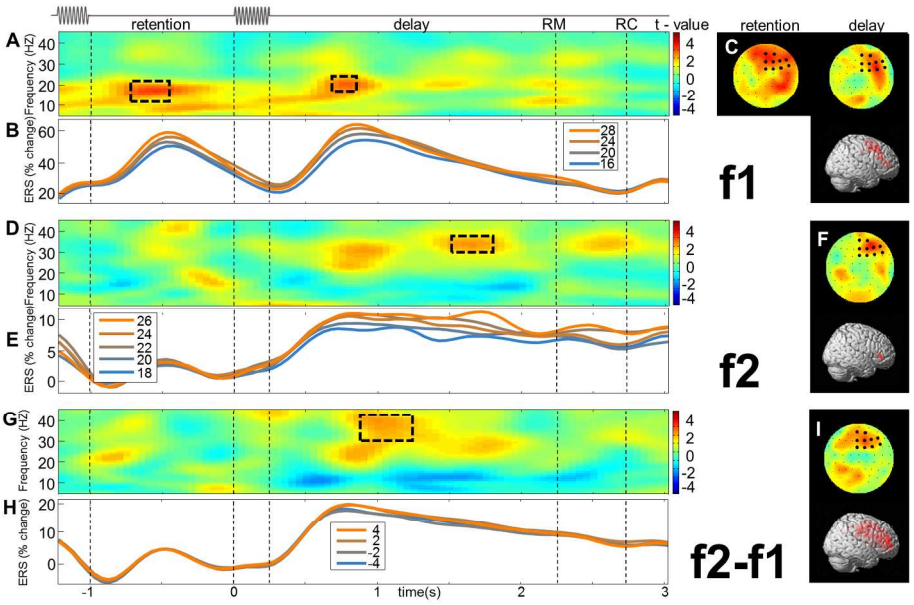

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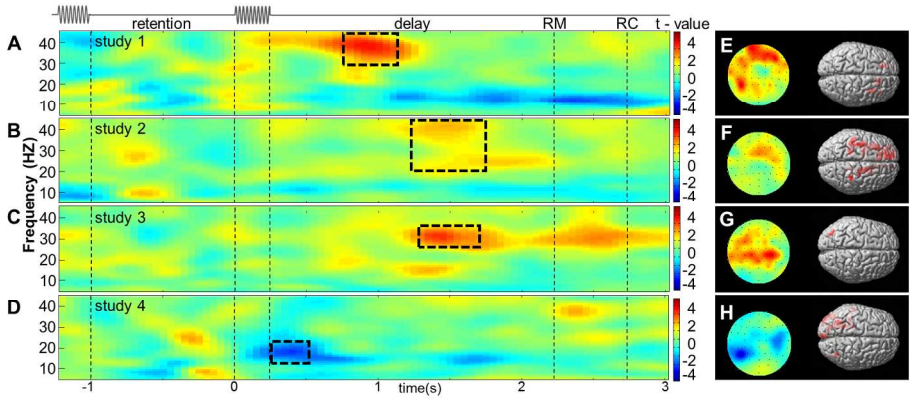

Statistical parametric maps, topographical distributions, and estimated sources of the choice contrast and the significant clusters in experiments 1 – 4. A Significant cluster for choices in a direct mapping to button presses (pcluster = 0.03, FWE-corrected) B Significant cluster for choices in a direct mapping to saccades (pcluster < 0.05, uncorrected) C Significant cluster for choices being mapped to target color with subsequent button presses (pcluster = 0.04, FWE-corrected) D Significant cluster being mapped to target color with subsequent saccades (pcluster = 0.04, FWE-corrected) E – H Left part: Topographical scalp distributions of the marked time-frequency windows for experiments 1 – 4 (dashed rectangles). Right part: 3D source reconstructions of the modulations by choice for the respective experiments.

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