Use your illusion: audiovisual perception and external perturbation are influenced by oscillatory activity

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Zusammenfassung

Im letzten Jahrzehnt hat sich die neurowissenschaftliche Forschung auf eine alte Beobachtung zurück besonnen: Identische Reize können unterschiedliche kortikale Antworten und damit auch unterschiedliche Perzepte auslösen. Was lange Zeit als Hintergrundrauschen in Abwesenheit externer Reize angesehen wurde, hat seitdem viel Aufmerksamkeit bekommen. So ist man sich immer öfter einig, dass Energie und Phase einer oszillatorischen Aktivität signifikanten Einfluss auf das Schicksal eines zukünftigen Perzeptes nehmen. Die Frage, ob die Verschaltung multisensorischer Information spezifische kortikale Prästimulus-Zustände voraussetzt wurde allerdings kaum untersucht. Daher wurden drei Studien konzipiert, die die Rolle von Prästimulus-Aktivität bei der Wahrnehmung audiovisueller Reize untersuchen sollten.

In der *ersten Studie* nutze ich den McGurk Effekt, um den Einfluss fortlaufender kortikaler Oszillationen - beschrieben durch Fluktuationen lokaler Erregbarkeit und Synchronisation zwischen Hirnarealen - auf die bevorstehende veränderliche Wahrnehmung identischer Reize zu erforschen. Der McGurk Effekt demonstiert den Einfluss visueller Hinweisreize auf auditorische Wahrnehmung. Nicht übereinstimmende Information beider Modalitäten kann zu einem neuen Perzept zusammenfließen, das weder dem auditorischen, noch dem visuellen Reiz entspricht - in etwa 60-80% der Durchgänge geben die Probanden an, eine Illusion wahrgenommen zu haben. Mit Hilfe der Magnetenzepahlographie (MEG) fand ich heraus, dass der Wahrnehmung des McGurk Effektes eine hohe Beta-Band Aktivität in parietalen, frontalen sowie temporalen Hirnarealen, insbesondere dem linken superioren Temporallappen (STG) vorangeht, von dem man annimmt, dass er einen Ort multimodaler Informationsintegration darstellt,. Dieses Gebiet ist in Durchgängen mit einer Illusion funktionell zu verteilten frontalen und temporalen Gebieten ent- und gekoppelt. Die Disposition, multisensorische Information zusammenzufügen, ist verstärkt, wenn der linke STG stärker mit

frontoparietalen Gebieten gekoppelt ist. Die illusorische Wahrnehmung wird dabei von einer Abnahme von Theta-Band-Aktivität im Cuneus, dem Precuneus und dem linken superioren Frontallappen begleitet. Während der Wahrnehmung der Illusion tritt eine ausgeprägte ereigniskorrelierte Aktivität im linken mittleren Temporallappen auf. Somit hängt der McGurk Effekt von fluktuierenden Hirnzuständen ab, was nahe legt, dass die funktionelle Konnektivität des linken STG noch vor der Reizdarbietung für das audiovisuelle Perzept ausschlaggebend ist.

In der zweiten Studie untersuchte ich die Sound Induced Flash Illusion (SIFI), ein Beispiel für den Einfluss auditorischer Information auf visuelle Wahrnehmung. Sie besteht in einem Perzept zweier visueller Stimuli bei Darbietung nur eines einzelnen visuellen Stimulus begleitet von zwei auditorischenReizen. Erneut nutze ich die MEG-Technik, um zu erarbeiten, inwiefern fortlaufende oszillatorische Aktivität vor der Reizdarbietung und der Zustand der Konnektivität des Gehirns eine unterschiedliche Wahrnehmung identischer Reize beeinflusst. Ich verglich die kortikale Aktivität bei Durchgängen, in denen die Teilnehmer *zwei* visuelle Stimuli wahrnahmen (also eine Illusion), mit Durchgängen, in denen die Teilnehmer nur *einen* visuellen Stimulus (also keine Illusion) wahrnehmen, und hielt somit die Reizdarbietung konstant. Die Teilnehmer nahmen die Illusion in etwa 50% der Durchgänge wahr. In Durchgängen mit einer Illusion fand ich stärkere Beta-Band Aktivität in einer links temporalen Sensorgruppe und verortete diese im linken mittleren Temporallappen (BA39). Außer den Unterschieden in der lokalen Beta-Band Aktivität gingen den illusorischen Wahrnehmungen außerdem eine erhöhtePhasensynchronizität im Beta-Band mit auditorischen Arealen sowie eine reduzierte Phasensynchronizität mit visuellen Bereichen voraus. Ich stellte fest, dass Phasensynchronizität im Alpha-Band zwischen visuellen und temporalen, parietalen und frontalen Arealen sowie Alpha-Band Phasensynchronizität zwischen auditorischen und visuellen Gebieten moduliert wird. Allerdings sind Studien zur externen Störung des aktuellen Hirnzustands vonnöten, um die Rolle der oszillatorischen Aktivität in multisensorischen kortikalen Gebieten besser zu beurteilen.

Dies habe ich in der *dritten Studie* behandelt.Ich replizierte meine Arbeit der zweiten Studie zur Sound Induced Flash Illusion und erweiterte diese durch transkranielle Magnetstimulation (TMS) mit einem einzelnen Puls. Ziel der Stimulation war das bilaterale Areal BA39. In dieser Studie bediente ich mich der Elektroenzephalographie (EEG), um den Einfluss fortlaufender oszillatorischer kortikaler Aktivität beim Menschen sowie das Verhältnis zwischen TMS und jener zu erfassen. Ich verglich die Aktivität aus Durchgängen, in denen Teilnehmer nach der Impulsgabe eine Illusion wahrnahmen mit Durchgängen, in denen Teilnehmer nach der Impulsgabe keine Illusion wahrnahmen und hielt somit die Reizdarbietung konstant. Dabei ermittelte ich, dass ein Anstieg der Gamma-Band-Energie im rechten temporalen Kortex signalisiert, dass eine Illusion zustandekommen wird.. Um zu testen, wie das TMS wirkt, teilte ich Durchgänge nach starker und schwacher Beta- und Gamma-Band Energie vor dem TMS-Puls auf. Dies diente dazu, den Einfluss des aktuellen Hirnzustands auf die Auswirkungen des TMS zu untersuchen. Das TMS reduziert starke oszillatorische Energie im Beta- und auch auch Gamma-Band, aber verstärkt schwache Energie sowohl am Stimulationsort, als auch im inferioren Frontallappen sowie in anterioren temporalen Gebieten. In Abhängigkeit der stärke der Beta-Band Energie vor dem TMS hat eine TMS-Impulsgabe einen differenzierenden Einfluss auf aufkommende Wahrnehmung.

In Anbetracht dieser drei Studien schließe ich, dass fortlaufende Fluktuationen oszillatorischer Aktivität vor der Reizdarbietung in multimodalen Hirnarealen sowie die veränderliche Einbindung dieser in ein verteiltes Netzwerk eine Disposition dafür bilden, ob verschiedene sensorische Informationsflüsse integriert werden oder nicht. Diese Befunde sind konsistent mit und erweitern neueste Erkenntnisse über die Rolle von Beta- und Gamma-Band Aktivität in Top-Down und Bottom-Up Netwerkprozessen multisensorischer Perzeption.

Die spektralen Fingerabdrücke der ihnen zu Grunde liegenden kognitiven Prozesse zu identifizieren kann also als Basis dienen, die neuronalen Korrelate des Bewusstseins zu erkunden.

Abstract

In the last decade, neuroscientific research has refocussed on the old observation, that identical stimuli can elicit different cortical responses and thus different percepts. What has for a long time been regarded as background noise in absence of external stimulation has since gained a lot of attention. There is now growing consensus, that power and phase of oscillatory activity significantly influence the fate of an upcoming percept. However, the question of whether multi-sensory information integration requires specific pre-stimulus brain states has rarely been assessed. Three studies were therefore designed to investigate the role of pre-stimulus activity in the perception of audiovisual stimuli.

In the *first study*, I used the McGurk effect to elucidate the impact of ongoing brain oscillations - indexed by fluctuating local excitability and inter-areal synchronisation - on upcoming varying perception of identical stimuli. The McGurk effect demonstrates the influence of visual cues on auditory perception. Mismatching information from both modalities can fuse to a novel percept that neither matches the auditory nor visual stimulus while an illusion is reported in 60-80% of trials. Using magnetoencephalography (MEG), I found that the perception of the McGurk effect is preceded by high beta activity in parietal, frontal, and temporal areas and pronounced in the left superior temporal gyrus, considered to be a site of multimodal information integration. This area is functionally (de-)coupled to distributed frontal and temporal regions in illusion trials. The disposition to fuse multi-sensory information is enhanced as the left STG is more strongly coupled to frontoparietal regions. Illusory perception is accompanied by a decrease in post-stimulus theta band activity in the cuneus, precuneus and left superior frontal gyrus. Event-related activity in the left middle temporal gyrus is pronounced during illusory perception. Thus, the McGurk effect depends on fluctuating brain states suggesting that functional connectedness of left STG at a pre-stimulus stage is crucial for an audiovisual percept.

In the *second study*, I investigated the Sound-Induced Flash Illusion (SIFI), which is an example for the influence of auditory information on visual perception. It consists of the perception of two visual stimuli upon presentation of only a single visual stimulus accompanied by two auditory stimuli. Again, I used MEG to assess the influence of ongoing pre-stimulus oscillatory activity and brain connectivity states on varying perception of invariant stimuli. I compared cortical activity from trials in which subjects perceived two visual stimuli (i.e., an illusion) with trials in which subjects perceived only one visual stimulus (i.e., no illusion), thus keeping the stimulation fixed. Subjects perceived the illusion in ~50% of trials. In trials containing an illusion, I found stronger pre-stimulus beta band activity in a left temporal sensor cluster and localised this to the left middle temporal gyrus (BA39). In addition to differences in local beta activity, illusory perceptions were preceded by increased beta band phase-synchrony with auditory areas as well as decreased phase synchrony with visual areas. Alpha band phase-synchrony between visual and temporal, parietal and frontal cortical as well as alpha band phase-synchrony between auditory and visual areas were found to be modulated. However, studies involving active external perturbations of the current brain state are needed in order to evaluate the role of oscillatory activity in multimodal cortical areas.

I addressed this in the *third study* by replicating our work on the sound induced flash illusion (SIFI) and extending it with single pulse transcranial magnetic stimulation (TMS). The target for stimulation was in the bilateral BA39. I used electroencephalography (EEG) to assess the influence of ongoing oscillatory activity on varying perception of invariant stimuli in humans as well as the relationship between TMS and ongoing oscillatory cortical activity. I compared activity from trials in which subjects subsequently perceived an illusion with trials in which subjects perceived no illusion, thus keeping the stimulation fixed. I found a strong increase in gamma band power in right temporal cortex signalling an upcoming illusion. Regarding TMS, I split trials into strong and weak pre-TMS beta and gamma band power in order to evaluate the influence of the current brain state on the TMS effect. TMS reduces strong oscillatory power in the beta as well as gamma band at the site of stimulation, but also in inferior frontal and anterior temporal areas but increases weak power. TMS to the right BA39 differentially influences upcoming perception depending on the strength of pre-TMS beta band power.

Based on these three studies, I suggest that ongoing pre-stimulus fluctuations of oscillatory activity in multimodal brain regions as well as its varying integration into a distributed network form predispositions whether different sensory streams will be integrated or not. These findings are consistent with and extend recent findings on the role in beta and gamma band activity in top-down and bottom-up network processes of multi-sensory perception. Identifying the spectral fingerprints of underlying cognitive processes can serve as a basis to exploration of the neural correlates of consciousness.

Conducted studies and own research contribution:

The studies in this thesis were co-authored and supported by a number of colleagues. They are listed below together with my own research contributions.

First Study: On the variability of the McGurk effect: Audiovisual integration depends on pre-stimulus brain states:

Authors: Julian Keil, Dr. Nadia Müller, Dr. Niklas Ihssen, Dr. Nathan Weisz

Published in Cerebral Cortex

I supported the planning of the design of the study, carried out the MEG recordings, performed the data analyses and drafted the manuscript.

Second study: Pre-Stimulus Beta Power and Phase Synchrony Influence the Sound-Induced Flash Illusion:

Authors: Julian Keil, Dr. Nadia Müller, Thomas Hartmann, Dr. Nathan Weisz

Currently submitted (current status at April 1st, 2012: Under review at Journal of Neuroscience)

I designed and implemented the study, carried out the MEG recordings, performed the data analyses and drafted the manuscript.

Third study: Pre-stimulus beta and gamma activity influence upcoming perception of the sound induced flash illusion: a combined EEG-TMS study.:

Authors: Julian Keil, Hannah Schulz, Teresa Übelacker, Thomas Hartmann, Dr. Nathan Weisz

Currently submitted (current status at April 1st, 2012: Under review at Cerebral Cortex)

I designed and implemented the study, carried out the EEG recordings, performed the data analyses and drafted the manuscript.

Abbreviations

ANOVA	Analysis Of Variance
BA	Brodmann Area
DICS	Dynamic Imaging of Coherent Sources
EEG	Electroencephalogram
e.g.	For example (Latin: exempli gratia)
ERF	Event Related Field
ERP	Event Related Potential
et al.	and others (Latin: et alii)
f	female
fMRI	functional Magnetic Resonance Imaging
Hz	Hertz
i.e.	that means
iEEG	intracranial EEG
LCMV	Linearly Constraint Minimum Variance
m	male
MEG	Magnetoencephalogram
MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
ms	milliseconds
PLV	Phase Locking Value
s	seconds
SIFI	Sound Induced Flash Illusion
STG	Superior Temporal Gyrus
TMS	Transcranial Magnetic Stimulation
tDCS	Transcranial Direct Current Stimulation

Far off, it seems to me, we hear the humming of the machinery of the mind and, from time to time, we gain fleeting glimpses of its action. (Penfield, 1954)

1. Introduction and Perspectives

Fluctuations in cortical activity were amongst the first phenomena observed in human electrophysiological research. In his report on the EEG, Hans Berger described a change in rhythm depending on rest or intellectual work (Berger, 1929). In the middle of the last century, Donald Hebb observed that it is impossible that the consequence of a sensory event should be uninfluenced by the existing activity, as the brain is continuously active and all excitation must be superimposed on this already existing excitation (Hebb, 1949). It is known from the work of Wilder Penfield that human brain stimulation can elicit a rich conscious phenomenology, including dream-like states and that repeated stimulation of the same cortical site typically produced different experiences, while stimulation of some other sites could evoke the same experience (Penfield, 1954).

The present work is based on these former observations. It tries to elucidate the meaning of the 'humming of the machinery of the mind', i.e. the role of the brain state expressed in frequency, phase and power of oscillatory cortical activity prior to stimulation. After a brief introduction to the field of brain states, perception and consciousness, I will present three electro-physiological experiments that have been accomplished in order to test my hypotheses.

1.1. Brain state dependency:

In his book "Rhythms of the brain", Buzsáki (Buzsáki, 2006) postulated that "the neuronal signal in response to a given environmental perturbation of the brain state is not an initial condition, but rather a modification of a perpetually evolving network pattern in the brain's landscape". Thus, in order to predict the state of a neuronal network, it is necessary to have knowledge of its recent history.

It has been observed since the beginning of electrophysiological research that ongoing cortical activity is reflected in oscillatory activity. Oscillatory activity, as measured with EEG or MEG, reflects rhythmic fluctuations of membrane potential (Lopes da Silva, 1991). It is generated by the summed post-synaptic potentials of large cortical areas, the so called local field potential, thus incorporating the activity of several thousands of neurons. The properties of oscillations can be described by amplitude (strength of the local field potential), frequency (fluctuations of the local field potential over time) and phase (current position in a cycle of the fluctuation). According to Pfurtscheller and Lopes da Silva (Pfurtscheller & Lopes da Silva, 1999) three factors determine the properties of EEG oscillations: 1) The intrinsic membrane properties of the neurons and the dynamics of synaptic processes, 2) the strength and extent of the interconnections between network elements and 3) the modulating influences from neurotransmitter systems.

The idea that the history of a neuronal network, defined as the brain state prior to a stimulation, influences the outcome of a stimulation has gained a lot of attention and support within the last decade. Accordingly, these oscillations of cortical activity and modulations of amplitude and phase of these oscillations do not represent random fluctuations, but in contrast, systematically impact how the brain processes external and internal stimuli and thus shapes perception and behavior. Frequency ranges of cortical activity that were ascribed a defined role were reexamined in the wake of this new view (Dalal et al., 2011). Alpha-band activity, that used to be considered as a marker of idling (Pfurtscheller, Stancák, & Neuper, 1996), has since been ascribed a functional role (Jensen & Mazaheri, 2010) in the allocation of processing resources and guidance of attention. A growing body of literature (Romei, Gross, &

Thut, 2010; Hanslmayr et al., 2007; Van Dijk, Schoffelen, Oostenveld, & Jensen, 2008) reports on pre-stimulus fluctuations of power and phase, and the influence on subsequent perception, however, mostly in the visual domain. Recently, Müller et al. (Müller & Weisz, 2011; Müller, 2011) described similar alpha-band effects in the auditory domain. The beta-band, mainly associated with motor activity, has been implicated in top-down processing of information. In this frequency range pre-stimulus influences on perception have recently been reported in audiovisual (Hipp, Engel, & Siegel, 2011) and visuo-tactile tasks (Lange, Oostenveld, & Fries, 2010).

Furthermore, both short term (e.g., previously presented stimuli) and long term influences (e.g., psychopathological states) have been associated with changes in stimulus processing. Stimuli presented in rapid succession in a so-called steady state paradigm evoke an oscillatory state in the brain marked by the same oscillatory frequency as the rate of stimulation. Perception of each stimulus thus depends on previously presented stimuli and the subsequently evoked cortical activation (Keil, Adenauer, Catani, & Neuner, 2009). The amplitude of this oscillation is also shaped by previous experience and psychopathology (Catani, Adenauer, Keil, Aichinger, & Neuner, 2009) and can in turn be influenced by therapeutic interventions (Adenauer et al., 2011).

1.2. Perturbing the state:

As mentioned above, electrical stimulation of the human cortex is a widely used technique to study the functional role of a certain cortical area since at least the middle of the last century, when Wilder Penfield stimulated different cortical areas during brain surgery (Penfield, 1954). More than 30 years ago, Merton and Morton (Merton & Morton, 1980) demonstrated that it is also possible to stimulate the human cortex through the scull. Percutaneous stimulation of the cortex by means of a magnetic coil (Amassian et al., 1989) is nowadays conventionally called transcranial magnetic stimulation (TMS). Thereby, a coil is placed on the scalp and a strong and rapidly changing magnetic field is produced orthogonally to the plane of the coil by first charging a large capacitor to a high voltage and then discharging it through the coil (Malmivuo & Plonsey, 1995). A high intensity TMS pulse whose magnetic field passes unimpeded through the skin and skull, induces a very short lasting (100-300μs) electrical pulse at a strength of 1.5-2.0 Tesla which leads to a synchronised high frequency burst of discharge in a relatively large population of neurons that is terminated by a long lasting GABAergic inhibition (Siebner, Hartwigsen, Kassuba, & Rothwell, 2009). This combination of artificial synchronisation of activity followed by depression effectively disrupts perceptual, motor, and cognitive processes in the human brain. This transient neuronal disruption has been termed a "virtual lesion" (Silvanto & Muggleton, 2008). However, there is growing evidence that TMS acts in a state-dependent fashion. The brain state at the time of stimulation can have a significant influence on the TMS effects directly at the stimulation site (Siebner et al., 2004; Silvanto, Muggleton, Cowey, & Walsh, 2007; Silvanto & Muggleton, 2008; Silvanto, Muggleton, & Walsh, 2008; Silvanto & Pascual-Leone, 2008; Silvanto & Pascual-Leone, 2012; Weisz et al. 2012). Furthermore, distant cortical regions can be influenced by the spread of activation to connected brain areas. Siebner and colleagues (Siebner et al., 2009) stressed that there is no simple relationship between the excitability of a region and the local activity. Therefore, the interpretation of state dependent effects is always speculative. However, the combination of TMS with EEG has emphasised that specific cortical frequency patterns are not mere epiphenomena but have a strong influence on behavior and perception (Thut & Miniussi, 2009). Moreover, Lorenz showed in a combination of TMS and MEG that it is possible to alter patterns of oscillatory cortical activity via TMS and thus influence the auditory phantom perception tinnitus (Lorenz, 2011). With respect to audiovisual integration, Bolognini et al. (Bolognini, Rossetti, Casati, Mancini, & Vallar, 2011) presented compelling evidence that the external polarisation of cortical areas modulates multi-sensory perception.

Using transcranial direct current stimulation (tDCS), the authors demonstrate that an illusory audiovisual perception is more or less likely depending on the polarity of the stimulation.

Potentially, an accurate examination of the brain state in terms of oscillatory activity prior to stimulation and the analysis of change of activity in local as well as remote cortical areas will help to understand how the external stimulation interacts with the brain state and how this interaction in turn modulates perception and behavior.

1.3. Illusions as a window to consciousness:

An important question regarding the influence of brain states is how they shape sensory integration, information processing and ultimately the way we consciously perceive the world. Thus, the subject of study is an introspective phenomenon (Dehaene & Naccache, 2001). Objectively measurable is only the response of the individual after it has perceived a combination of input streams. Different cortical areas are specialised for detecting and processing different types of sensory signals and, to be useful for multi-sensory perception, the information must be combined. The mismatch between information from different modalities is the basis of audiovisual illusions that hint at the way sensory areas are interconnected (Eagleman, 2001). Audiovisual illusions might be seen as the counterpart of inattention blindness or change blindness. It is not that a stimulus that is salient in isolation is not perceived, but that two or more stimuli that are salient in isolation give rise to a novel combined percept. But what is the content of perception and how do multi-sensory stimuli become conscious? Crick and Koch (Crick & Koch, 2003) ask these questions searching for the neural correlates of consciousness and argue that novel objects need to be integrated in perceptual binding. The activity of several essential nodes must be made to act together. Based on these ideas, Siegel et al. (Siegel, Donner, & Engel, 2012) argue that cognitive processing and information integration is achieved through the formation of large transient coalitions of neurons which in turn compete with each other. They build an analogy to politics: One coalition typically rules until it is overturned by another. In the brain, the winning coalition governs a percept, thought or action. Furthermore, the authors propose that frequency-specific correlated oscillations in distributed cortical networks may provide indices, or 'fingerprints', of the network interactions that underlie cognitive processes. Therefore, these fingerprints could serve to identify canonical neuronal computations, the acting together of the essential nodes as proposed by Crick and Koch (Crick & Koch, 2003), which are commonly inferred, but so far not directly accessed. Posner (Posner, 2012) argues for an overlap between attention and consciousness, and suggests the study of the processes underlying attention might help illuminate dissociations but also common principles. Active inhibition (and possible) attention vary on a trial by trial basis as described by Dehaene et al. (Dehaene & Naccache, 2001). However, no specific process has been proposed so far. The remaining question is: What are the nodes of the audiovisual perception network and how do they act together to form transient coalitions? With respect to the underlying cognitive processes, Witten et al. (Witten & Knudsen, 2005) suggest that it is the reliability of information that captures the percept. Concerning the question how the central nervous system represents stimulus reliability and weights the estimates of stimulus location accordingly, Bulkin et al. (Bulkin & Groh, 2006) state that the visual system excels at spatial acuity. In contrast the auditory system gives more precise temporal information and appears to dominate perception of when events occur. When subjects make judgments about the timing of temporally mismatched visual–auditory events, the auditory percept 'wins'. It seems that the brain weights sources of sensory information according to their assumed reliability when producing a unified percept. However, regarding the cross-modal enhancement of neuronal activity, Stein and Meredith (Stein & Meredith, 1993) stated the principle of inverse effectiveness, positing that the cross-modal influence is at maximum, when the contributing unimodal stimuli are minimally effective. Therefore, a multi-sensory illusion is likely to occur, when either none of the input modalities is sufficiently reliable to evoke a percept - a filling in process also suggested by Pessoa and DeWeerd (Pessoa & De Weerd, 2003) - or the current state of the brain favors the cross-modal influence, e.g., by enhanced connectivity.

1.4. Spectral fingerprints of top-down and bottom-up processing:

Invasive and noninvasive studies in humans under normal physiological and pathological conditions converged at the proposition that the amplitude and phase of neural oscillations implement cognitive processes such as sensory representations, attentional selection, and dynamic routing or gating of information (Schyns, Thut, & Gross, 2011). The emergence of rhythmic fluctuations or oscillations requires specific network properties such as local neuronal assemblies that are to some extent connected by long-range inhibitory interneurons (Buzsáki et al. 2004). Such long-range neurons can dynamically link the local assemblies (Pfurtscheller & Lopes da Silva 1999; Varela et al. 2001) so that the firing of single neurons becomes coordinated. On a macroscopic level these single coordinated neurons reflect an oscillation (Buzsáki 2006). Siegel et al. (Siegel et al., 2012) suggested that different frequencies of coherent oscillations reflect different directions of the flow of cortical information. Specifically, gamma-band activity has been implicated in bottom-up or feed-forward processes, whereas the beta-band has been associated with top-down or feed-back interactions. Starting with the influential review by Engel and Fries (Engel & Fries, 2010), beta-band activity has become more and more connected with signalling the status quo, resting state activity, and top-down control. As outlined by Dalal et al. (Dalal et al., 2011) beta-band activity in the EEG and MEG has usually been related to tactile processing, motor cortex activity, and a prediction of choice (Donner, Siegel, Fries, & Engel, 2009), all of which seem to reflect a local suppression of ongoing rhythmic activity by cortical activation (Pfurtscheller 1999). Aside from the role of beta-band activity in the realm of motor activity, this frequency range has been connected to the communication between distant cortical areas. Buszaki (Buzsáki & Draguhn, 2004) as well as von Stein (von Stein & Sarnthein, 2000) stated that lower frequencies are better suited for long-range connectivity. This has also been proposed by Kopell et al. (Kopell & Ermentrout, 2000) based on computational model considerations.

Besides the power of a given frequency the phase of the oscillation carries important information. Schyns et al. (Schyns et al., 2011), for example, state that the combination of power and phase codes 2.4 times more information than power alone. Phase defines the current position in a given cycle of the fluctuation and systematically affects the probability of a single neuron to fire (Jacobs et al. 2007). A consistent phase difference between two neuronal populations points to a systematic relation between them and has been interpreted as a measure of communication (Lachaux et al. 1999; Varela et al. 2001).

Siegel et al. (Siegel et al., 2012) propose a compelling framework for the interplay between bottom-up and top-down processes as well as for the interactions between different cortical layers as the supposed origin of specific oscillations. The authors assume that the biophysical properties of such circuit mechanisms determine the frequency bands of neuronal oscillations. Furthermore, these circuit mechanisms are believed to determine canonical computations that constitute the elementary building blocks of cognition. These computations can thus be combined and applied to different inputs in different neuronal networks to yield various cognitive functions. Gamma-band oscillations and feed-forward projections in superficial layers may lead to bottom-up interactions in the gamma-band. Conversely, slower rhythms and feed-back projections in deep layers may underlie top-down interactions in slower frequency ranges in particular in the beta-band. The authors state, that the laminar specificity of cortical oscillations and long-range projections may thus be the key for linking different directions of information processing with different frequency bands of large-scale coherent cortical oscillations. Regarding the biophysical substrate of the proposed general multi-sensory superior temporal cortex, Beauchamp (Beauchamp, 2005) suggest a patchy organisation, in which neighbouring patches respond primarily to unisensory auditory or visual information. Unisensory information might be translated into a common code and integrated in multi-sensory regions that lie between the unisensory patches. Multiple frequencies sent over one channel (i.e., multiplexing, Schyns et al., 2011) might in turn signal this local as well as distant feed-forward and feed-back information transfer. Canonical operations can be achieved using distinct frequencies for distinct operations. Temporally or spatially linked beta- and gamma-band oscillations could therefore be a marker of long range connectivity or integration of multiple sources, either locally in the patchy organisation of multi-sensory cortical areas or in diverse networks between early sensory and higher-order cortical areas.

1.5. Overview of studies:

Several important research questions arising from the literature outlined above have been addressed in the current work:

1) How do different markers of local as well as network pre-stimulus oscillatory activity influence the effect of external stimulation?

2) What specific frequencies of ongoing pre-stimulus oscillations are associated with an upcoming illusion?

3) Is it possible to externally influence ongoing oscillatory activity and dependent perception?

In the first study, I used the McGurk illusion (McGurk & MacDonald, 1976) - an example of how visual information can influence auditory perception - to examine the influence of pre-stimulus oscillatory activity on upcoming perception. The experiment was designed to compare instances of illusory perception that constitute a fusion of auditory and visual information with non-illusory trials, in which one modality governs the perception. Thus, in this experiment as well as in the following studies, the stimulation was kept identical, but the result of the stimulation - the percept or the modulation of cortical activity - was critically influenced by the oscillatory activity prior to stimulation. In this as well as the two following experiments, participants were asked to indicate their subjective perception using a forced choice task. No feedback was given, as the labels 'correct' and 'incorrect' cannot be applied to subjective perception. In line with studies on processing of congruent versus incongruent audiovisual stimulation (Calvert, Campbell, & Brammer, 2000), the left superior temporal cortex was activated stronger during the perception of the - subjectively congruent - illusion depending on an integration of auditory and visual information. More importantly, the pre-stimulus cortical activity in the left superior temporal cortex predicted an upcoming illusion. Increased beta-band power in the left superior temporal cortex indicated that a specific frequency - recently associated with top-down influences on perception in a multi-sensory integration area - predisposes audiovisual integration. Furthermore, increased phase coupling with frontal and temporal areas as well as decreased phase coupling with occipital areas in the same time and frequency range indicate the importance of network integration in addition to local processes. However, these results might be specific to the complex stimulus material used in the first study, which is associated with face and voice processing. Therefore, the second study applied the much simpler sound induced flash illusion (Shams, Kamitani, & Shimojo, 2000), which is an example of how auditory information influences visual perception. Although the direction of influence is reversed, pre-stimulus beta-band in the left junction between temporal, parietal, and occipital cortex, previously described as a multi-sensory area closely linked to the superior temporal cortex (Beauchamp, 2005), predicted an upcoming illusory perception. Additionally, increased phase coupling with higher auditory cortex and decreased phase coupling with higher visual processing areas in the same time and frequency range signaled an upcoming illusion. Thus, the second study could replicate the most important findings of the first experiment and add evidence to the proposed role of beta-band activity in top-down influence on perception. Supplementary to these findings, the strength of phase coupling between the left multi-sensory area and higher auditory cortex in each single trial predicted the fate of an upcoming stimulus. The stronger both areas were connected, the more likely was an influence of auditory information and therefore an illusion. The third study was designed to replicate the findings from the first two studies and to further evaluate the role of pre-stimulus activity in multi-sensory cortical areas by externally perturbing these with single pulse TMS. This virtual lesion approach was chosen to assess the necessity of this region for audiovisual integration and the perception of the illusion. The experimental setup was the same as in the second study. However, cortical activity was measured by means of EEG instead of MEG and single-pulse TMS was applied 500 ms prior to the onset of the audiovisual stimulus to bilateral temporo-parietal cortices in fifty percent of the trials. In line with the first two studies, pre-stimulus power significantly influenced upcoming perception, however, location as well as frequency range were different. Local gamma-band activity in the right temporal cortex predicted an upcoming illusion. However, local and global beta-band power prior to TMS significantly influenced subsequent perception so that illusory perception was more likely to be preceded by strong beta-band power before the TMS. Nonetheless, local gamma-band power in the right temporal cortex could be a different side of the same process as Beauchamp (Beauchamp, 2005) identified multi-sensory areas in left and right temporal and temporo-parietal cortex. Moreover, the gamma-band power increase might be the signature of local processing in contrast to the long-range network processes signaled by the beta-band. Importantly, sorting trials by the pre-TMS beta-band power revealed an increased likelihood of the illusion depending on high pre-TMS beta-band power, thereby supporting the prominent role of beta-band power in audiovisual integration. By revealing the influence of pre-TMS power the third study further extended the previous findings. Pre-stimulus power not only significantly influences upcoming audiovisual integration and perception, but also impacts the effect of TMS. This state-dependent effect of TMS is in line with previous findings (Siebner et al., 2009; Silvanto et al., 2008) and underlines the importance of the brain state in the processing of external stimulation.

1.6. Overall conclusions:

Based on the three studies conducted in the framework of the current thesis, I conclude that the brain state prior to stimulation critically shapes the fate of the stimulation. High pre-stimulus power in multi-sensory cortices abets audiovisual integration and thereby influences perception. In line with different roles in top-down and bottom-up processes, beta- and gamma-band oscillatory activity were found to play an important role in local but also in distant network processes. Pre-stimulus power not only influences the effect of visual or auditory stimuli, but also of induced electrical stimulation by a magnetic pulse. In accordance with previous studies oscillatory power but also perception was found to be differentially modulated depending on pre-TMS power. The combination of different electrophysiological methods, external stimulation, and measures of the subjective perception further advanced our understanding of the fingerprints of cortical processes underlying perception, behavior and ultimately consciousness. The present work opens up a number of starting points for future research that might grant fleeting glimpses of the action of the ’machinery of the mind‘.

2. First study: On the variability of the McGurk effect: Audiovisual integration depends on pre-stimulus brain states

2.1. Introduction

While there is a substantial body of literature about the neural basis of unimodal sensory perception, multimodal information integration has come into focus only recently (Calvert, Spence, & Stein, 2004). Integration of information from multiple modalities is crucial and representative for our everyday life. A typical example is speech perception, in which, apart from the actual sound, visual cues from lip movements also have a significant influence on what we actually perceive as being said (van Wassenhove, Grant, & Poeppel, 2005). A classical demonstration that visual information can significantly impact speech perception is the so-called McGurk effect, first described by McGurk and MacDonald (McGurk & MacDonald, 1976). In this illusion, an auditory syllable is dubbed with a video of lip movements uttering an incongruent syllable (e.g., a video of an actor pronouncing the syllable "ga" is shown together with the audio stream of the syllable "ba"). Participants frequently report having heard a syllable that neither matches the unimodal visual nor acoustic source (e.g., "da", see figure 1) and do not typically notice the incongruence between the acoustic and visual inputs (Möttönen, Krause, Tiippana, & Sams, 2002). Despite being a robust finding on average, the illusory percept does not occur with equal probability in all participants and also fluctuates on a trial-by-trial basis within one participant (~60-80% "fusion" percepts). One way to conceive of audiovisual integration at a neuronal level is that these perceptions depend on the activity of multi-sensory cell assemblies, which receive convergent input from multiple sensory modalities. The existence of such multimodal neurons has been shown at several hierarchical levels from midbrain to cortex (Stein & Meredith, 1993; Stein, London, & Wilkinson, 1996; Stein, 1998; Bizley, Nodal, Bajo, Nelken, & King, 2007; Kayser & Logothetis, 2007; Kayser, Petkov, Augath, & Logothetis, 2007; Ghazanfar, Chandrasekaran, & Logothetis, 2008; Kayser, Logothetis, & Panzeri, 2010). Regarding the McGurk illusion, an increasing body of evidence points to the left superior temporal gyrus (STG) as a crucial structure (Calvert et al., 2000) of audiovisual information integration (Barraclough, Xiao, & Baker, 2005; Stevenson & James, 2009; Dahl, Logothetis, & Kayser, 2010), which in the case of non-matching information leads to a non-existent percept. Recent iEEG (Besle et al., 2008), EEG (van Wassenhove et al., 2005); (Cappe, Thut, Romei, & Murray, 2010) and MEG (Arnal, Morillon, Kell, & Giraud, 2009) studies propose neural routes between auditory and visual areas and STG in speech perception. These studies found, that audiovisual interactions - especially of ecologically valid stimuli (i.e. speech) - are expressed in reduced evoked responses mediated by saliency and redundancy of information. These findings suggest rules of audiovisual integration beyond the general principles of response enhancement of multi-sensory integration established for multi-sensory cell assemblies (Calvert et al., 2004).

Exploiting the perceptual variability to the invariant incongruent stimulus, the aim of the current study was to elucidate the factors that determine multi-sensory integration beyond unimodal stimulus properties (e.g. visual speech), especially pre-stimulus oscillatory activity, that is, the brain state in terms of local and inter-areal synchronisation at the time of the incongruent stimulus' entry into the system. Several recent studies have shown the influence of pre-stimulus activity on perception in general (and especially near-threshold). Alpha band phase (Mathewson, Gratton, Fabiani, Beck, & Ro, 2009; Busch & Vanrullen, 2010) and power (Romei et al., 2010) have been reported to influence the perception of visual stimuli. Growing evidence suggests that alpha rhythms reflect the excitatory–inhibitory balance within sensory and motor regions, with strong alpha activity indicating an inhibitory state (Klimesch, 1999; Weisz, Dohrmann, & Elbert, 2007). However, apart from fluctuations of relatively local activity (i.e., at brain region level), the integration of a region into a distributed network via inter-regional coupling is also subject to variability. While some evidence exists for post-stimulus impacts of inter-areal coupling on conscious perception (Dehaene, Changeux, Naccache, Sackur, & Sergent, 2006; Melloni et al., 2007), pre-stimulus influences have only recently become a focus of research (Hipp et al., 2011). To date, no study has investigated ongoing cortical pre-stimulus influences on the McGurk illusion. Beauchamp et al. (Beauchamp, Nath, & Pasalar, 2010) conducted an important study within this context using a "virtual lesion" approach The authors were able to show that applying TMS to left STG within a window of ~100 ms around the stimulus significantly diminished the proportion of trials in which the illusion was perceived. Importantly, this effect included pre-stimulus periods, thus implying the importance of the current state of the left STG (and potentially therewith connected regions).

A growing amount of empirical evidence suggests that conscious perception involves a widespread neuronal network supplementary to activations of sensory and association regions (Koch, 2004; Dehaene et al., 2006). A recent review also proposes that the function of the STG is not only restricted to audiovisual integration but varies with task-dependent network connections (Hein & Knight, 2008). This means that in addition to considering measures of local brain activity, it also is important to investigate functional network states (Buzsáki, 2006; Senkowski, Schneider, Foxe, & Engel, 2008), frequently manifested in synchronisation of phases of oscillatory activity (Tass, Rosenblum, Weule, & Kurths, 1998; Varela, Lachaux, Rodriguez, & Martinerie, 2001; Fries, 2005).

Following the literature reviewed above, we hypothesise that pre-stimulus increases of local power in left STG at higher frequencies (beta/gamma) or relative desynchronisation at lower (theta/alpha) frequencies, reflecting a state of perceptual readiness, could be crucial for an illusion following an invariant stimulus, as well as increased phase coupling of the left STG (and thereby a more efficient spreading of its information) with distributed regions relevant for conscious perception. Both local power changes and long-range connectivity are expected to correlate with the individual tendency to experience the McGurk illusion - that is, a fusion between auditory and visual information. We used magnetoencephalography (MEG) to identify responses in the time-frequency-sensor space, differentiating between "unimodal" perceptions (i.e. no fusion of modalities) and the perception of a fusion of both modalities within the incongruent trials. We subsequently localised the sources of effects in the pre- and poststimuls interval using adaptive linear spatial filtering (so called "beamforming", Van Veen, van Drongelen, Yuchtman, & Suzuki, 1997; Gross et al., 2001). Phase synchrony was then computed between the principal region of interest (left STG) and the whole brain volume in order to assess functional network states differentiating the perceptual categories. Our data show that special pre-stimulus conditions are indeed necessary at a local activation level of left STG (increased beta power) as well as at the level of functional connectivity (increased coupling of left STG to frontoparietal areas) in order for an illusory percept to subsequently emerge.

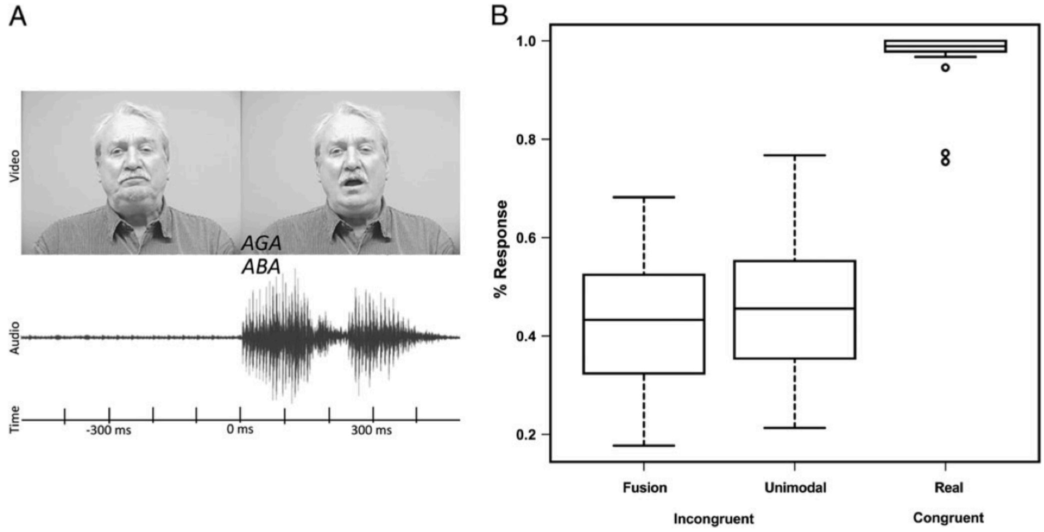

Figure 1:

Trial and timing overview with relative responses. (A) Example trial with two video frames from a video used in this experiment (top row), the audio trace of the syllable "aba" presented simultaneously to the video (middle row). Mouth movement and audio onset occur at time 0 ms. The interval prior to this is referred to as "pre-stimulus". (B) Box plot with responses relative to the total number of trials per category. On average, congruent trials were correctly identified in 96.19 % of cases. A "fusion" percept was reported in 41.61% of incongruent trials, whereas a unimodal percept was reported 48.02% of the time.

2.2. Methods:

2.2.1. Subjects:

17 (6 m/11 f, mean age 24.9) paid volunteers participated in this study. All participants gave their written informed consent. All participants were right-handed, had normal hearing and normal or corrected-to-normal vision.

2.2.2. Experimental Design and Apparatus:

Participants were informed about the experimental procedure and were introduced to the facilities. They were then prepared for the recording session and seated in the magnetically-shielded room.

The experiment consisted of 390 trials in which we showed videos of an actor pronouncing the syllables “aba”, “ada”, or “aga”. The stimuli were presented via Psyscope X (http://psy.ck.sissa.it/) on a MiniMac (Apple Inc.). Two-thirds of the trials contained a mismatching, incongruent audio stream (visual “ada” / auditory “aba” or visual “aga” /auditory “aba”) while the videos were the same as in the congruent condition. Using a forced choice task, participants had to indicate by pressing a button whether they had perceived “aba”, “ada”, “aga” or something else (“other”). Videos were paused for a randomised duration (2000 - 4000 ms) after the first video frame (showing a neutral face with closed mouth, see figure 1 A) in order to make the onset of the audio stream and mouth movement unpredictable. Importantly, no visual speech cues preceded differentiating auditory information, as all syllables started on “a-“. The visual stimuli were presented on a screen inside the magnetically-shielded MEG acquisition room via a video projector (DLA-G11E, JVC, Friedberg, Germany) and a set of mirrors positioned outside the room. The audio streams were presented with an analogue-to-digital converter (Motu 2408) via amplifiers (Servo 200, Samson) and a 6.1 m-length, 4 mm-diameter tube system (Etymotic Research, ER30). Sounds were corrected for the distortions introduced by the tube system.

2.2.3. Data Acquisition and Analysis:

Magnetoencephalographic (MEG) recording was conducted using a 148-channel magnetometer (MAGNES 2500 WH, 4D Neuroimaging, San Diego, USA). A subject-specific headframe coordinate reference was defined by means of five anatomical landmarks. These head fiducials, five coils, and the subject’s head shape were digitised with a Polhemus 3Space

Fasttrack at the start of each session. The subject's head position relative to the pickup coils and the MEG sensors were estimated before and after each session to ensure that no large movements occurred during data acquisition.

Subjects were lying supine in a comfortable position. They were instructed to lie still during the stimulation and to avoid eye movements and blinks as much as possible. Continuous data sets were recorded with a sampling rate of 678.17 Hz (bandwidth 0.1 - 200 Hz). A video camera installed inside the MEG chamber allowed subjects' behaviour and compliance to be monitored throughout the experiment.

After data acquisition, epochs of four seconds (+/- 2s) around speech onset were extracted from the raw data. Epochs were visually inspected for EOG, ECG, or movement artefacts. Trials were categorised according to the combination of type of video, type of audio, and type of response into two categories: 1) fusion (mismatch between auditory and visual stimulus and response that neither matched the auditory nor the visual information); and 2) unimodal (mismatch between auditory and visual stimulus and response that matched either the auditory or the visual information). The numbers of trials for the two different categories were equalised for each subject by random omission to ensure comparable signal-to-noise ratios for both perceptual categories. Resulting epochs were filtered with a 1 Hz high-pass filter (zero-phase, Butterworth) before the analysis of oscillatory activity. As the pre-response activation was the main interest of the study, no baseline was defined and outputs of the sensor - and source-space analysis for the conditions were directly compared. For the analysis of event-related activity, single trials were low-pass filtered with a 30 Hz zero-phase Butterworth filter prior to averaging.

For the time-frequency analysis, a multitaper FFT time-frequency transformation with frequency dependent Hanning tapers was computed (time window: $\Delta t=5/f$; spectral smoothing: $1/\Delta t$). Average event-related activity was subtracted from the single trials before computing the time-frequency transformation in order to remove the dominant pattern introduced by the evoked response on ongoing induced oscillatory activity. This procedure resulted in single-trial estimates of oscillatory power between 2 Hz and 40 Hz in 2-Hz steps.

A linear constrained minimum variance beamformer algorithm (LCMV, Van Veen et al., 1997) was used to identify the sources of the effects found in the time-series analysis. Source analysis was performed for an activation interval of 550 ms until 650 ms after sound onset based on the effect identified on the sensor level (see Results). The source analysis was separately conducted on the waveforms of the two conditions and the difference between projected sources was computed in the statistical analysis. Dynamic imaging of coherent sources (DICS, Gross et al., 2001) — a frequency-domain adaptive spatial filtering algorithm — was used to identify the sources of the effects found in the time-frequency domain. This algorithm has proven to be particularly powerful in localising oscillatory sources. Source activity was interpolated onto individual anatomical MRI images and subsequently normalised onto a standard MNI brain using SPM8 in order to calculate group statistics and for illustrative purposes.

The functional connectivity of neuronal activity between cortical regions of interest and the whole brain volume was analysed in terms of phase synchrony (Lachaux, Rodriguez, & Martinerie, 1999). Phase synchrony was computed for the time and frequency of interest as identified by the sensor-level analysis and for the regions of interest as identified by the source analysis. If the phase differences between two oscillators are constant, they are likely to communicate with each other, whereas uniform distributions of phase differences indicate the independence of two oscillators. We first Fourier-transformed the data at sensor level for the time and frequency range identified in the time-frequency analysis (multitaper analysis, DPSS tapers) and extracted the complex values containing phase information. These complex values were then projected into source space by multiplying them with the accordant beamformer spatial filters. Spatial filters were constructed from the covariance matrix of the averaged single trials at sensor level and the respective leadfield by a Linearly-Constrained Minimum Variance (LCMV) beamformer (Van Veen et al., 1997). Through this we obtained complex values for each voxel and trial, which were used for later analysis. Frequencies of interest were defined based on the effects found in the time-frequency analysis and confirmed based on a comparison between the "fusion" and "unimodal" trials. The complex values were first converted into angles (radians) and the difference was calculated between the reference voxel and all other voxels for each trial. From these values we calculated the circular mean over all trials and employed a Fisher-Z transformation in order to ensure normal distribution over subjects. Finally, the "fusion"-trial values were subtracted from the "unimodal"-trial values. For a global phase locking estimate we calculated the absolute value and averaged these over all voxels. This procedure yields a measure reflecting large modulations of phase locking between the trial categories, disregarding precise anatomical information as well as the sign of the changes. By performing a t-test, the frequencies that are specifically modulated according to the trial category could be extracted. In a second step, we disclosed the main regions that (de-)synchronise their phases with the regions identified with the DICS beamformer at the obtained frequency bands of interest. Phase synchrony therefore was calculated for these significant frequencies and both conditions separately. This was done for the regions identified with the DICS beamformer with all other voxels in the brain. By statistically testing the two trial categories (voxel by voxel paired t-test), we obtained the main regions involved in modulations of phase synchrony with the seeding regions.

2.2.4. Statistical Analysis:

In order to define relevant time and frequency windows, a cluster-based (at least 2 sensors per cluster) dependent-samples t-test with Monte-Carlo randomisation was performed on the sensor data (Maris & Oostenveld, 2007). This method allows for the identification of clusters of significant differences in 2D and 3D (time, frequency and space), effectively controlling for multiple comparisons. Clusters were defined as significant if the probability of observing larger effects from shuffled data was below 5%. The cluster-level test statistic is defined as the sum of the t statistics in 2D or 3D space in the respective cluster. For the identification of the probable neuronal generators of the observed sensor effects, statistical comparisons at the source level were computed using dependent-samples t-tests. Results on the source level were thresholded and corrected for multiple comparisons using AlphaSim (http://afni.nimh.nih.gov/afni/).

Reaction tendencies were computed as a representation of the individual's behaviour. This relative proportion of "fusion" reactions (number of "fusion" trials divided by the number of all incongruent trials; high numbers indicate a large tendency towards a fused percept) in all incongruent trials was correlated with the individual differences (cortical activity or functional connectivity for the "fusion" trials versus "unimodal" trials) at the source level for the time-frequency analyses. This analysis indicates with which neuronal processes the inter-individual predisposition to perceive the McGurk illusion is associated.

All aspects of offline treatment of the MEG signals were accomplished using fieldtrip (Oostenveld, Fries, Maris, & Schoffelen, 2011), an open source signal processing toolbox for Matlab (www.mathworks.com). Anatomical structures corresponding to the statistical effects are labelled according to the Talairach atlas.

2.3. Results:

2.3.1. Behavioural Data:

Participants were presented with audio streams and either matching or mismatching videos. After each video, subjects had to report their perception, which in the case of incongruent audiovisual input could either be a fusion of the auditory and visual input or a perception of only one modality ("unimodal"). In the analysis of the reaction tendency, which was computed as the relative proportion of "fusion" responses in all incongruent trials, we found no difference between the reaction tendencies towards a "fusion" versus a "unimodal" response ($t = -0.8784$, $df = 16$, $p = 0.39$, see figure 1B for details).

2.3.2. Event-Related Activity:

Event-related activity was compared between the "fusion" trials and the "unimodal" trials and revealed differential activity for both response categories. The amplitude in the "fusion" trials was significantly more pronounced between 550 ms and 650 ms after the sound onset ($p < 0.05$, figure 2A) in a left fronto-parietal sensor cluster (figure 2B). Source analysis using the LCMV beamformer (Van Veen et al., 1997) suggests that the left middle temporal gyrus (lMTG) is the source of this difference (MNI coordinates [-56 -47 2], $p < 0.05$, figure 2C). This indicates a differential processing between the two perceptual categories arising approximately 100 ms post-stimulus offset. The lMTG as well as the lSTG have been reported to be involved in the processing of audiovisual stimuli in hemodynamic (Calvert et al., 2000); (Beauchamp, Lee, Argall, & Martin, 2004) and electrophysiological (van Wassenhove et al., 2005; Besle et al., 2008; Arnal et al., 2009; Cappe et al., 2010) studies. Moreover, Saint-Amour et al., (Saint-Amour, De Sanctis, Molholm, Ritter, & Foxe, 2007) and Möttönen et al., (Möttönen et al., 2002) have reported mismatch processing in the left temporal lobe for congruent versus incongruent audiovisual stimuli showing that incongruence in the visual modality elicits auditory mismatch responses.

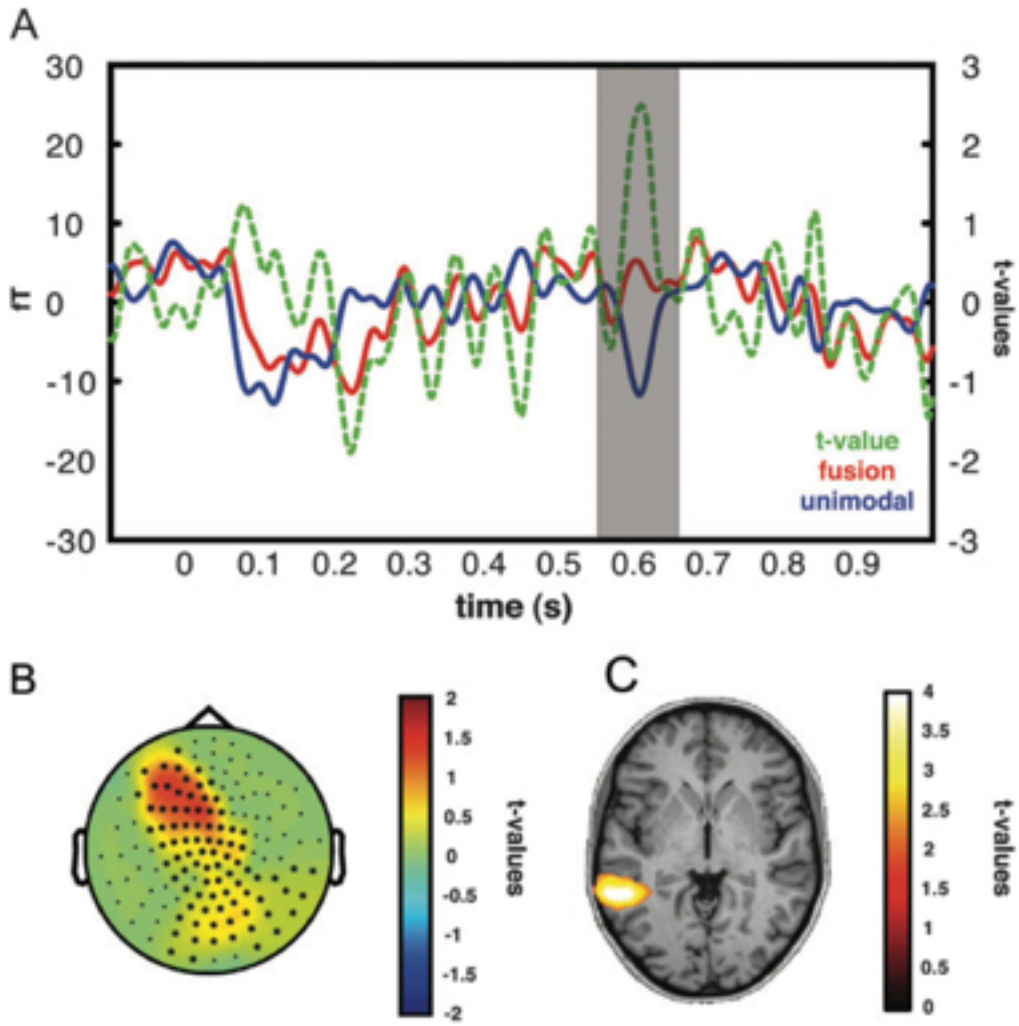

Figure 2:

Summarised results of the timecourse-analysis. (A) Event-related field trace of the positive sensor cluster for the "fusion" (red), and "unimodal" (blue) trials as well as the t-values for the comparison between the two conditions (green). (B) Topography (t-values, "fusion" vs. "unimodal" trials) of the positive sensor cluster (masked for statistical significance) found in the statistical analysis between 550 ms and 650 ms after sound onset. (C) Source projection (t-values, "fusion" vs. "unimodal" trials) of the effect found in the ERF analysis based on the LCMV analysis masked for statistical significance.

2.3.3. Oscillatory Activity:

We were specifically interested in the influence of ongoing oscillatory brain activity on varying perception of an invariant physical stimulus. For this purpose, we statistically compared the non-baseline corrected time-frequency representations of fusion and unimodal trials (see Methods). This analysis revealed two significantly different clusters in time-frequency-sensor space of oscillatory activity between the “fusion” and “unimodal” trials: one positive before sound onset (i.e., greater power in the “fusion” trials) and one negative after sound onset (i.e., less power in the “fusion” trials).

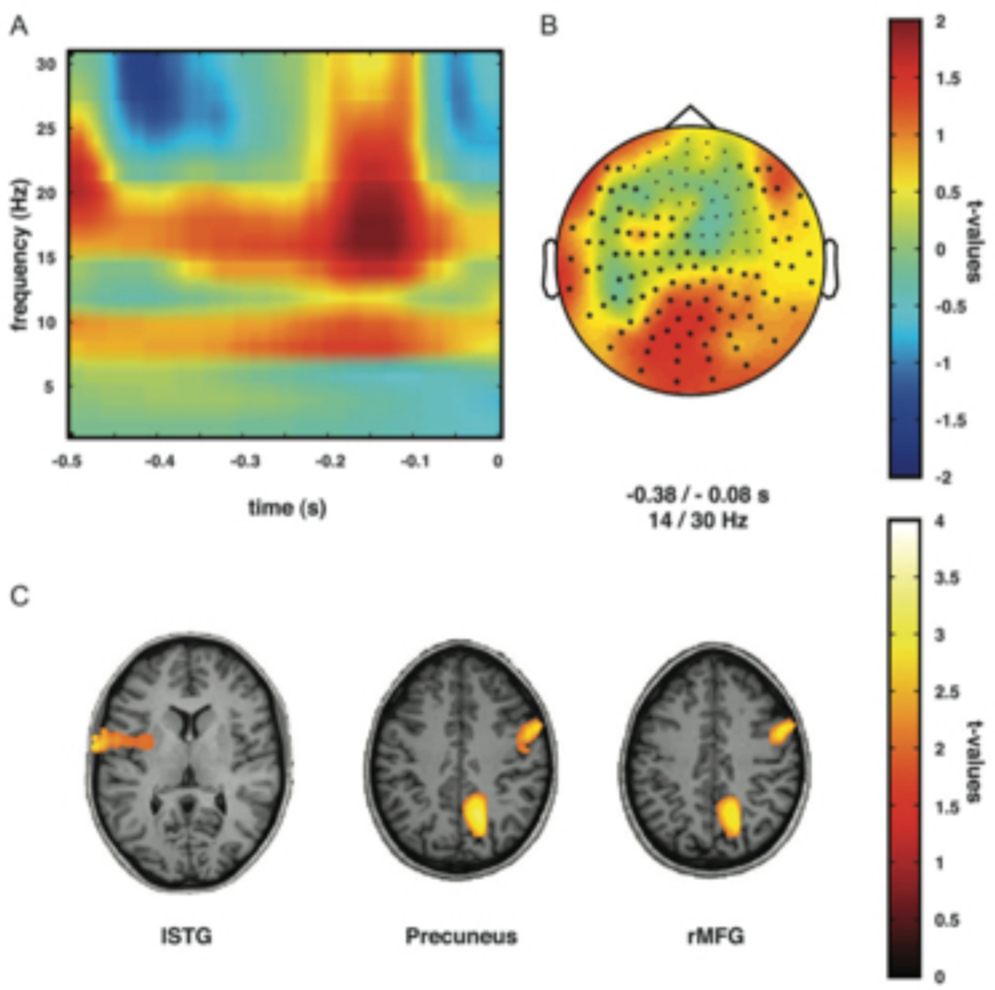

Figure 3:

Summarised results of the pre-stimulus time-frequency-analysis. (A) Time-frequency representation of the pre-stimulus interval at sensor level for the comparison between “fusion” and “unimodal” trials. Time 0 ms indicates the onset of mouth movement and audio stream. (B) Topography (14-30 Hz, -380 to -80 ms) of the positive beta band cluster found in the pre-stimulus interval at sensor level for the comparison between “fusion” and “unimodal” trials. (C) DICS source projection of the beta band effect found at sensor level. Left superior temporal gyrus (left), precuneus (middle) and right middle frontal gyrus (right) were identified as possible generators of the beta band effect. Displayed are t-values of the comparison between trials with a “fusion” percept versus a “unimodal” percept masked for statistical significance.

2.3.4. Pre-stimulus Activity:

From -380 ms to -80 ms before the sound onset, the “fusion” trials produced greater beta-band (14-30 Hz) power ($p<0.05$). The nonparametric permutation analysis revealed a sensor cluster comprised of bilateral fronto-temporal and parietal sensors in which this difference reached significance (figure 3A and B), indicating different perception depending on the pre-stimulus brain state. Recently, Hipp et al. (Hipp et al., 2011) have reported on perception-related beta-synchrony network in audiovisual perception, although no power-effects were found. In contrast to experiments with unimodal visual near-threshold stimuli (Hanslmayr et al., 2007; Romei et al., 2010), no effects were found in the alpha band. Due to the low spatial acuity of topographic sensor maps, a correct interpretation of the results requires the identification of possible cortical generators. Beamformer source analysis (DICS, Gross et al., 2001) suggests that three sources are involved in the generation of the effect found at the sensor level: left superior temporal gyrus (lSTG, [-75 1 7], $p < 0.05$), precuneus ([14 -60 38], $p < 0.05$) and right middle frontal gyrus (rMFG, [53 5 42], $p < 0.05$, figure 3C). This underscores the role of the lSTG in the perception of the McGurk effect, as suggested by Beauchamp et al. (Beauchamp et al., 2010) and partially overlaps with regions of a beta synchronised functional network proposed by Hipp et al. (Hipp et al., 2011) consisting of frontal, posterior parietal and lateral occipital areas. A high positive correlation between the reaction tendency towards the “fusion” percept and the voxel-wise beta power difference values for the comparison between “fusion” and “unimodal” trials was found in the right inferior frontal gyrus ($r \sim 0.81$, rIFG, [67 28 4], $p < 0.001$, see figure 4). This underlines the involvement of frontal processes in this effect. Importantly, while pre-stimulus beta band power in left STG differentiated between the "unimodal" and "fusion" trials, power levels in this region did not linearly correlate with the reaction tendency. This indicates that processes at the level of the left STG alone may be insufficient in explaining an upcoming illusory percept and suggests, that information from this region needs to be efficiently distributed to distant cortical regions.

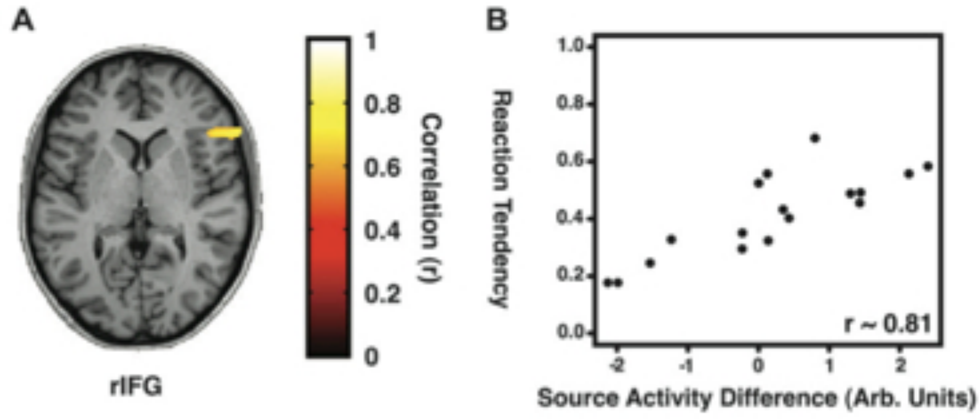

Figure 4:

Correlation between the tendency towards a "fusion" percept and the voxel-wise power difference values for the comparison between "fusion" and "unimodal" trials. Right inferior frontal gyrus (A) displayed a high positive correlation (B) with the "fusion" versus "unimodal" power difference. Displayed are correlation indices r masked for statistical significance. Positive reaction tendency indicates a high tendency towards a "fusion" percept.

In order to test this hypothesis, the left STG as the primary source identified by DICS and suggested by the literature was subsequently chosen as the seeding region of interest for the analysis of phase synchrony with all other voxels. In line with Hipp et al. (Hipp et al., 2011), we found a significant difference between the two perceptual categories in the beta band. The analysis of phase synchrony between the left STG and the whole brain volume revealed an increase ($p < 0.001$) in phase synchrony for the "fusion" trials relative to "unimodal" trials with left middle frontal gyrus and right middle temporal gyrus as well as a decrease ($p < 0.001$) in phase synchrony with medial frontal and bilateral superior temporal gyrus as well as left fusiform gyrus (see figure 5A). Notably, we found a decrease in phase synchrony with the left BA22, while the beta band power increase was found in our seeding region in the left STG. Phase synchrony correlated highly ($p < 0.001$) with the tendency towards the fusion percept in the bilateral superior parietal areas, cingulum, left middle occipital gyrus and right posterior superior temporal gyrus. Negative correlations ($p < 0.001$) were found in the right anterior superior temporal gyrus and the right inferior temporal lobe (see figure 5B). In sum, these results suggest that the functional connection between the left STG and the frontal and parietal areas as well as the disconnection from inferior temporal areas and the BA22 prior to stimulus onset facilitates subsequent multimodal information integration.

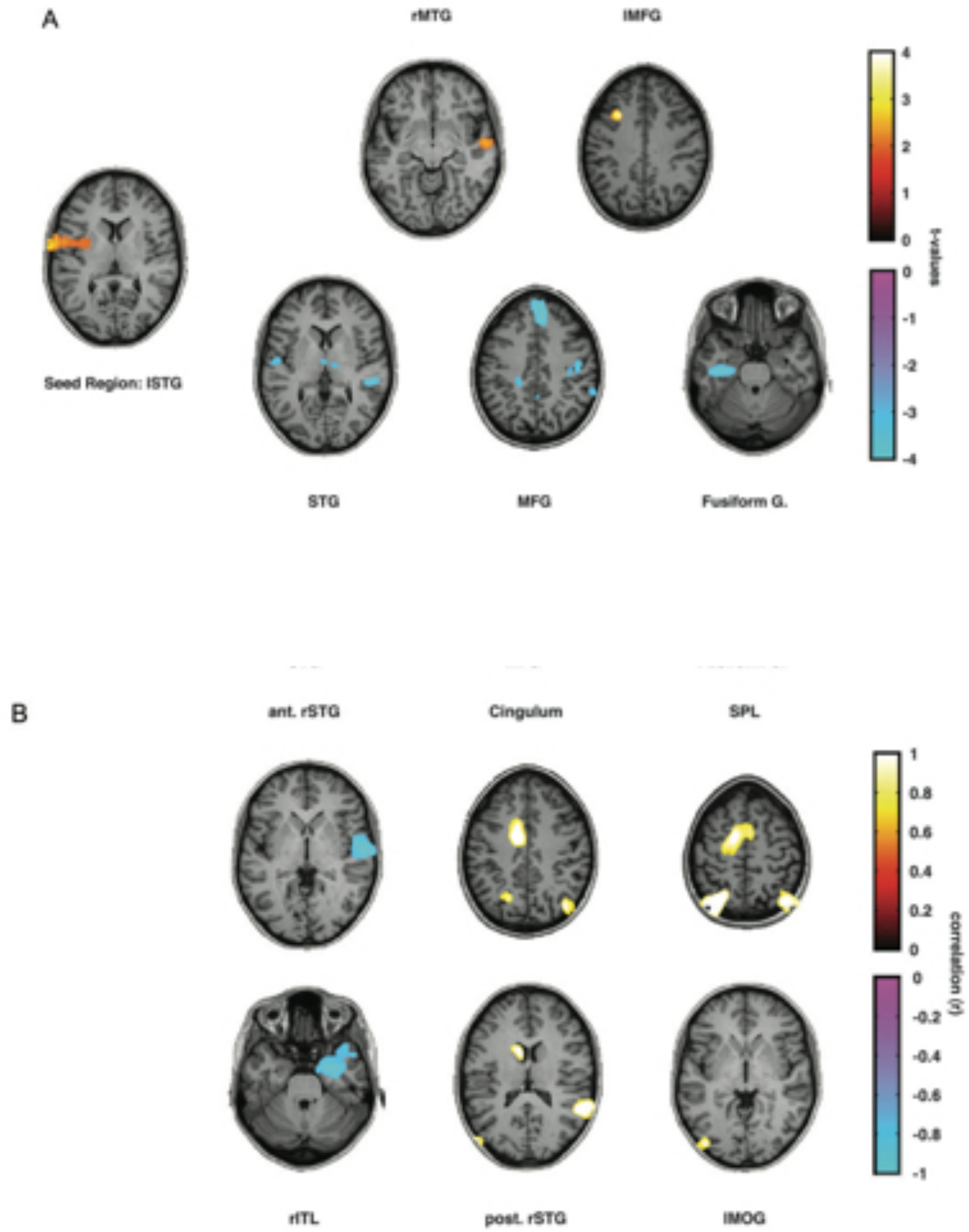

Figure 5:

Phase synchrony between the seed region in left superior temporal gyrus (far left) and the whole brain volume as well as correlation with the tendency towards a “fusion“ percept. (A) Displayed are t-values of the comparison between trials with a “fusion” percept versus a “unimodal” percept masked for statistical significance. Right middle temporal gyrus (top left) and left middle frontal gyrus (top right) were found to be functionally coupled to the lSTG. Bilateral superior temporal gyrus (bottom left), medial frontal gyrus (bottom middle) and left fusiform gyrus (bottom right) were found to be functionally decoupled from the lSTG. (B) Correlation between the tendency towards a “fusion” percept and the voxel-wise difference values for the comparison between “fusion” and “unimodal” trials for the phase synchrony with the lSTG. Displayed are correlation indices r masked for statistical significance. Anterior right superior temporal gyrus (top left) and right inferior temporal gyrus (bottom left) displayed high negative correlations. Bilateral superior parietal lobule (top right), cingulum (top middle), posterior right superior temporal gyrus (bottom middle) and left middle occipital gyrus (bottom right) displayed high positive correlations.

2.3.5. Post-Stimulus Activity:

From 200 ms to 600 ms after sound onset, the “fusion” trials produced less theta-band (3-7 Hz) power ($p<0.05$) than the "unimodal" trials. The nonparametric permutation analysis revealed a bilateral frontal and parietal sensor cluster in which this difference reached significance (figure 6A and B). Source analysis was again used to indentify possible cortical generators of this effect. Beamformer source analysis (DICS, (Gross et al., 2001) suggested Cuneus ([9 -84 5], $p < 0.05$), left superior frontal gyrus ([-14 47 39], $p < 0.05$) and precuneus ([-20 -69 50], $p < 0.05$) as the sources of the effect found at the sensor level (figure 6C).

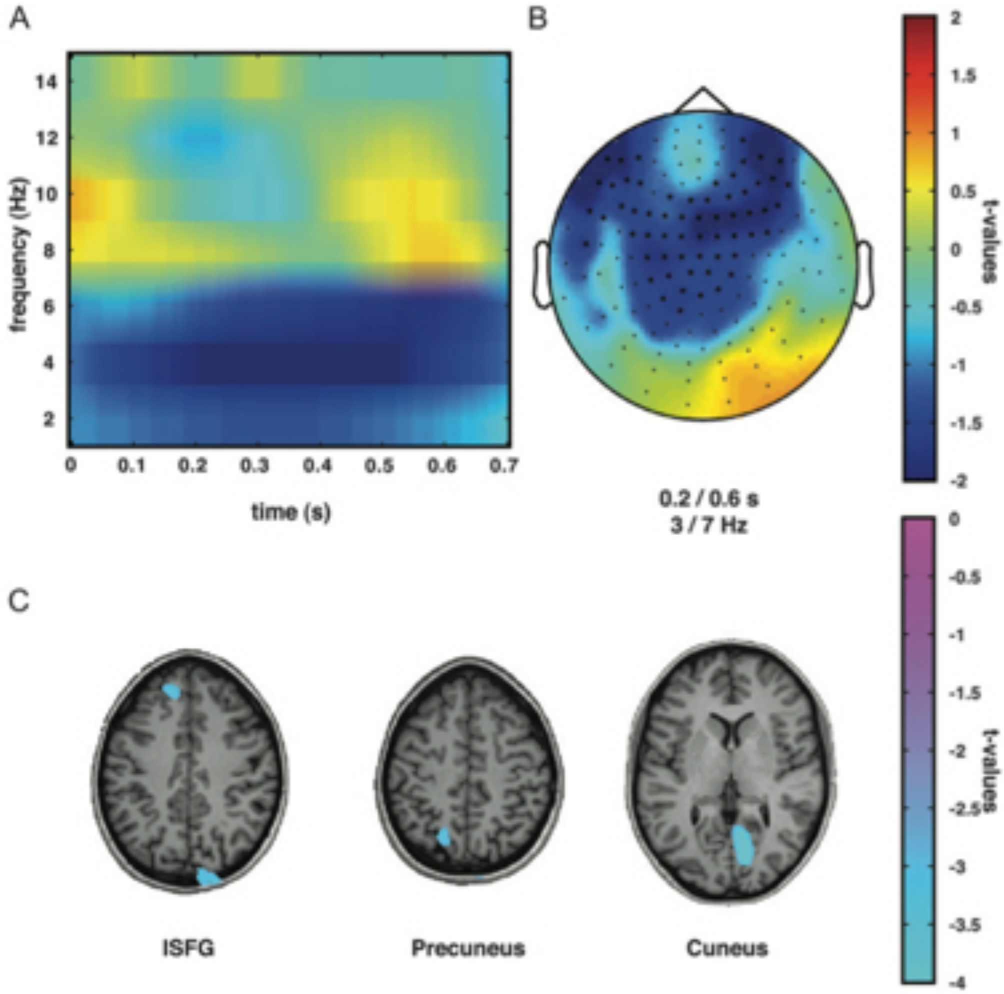

Figure 6:

Summarised results of the post-stimulus time-frequency-analysis. (A) Time-frequency representation of the post-stimulus interval at sensor level for the comparison between "fusion" and "unimodal" trials. Time 0 ms indicates the onset of mouth movement and audio stream. (B) Topography (3-7 Hz, 200 to 600 ms) of the negative theta band cluster found in the post-stimulus interval at sensor level for the comparison between "fusion" and "unimodal" trials. (C) DICS source projection of the theta band effect found at sensor level. Left superior frontal gyrus (left), precuneus (middle) and cuneus (right) were identified as possible generators of the theta band effect. Displayed are t-values of the comparison between trials with a "fusion" percept versus a "unimodal" percept masked for statistical significance.

Between the reaction tendency towards the "fusion" percept and voxel-wise power difference values between "fusion" and "unimodal" trials we found a high positive correlation in the right superior frontal gyrus (rSFG, [25 63 19], $r \sim 0.76$, $p < 0.05$) and a high negative correlation in the right inferior frontal gyrus (rIFG, [50 36 -12], r~-0.72, $p < 0.05$, figure 7). The timing of this effect, the location of the generators of the theta band modulation as well as the areas correlating with behavior point to a processing of mismatching information (Keil, Weisz, Paul-Jordanov, & Wienbruch, 2010). This has already been reported numerous times in the analysis of the McGurk effect (Möttönen et al., 2002; Saint-Amour et al., 2007) and has been indicated by our analysis of event-related activity. Since the theta effects did not point to the involvement of left STG either at a differential level (i.e., comparing the conditions) or at a correlative level, we refrained from further analysis of functional connectivity for the post-stimulus period.

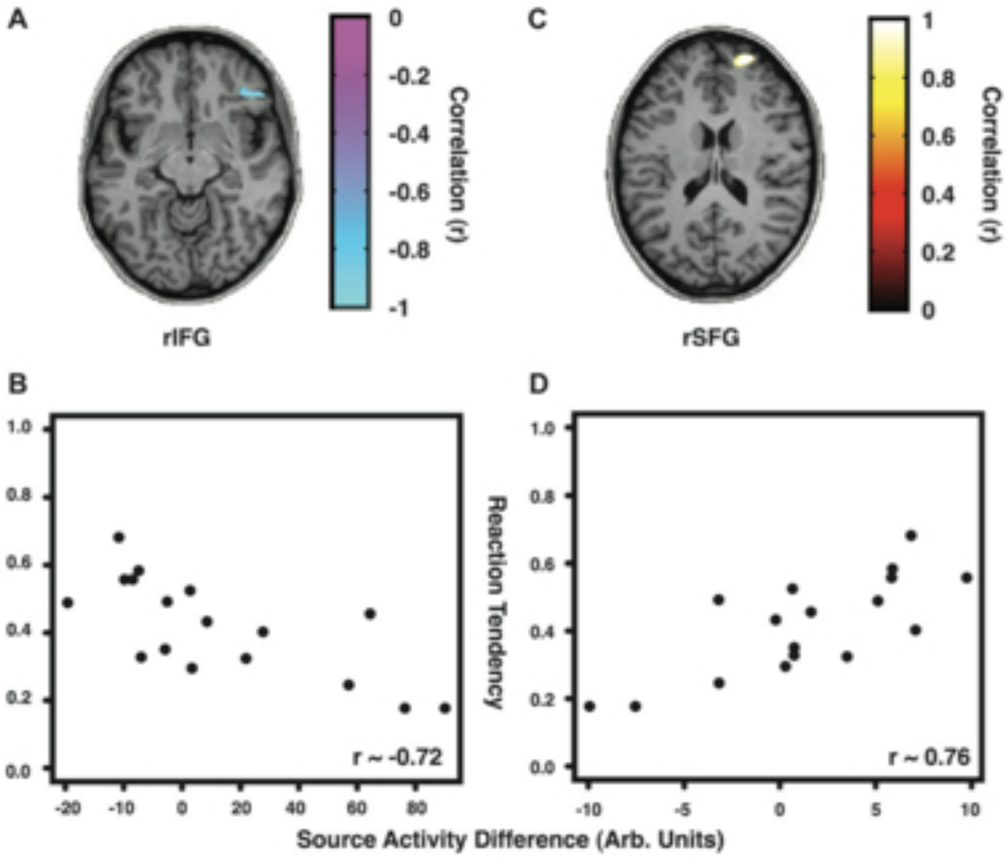

Figure 7:

Correlation between the tendency towards a "fusion" percept and the voxel-wise power difference values for the comparison between "fusion" and "unimodal" trials. Right inferior frontal gyrus (A and B) displayed a high negative correlation. Right superior frontal gyrus (C and D) displayed a high positive correlation with the "fusion" versus "unimodal" power difference. Displayed are correlation indices r masked for statistical significance. Positive reaction tendency indicates a high tendency towards a "fusion" percept.

2.4. Discussion:

Increasing evidence demonstrates that conscious perception requires brain states marked by specific patterns of oscillatory brain activity expressed in local modulations of synchronous activity and synchronised activity between brain regions. Most of the support for this notion comes from studies of visual modality that examine whether or not a stimulus was perceived (e.g., near-threshold stimuli; (Kranczioch, Debener, Maye, & Engel, 2007; Hanslmayr et al., 2007; Romei et al., 2010). The overwhelming majority of these studies show a relationship between visual cortex alpha activity and behaviour. They indicate that for "simply" perceived versus not perceived distinctions, low-level visual cortical regions must be in a relatively desynchronised alpha state, reflecting an increased excitability of visual regions. Our study embraces the notion of the relevance of pre-stimulus states, but surpasses previous studies in two important regards. First, we investigated the relevance of pre-stimulus brain states with respect to a conceptually more complex type of perception (i.e., audiovisual integration) and contrasted two categories of perception. We specifically aimed at identifying neurophysiological processes that upon invariant incongruent stimulation differentiate occasions when participants perceive an illusion from those when, they do not. Thus, the distinction relevant to our study concerned the content of the percept rather than whether or not a stimulus was perceived. A popular notion within perception research is that increasingly complex types of perception (e.g., of objects or faces) require the activation of distinct cortical association regions (Kanwisher, 2000), also known as "essential nodes" (Zeki & Bartels, 1998; Zeki, 2003; Koch, 2004). The left STG is one brain region that has frequently been considered as such an essential node with respect to the McGurk illusion and audiovisual integration in general (Beauchamp et al., 2004; Barraclough et al., 2005; Stevenson & James, 2009; Dahl et al., 2010). Secondly, our study also surpasses previous efforts since it focuses on the influence of pre-stimulus functional network states on complex speech perception at the source level rather than at the surface sensor level. Trial-by-trial fluctuations have been reported at the sensor level (Kranczioch et al., 2007; Hanslmayr et al., 2007), but on top of missing statements about which brain regions (de-)couple, the sensor approach strongly suffers from the confounding factor of volume conduction. This confounding factor is strongly attenuated at the source level, particularly with the use of adaptive linear spatial filtering (‘‘beamforming’’, (Schoffelen & Gross, 2009). The influence of oscillatory synchronisation has recently been demonstrated (Hipp et al., 2011), but only with respect to a simple ambiguous audiovisual stimulus.

The main findings of this investigation are: 1) the perception of the McGurk illusion is marked by relatively increased pre-stimulus beta activity in distributed cortical regions, in particular the left STG; 2) compared to unimodal perceptions, audiovisual integration is characterised by a complex pattern of beta-band coupling and decoupling of the left STG with frontal and temporal regions; and 3) the interindividual tendency to "fuse" auditory and visual information is not marked by absolute power increases in the left STG per se, but by increased right frontal beta activity, increased coupling of the left STG with frontoparietal areas and decreased coupling with right temporal areas.

2.4.1. The Perception Of The McGurk Illusion Is Marked By Relatively Increased Pre-Stimulus Beta Activity In Distributed Cortical Regions

Several studies have already been performed on the comparison between congruent and incongruent audiovisual stimuli with regard to post-stimulus activity (Senkowski et al., 2008). However, this does not take into account the current brain state at the time when sensory stimulation impinges on ongoing and constantly fluctuating brain activity. Whereas the STG is more strongly activated by congruent than by incongruent stimuli – thus pointing to a role in integrating highly correlated information (Beauchamp et al., 2004), we found more pronounced activity in the lMTG posterior to the STG in the ERF analysis in the “fusion”-trials, suggesting a stronger activation for perceived congruence. It has been shown that presenting auditory stimuli along with incongruent visual information elicits auditory mismatch responses in temporal cortical areas (Möttönen et al., 2002; Saint-Amour et al., 2007). More importantly, we identified the relative pre-stimulus increase of oscillatory activation in lSTG prior to a “fusion” percept compared to a “unimodal” percept within the identical incongruent stimulus category. This suggests that it is not only the congruency that activates the lSTG and possibly lMTG, but also that effective integration of multiple sensory information streams depends on prior activation. Local beta band power might reflect the predisposition of the left STG for integrating multimodal information. Furthermore, whereas lSTG activation putatively reflects a predisposition towards multi-sensory integration, the perception of this integration, which we see in the present illusion, might also depend on inter-areal coupling of this region at pre-stimulus stages via phase-coupled oscillations in the beta range. Thus, STG could indeed be an essential node for audiovisual integration, whose output however needs to spread to "workspace" regions (Dehaene et al., 2006); see below) in order to become consciously accessible. A recent review (Senkowski et al., 2008) presents the hypothesis that it is likely that post-stimulus multimodal processing in natural environments depends on a complex network involving frontal, parietal and temporal regions as well as primary sensory areas rather than a direct synchronisation between early sensory areas. However, regardless of the precise functional cause, our study clearly argues for the importance of pre-stimulus "states" in the case of the left STG. Without any direct experimental control of the "baseline" period it is not possible to state to what extent fluctuating levels of selective attention could promote illusory "fusions". Importantly, by showing that the illusory percept depends on the pre-stimulus integration of the multi-sensory region (left STG) into a distributed cortical network, our study implies that these mechanisms form a predisposition prior to stimulation rather than being elicited by the incongruent stimulus itself. It is however worth noting that, at post-stimulus intervals, differences in event-related activity between the conditions were identified in the left MTG ~100ms following stimulus offset, whereas the relatively decreased level of induced theta activity in the illusion condition was mainly localised to the superior frontal gyrus, cuneus and precuneus. Whereas the varying durations of the audio stream in the various videos could explain the long duration of the induced theta-band modulation, the present post-stimulus results of theta-band modulation as well as the difference in the event-related activity could represent a more general mismatch detection process (Keil et al., 2010).

This mismatch detection process likely works at higher cognitive levels rather than at the sensory level, as conflicting information must be coordinated with behaviour. Calvert (Calvert et al., 2000) argues that although integration of modality-specific information occurs in the STG, it may be followed by more elaborate processing in upstream heteromodal areas (MTG). Importantly, we compared brain responses within a stimulus category and thereby excluded strong mismatches of the physical stimulus features, which can be found when comparing between stimulus categories. Our results point to a differential processing of perceived stimulus quality in absence of changes in stimulus material.

2.4.2. Audiovisual Integration Is Characterised By A Complex Pattern Of Beta-Band Coupling And Decoupling Of Left STG With Frontal And Temporal Regions

In addition to hinting at the importance of functional coupling of the left STG with parietal and frontal areas, our data indicate a pre-stimulus functional decoupling of the left STG from regions processing voice (BA22) and facial information (left fusiform region). This counterintuitive result could suggest a relevant representational state that favours a McGurk illusion: a stronger integration of both sensory streams, resulting in an illusory percept in the case of incongruent information, could be a consequence of "filling in" mechanisms required in the case of degraded unimodal information to the left STG (Pessoa & De Weerd, 2003). Reduced functional coupling between left multimodal integration regions and lower level sensory areas at pre-stimulus intervals may constitute a predisposition for a subsequently degraded representation of the separate unimodal information. Since the sensory cues from the individual modalities will not suffice in developing a coherent representation, the enhanced pre-stimulus beta activity in the left STG could then be interpreted as a compensatory mechanism for more efficient information integration from both modalities. Conflicting or ambiguous information will then be fused to a percept of a non-existing stimulus. Interestingly, we observed a decoupling from left BA22 despite the local power increase in the left STG and an approximately 2 cm (MNI space) distance between the sources. This indicates not only independence between phase synchrony and power as well as the power of beamformer source analysis to segregate activity from sources in spatial proximity (Gross et al., 2004), but also underscores the role of the left STG as a multi-sensory region that integrates information from lower level sensory areas.

Taken together, our results of pre and post-stimulus effects underscore the importance of state dependency on multimodal integration as well as perception. This finding confirms and extends a recent TMS report (Beauchamp et al., 2010) showing that application of TMS to the left STG is most efficient in reducing illusory McGurk percepts if applied during a time window between -100 ms and 100 ms relative to stimulus onset. Crucial for our interpretations, we did not apply so-called "baseline corrections" to our data but directly compared the output of the time-frequency calculation. By applying “baseline corrections", the strong pre-stimulus effect would have falsely led to effects in the post-stimulus interval. Whereas it is likely that the pre-stimulus frontal and parietal areas found here represent non-sensory higher-order brain regions, we cannot rule out the possibility that these regions are also directly activated by multimodal input, since most studies in this area recorded single or multiunit activity only from a spatially restricted region of interest (usually the STG, based on anatomical connections to the auditory and visual cortex; (Ghazanfar et al., 2008)) or BOLD activity with a low temporal resolution (Calvert et al., 2000). Hipp and colleagues (Hipp et al., 2011) have recently suggested the involvement of a fronto-parieto-occipital beta-band network in audiovisual perception, but more studies using time-sensitive methods with broad spatial coverage (e.g. EEG, MEG, ECoG or TMS) are required in order to shed light on this issue.

2.4.3. Fusion Between Auditory And Visual Information Is Marked By Power Increases In Right Frontal Cortex And Modulated Coupling Of Left STG With Frontoparietal And Temporal Networks

In accordance with the data presented above and the existing literature on hemodynamic studies (Beauchamp et al., 2004; Ghazanfar et al., 2008; Stevenson & James, 2009), intracranial recordings (Barraclough et al., 2005; Besle et al., 2008; Dahl et al., 2010), EEG studies (van Wassenhove et al., 2005; Cappe et al., 2010) and MEG studies (Arnal et al., 2009), we argue that while the STG is a locus of multimodal information integration, the subsequent conscious perception of this integration depends on a larger distributed network that communicates via phase synchronised activity in the beta band. The correlation between local beta activity and the tendency to subsequently perceive the McGurk effect as well as the enhanced communication with a frontoparietal system may therefore signify a top-down initiated, enhanced predisposition to integrate upcoming information and a more efficient transfer of this multi-sensory information to consciousness or attention-relevant brain regions.

The impact of functional connectivity states at pre-stimulus intervals has rarely (Beauchamp et al., 2010) been reported with specific regards to conscious perception, yet post-stimulus functional network involvement has been indicated several times (Dehaene et al., 2006; Melloni et al., 2007). Recent notions suggest that we only become aware of representations in sensory and association areas if these engage a distributed frontoparietal ("workspace") system (Dehaene et al., 2006). We argue that network processes reflected by modulation of both local power and long-range synchrony could already systematically determine multimodal integration at a pre-stimulus level. Local computations in the STG might be insufficient in eliciting a conscious percept and require an efficient transfer of processed information to a frontoparietal network, reflected in the focal frontal correlation of beta power and the individual tendency to perceive an audiovisual fusion. Whereas coupling between the left STG and frontal and parietal areas might represent integration into a consciousness network, decoupling of sensory areas from the left STG can be equally as important for illusory perceptions as discussed above. This is underlined by correlations with the individual tendency to perceive a fusion. Parietal and frontal areas as well as areas on the border between temporal, parietal and occipital cortex show a high correlation between beta band coupling and the individual perception tendency. Right temporal areas show a decreased beta band coupling with left STG, that is negatively correlated to the individual tendency to perceive a fusion. Hein et al. (Hein & Knight, 2008) recently proposed, that the function of superior temporal areas varies depending on the task. The present results could thus indicate, that relative decoupling represents a statistically increased coupling favouring unimodal perception. In this way, a unimodal versus a fused perception depends on the current state of coupling within a larger perception-related network and the left STG.

2.4.4. Conclusion:

Previous research has demonstrated the role of the left STG in multisensory information processing. In this study, we show for the first time that the conscious (illusory) percept of a fusion between auditory and visual information, as seen in the McGurk effect, critically depends both on pre-stimulus local beta band activity as well as on the current functional state of a distributed information-processing network. In particular with regards to the left STG, which has been the focus of a lot of research as a region of audiovisual integration, our results imply that ongoing pre-stimulus fluctuations of oscillatory activity as well as fluctuating integration of this region into a distributed network form predispositions whether different sensory streams will be fused or not. For the left STG this predisposition effect appears to be more important than the actual processes elicited by the delivery of the stimulus. A hypothesis derived from our results is that the McGurk illusion is promoted when the functional state prior to stimulus onset favours a degraded representation of unimodal information in the left STG (decoupling effects). This stimulates a more efficient integration of the degraded individual sensory streams in order to produce a coherent percept (local power effect). Furthermore, in order to consciously perceive the illusory percept, "incorrectly" integrated information from the left STG has to be transferred to frontoparietal systems (coupling effects).

3. Second study: Pre-Stimulus Beta Power and Phase Synchrony Influence the Sound-Induced Flash Illusion.

3.1. Introduction:

In “The Organization of Behavior”, Hebb (Hebb, 1949) stated that “electrophysiology of the central nervous system indicates [...] that the brain is continuously active [...] and an afferent excitation must be superimposed on an already existent excitation. It is therefore impossible that the consequence of a sensory event should often be uninfluenced by the existing activity“. It is surprising that the brain state at time of sensory stimulation has only recently become a focus of research. A number of researchers (Romei et al., 2010; Hanslmayr et al., 2007; Van Dijk et al., 2008) have reported on pre-stimulus fluctuations and perception. Whereas these studies focus on perceived-versus-not-perceived distinctions between visual stimuli influenced by modulations in alpha band activity, we recently showed that pre-stimulus beta band activity in multisensory regions influences the perception of an audiovisual illusion— a condition in which participants are *always* report a percept. Beta band activity is often reported alongside alpha band modulations but has received less attention. Laufs (Laufs, Krakow, Sterzer, Eger, & Beyerle, 2003) suggested that beta band oscillations index spontaneous cognitive operations during rest. Modulations in beta band activity may constitute a crucial feature for varying perceptual predispositions. Engel and Fries (Engel & Fries, 2010) put forward that beta band activity is associated with endogenous top-down influences in the cognitive domain. Using the McGurk effect (Keil, Müller, Ihssen, & Weisz, 2011), we showed that beta power in left STG and phase coupling to frontal and parietal and decoupling from auditory and visual sensory areas abets audiovisual integration and illusory perception. Using a tactile-visual double-flash paradigm, Lange et al. (Lange et al., 2010) also reported on modulations in the beta range. Hipp et al. (Hipp et al., 2011) tell of beta band modulations in large-scale cortical networks playing a role in perception of bistable, ambiguous stimuli. The SIFI (Shams et al., 2000), however, does not consist of bistable, ambiguous stimuli, but a single visual stimulus is accompanied by two auditory stimuli. Both stimuli are salient in isolation and don‘t produce a high number of false responses. Their combination, however, results in an illusion of a second visual stimulus. Previous studies (Shams, Kamitani, Thompson, & Shimojo, 2001; Shams, Iwaki, Chawla, & Bhattacharya, 2005; Mishra, Martinez, Sejnowski, & Hillyard, 2007; Mishra, Martinez, & Hillyard, 2010) report rates of illusion between ~45 % and 81 % of trials and report modulations of visual cortex through sound as well as interactions between audiovisual and auditory and visual stimulation. These studies have concordantly identified superior temporal regions alongside primary visual and auditory regions as a source of this effect. Mishra et al. (Mishra et al., 2010) argue that this is not due to a response bias but to a perceptual experience of the illusion. Cappe et al. (Cappe et al., 2010) agree with this as they found distinct configurations of cortical sources associated with audiovisual stimuli.

In the present study we are interested in pre-stimulus states that predispose audiovisual integration and inter-areal synchronisation. We hypothesise that both aspects of macroscopic activity determine the flow of information once the stimulus impinges on the system. A special emphasis was placed on pre-stimulus beta band dynamics.

3.2. Materials and Methods:

3.2.1. Subjects:

14 (1 male, 13 female, mean age 23.6) paid human volunteers participated in this study. All participants gave their written informed consent. All participants were right-handed, had normal hearing and normal or corrected-to-normal vision. Prior to the experiment,

participants received detailed instructions regarding the procedure of the experiment and subsequently gave their written informed consent. The procedures of the experiment were approved by the Ethics Committee of the University of Konstanz.

3.2.2. Experimental Design and Apparatus:

The experiment consisted of 600 trials in which we presented small dots and short tones in four blocks of 150 trials each. The stimuli were presented via Psyscope X (http://psy.ck.sissa.it/) on a MiniMac (Apple Inc.). 390 trials contained the critical mismatching stimuli (1 dot, 2 tones). We followed the description of Shams (2002, experiment 2) in the presentation of stimuli. A fixation cross was displayed throughout the entire stimulus presentation. Visual stimuli were presented for 17 ms, auditory stimuli for 7 ms, and the second stimuli followed after an inter-stimulus interval of 50 ms (see figure 8A). In order to make the onset of stimulation unpredictable, a random pause between 700 ms and 1400 ms was inserted between the onset of the fixation cross and the presentation of stimuli. Using a forced choice task with a 500-ms delay following stimulus offset, participants had to indicate whether they had perceived zero, one or two visual stimuli by pressing a button. The important dependent variable in this investigation was thus the subjectively perceived content of the audiovisual sensation. The visual stimuli were presented on a screen inside the magnetically shielded MEG acquisition room using a video projector (DLA-G11E, JVC, Friedberg, Germany) and a set of mirrors positioned outside the room. The screen was positioned 60 cm above the subject, the fixation cross had a size of 1.5 by 1.5 cm and visual stimuli were presented 5.5 cm below the fixation cross with a radius of 1 cm. The audio stimuli were 1000 Hz sine wave tones presented with an analogue-to-digital converter (Motu 2408) using amplifiers (Servo 200, Samson) and a 6.1-m-long, 4 mm-wide tube system (Etymotic Research, ER30).

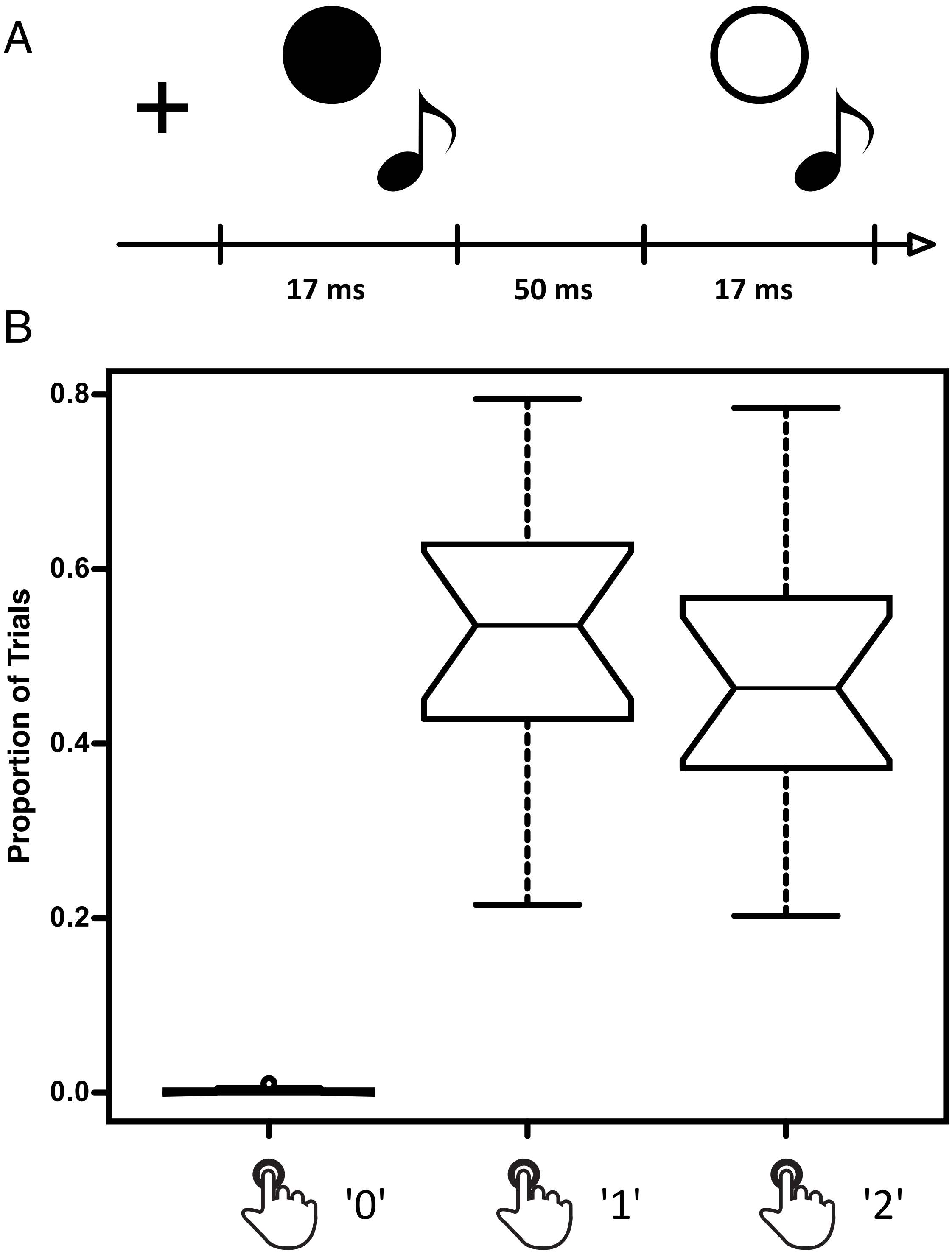

Figure 8:

(A) Schematic representation of a critical trial in the present study. The presentation of the fixation cross was followed by that of a short visual stimulus accompanied by a short auditory stimulus. After an interval of 50 ms, the second auditory stimulus was presented. (B) Behavioral results in the present study. Subjects perceived a sound-induced flash illusion (response „2“) in 46% of critical trials.

3.2.3. Data Acquisition and Analysis:

Magnetoencephalographic (MEG) recording was conducted using a 148-channel magnetometer (MAGNES 2500 WH, 4D Neuroimaging, San Diego, USA). A subject-specific headframe coordinate reference was defined by means of five anatomical landmarks. These head fiducials, five coils, and the subject's head shape were digitised using a Polhemus 3Space Fasttrack at the start of each session. The subject's head position relative to the pickup coils and the MEG sensors were estimated before and after each session to ensure that no large movements occurred during data acquisition.

Subjects were lying comfortably in a supine position. They were instructed to remain still during the stimulation and to avoid eye movements and blinks as much as possible. Continuous data sets were recorded with a sampling rate of 678.17 Hz (bandwidth 0.1 - 200 Hz). A video camera installed inside the MEG chamber allowed the monitoring of subjects' behaviour and compliance throughout the experiment.

After data acquisition, epochs of four seconds (+/- 2s) around stimulus onset were extracted from the raw data. Epochs were visually inspected for EOG or movement artefacts. Critical trials (one visual stimulus and two auditory stimuli) were grouped according to their response into two categories: „no illusion“ (response „1“) and „illusion“ (response „2“). The numbers of trials for the two different categories were equalised for each subject using random omission in order to ensure comparable signal-to-noise ratios for both perceptual categories. Resulting epochs were filtered with a 1-Hz high-pass filter (zero-phase, Butterworth) prior to the analysis of oscillatory activity. As the pre-stimulus activation was the main interest of the study, no baseline was defined and outputs of the sensor- and source-space analysis for the conditions were directly compared. For the analysis of event-related activity, single trials were low-pass filtered using a 30-Hz zero-phase Butterworth filter prior to averaging and were then converted to the root mean square.

For the time-frequency analysis, a wavelet time-frequency transformation with Morlet wavelets was computed (wavelet length = 7 cycles, size of the gaussian taper = 3). Average event-related activity was subtracted from the single trials before computing the time-frequency transformation in order to remove potential effects of dominant evoked response that bled into the baseline period. This procedure resulted in single-trial estimates of oscillatory power between 5 Hz and 40 Hz in 2-Hz steps.

A linear constrained minimum variance beamformer algorithm (LCMV, Van Veen et al., 1997) was used to identify the sources of the effects found in the time-series analysis as well as to localise primary auditory and visual areas for the analysis of connectivity. Source analysis was performed for an activation interval of 265 ms to 280 ms after stimulus onset based on the effect identified at sensor level (see Results) and for the interval of the N1 component (115 ms to 135 ms after stimulus onset for the visual domain and 80 ms to 100 ms for the auditory domain). Spatial filters were computed for the interval between 100 ms and 400 ms after stimulus onset. Here, the baseline was used from -100 ms until -80 ms before stimulus onset with an interval for the computation of the spatial filter between -400 ms and -100 ms before stimulus onset. The source analysis was separately conducted on the waveforms of the two conditions and the difference between the projected sources was computed in the statistical analysis. Dynamic imaging of coherent sources (DICS, Gross et al., 2001) — a frequency-domain adaptive spatial filtering algorithm — was used to identify the sources of the effects found in the time-frequency domain. This algorithm has proven to be particularly powerful in localising oscillatory sources. Source activity was interpolated onto individual anatomical MRI images and subsequently normalised onto a standard MNI brain using SPM8 in order to calculate group statistics and for illustrative purposes.

The functional connectivity of neuronal activity between cortical regions of interest and the whole brain volume was analyzed in terms of phase-locking values (Lachaux et al., 1999).

Phase synchrony was computed for the time and frequency of interest as identified by the sensor-level analysis and for the regions of interest as identified by the source analysis and primary visual and auditory cortices. If the phase differences between two oscillators are constant, these oscillators are likely to interact with each other or share a common driving force. Uniform distributions of phase differences indicate the independence of two oscillators. We first computed sensor-level cross-spectral density (CSD) for the time and frequency range identified in the time-frequency analysis (multitaper analysis, DPSS tapers). These CSD values were then projected into source space by multiplying them with the accordant beamformer spatial filters. Spatial filters were constructed from the covariance matrix of the averaged single trials at sensor level and the respective leadfield by a Linearly-Constrained Minimum Variance (LCMV) beamformer (Van Veen et al., 1997). We subsequently calculated phase-locking values between the regions of interest and all other sources in order to identify the regions in which functional coupling differentiated between subsequent perceptions.

In the present study, we were interested in the degree to which functional connectivity is predictive of upcoming percepts. In order to assess this at the single-trial level, we further examined the functional coupling identified in the phase synchrony analysis. Singe trial complex time-frequency values were thus projected into source space via frequency-domain adaptive spatial filtering (Gross et al., 2001) and the phase for each cortical source was computed from the complex values. For each identified source pair, the single trial phase difference between the sources was subtracted from the mean of the single trial phase difference in order to assess the stability. These deviance values from the mean were sorted into subject-individual quartiles and the proportion of "illusion" trials was computed for each phase quartile. Figure 9 illustrates this approach, which has been similarly used by Hanslmayr and colleagues (Hanslmayr et al., 2007), albeit at the sensor level. To further support this analysis, split the single trial deviance values per subject randomly into two datasets. Then we performed a binomial one-way ANOVA for the effect of phase deviance on perception to fit a generalised linear model for the first dataset. This model was then used to predict the effect of phase deviance on perception. The prediction was subsequently compared with the second dataset using a Chi^2-test. The angle of phase difference between cortical sources for the trials in the four quartiles and power-to-power correlation between cortical sources were computed as a test for spurious synchrony due to local power increase or volume conduction.

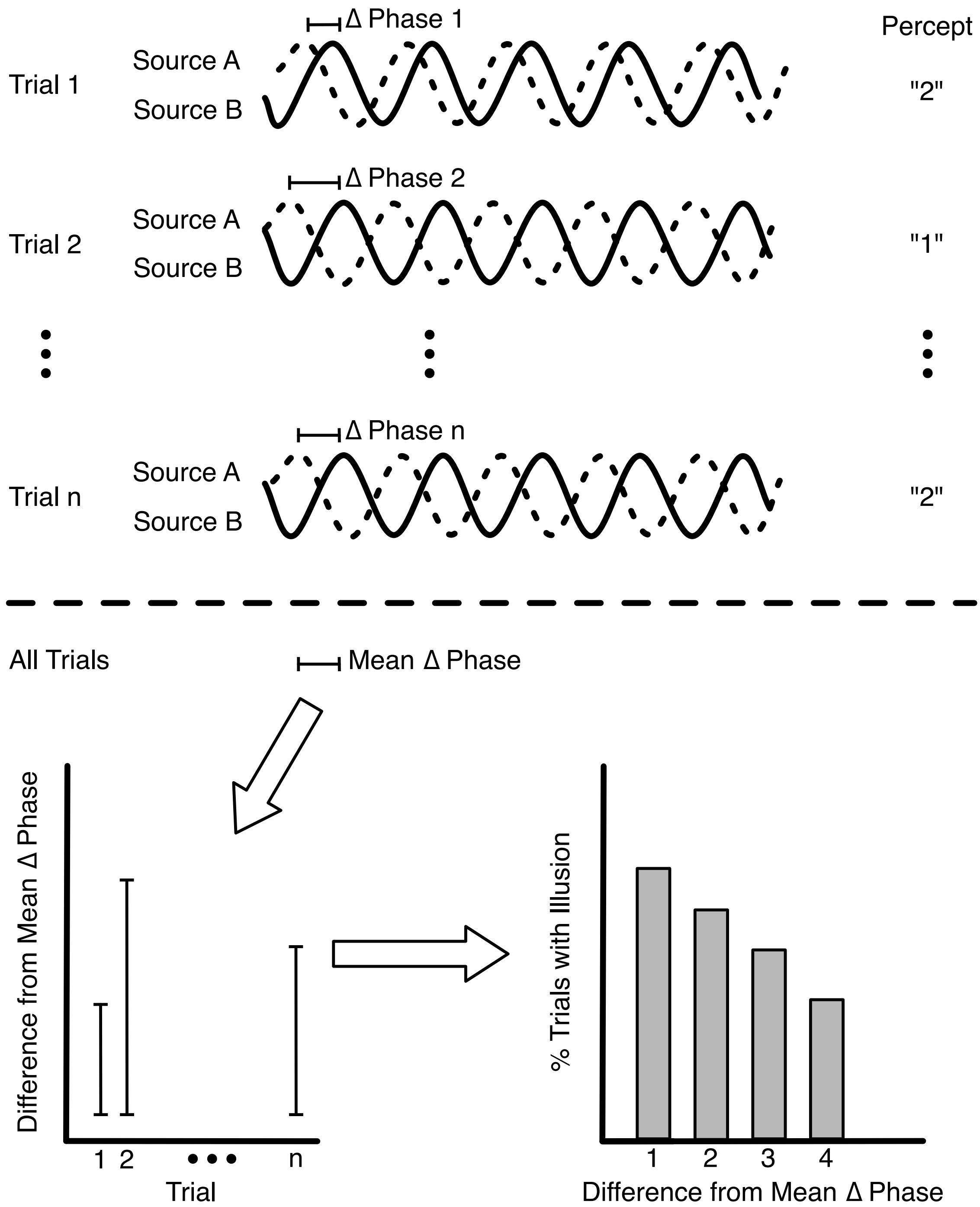

Figure 9:

Schematic description of the source phase difference analysis procedure. In a first step, phase difference (Δ phase) between cortical sources for every trial and the mean Δ phase were computed. In a second step, the difference between the mean Δ phase and each individual Δ phase was computed. These differences between Δ phase values were binned into subject-individual quartiles and the relative proportion of illusion trials per quartile was counted.

3.2.4. Statistical Analysis:

In the analysis of event-related activity, we applied a dependent-samples t-test with Monte-Carlo randomisation and Holms correction for multiple comparisons. In order to define relevant time and frequency windows, a cluster-based (at least two sensors per cluster) dependent-samples t-test with Monte-Carlo randomisation was performed on the sensor data (Maris & Oostenveld, 2007). This method allows for the identification of clusters of significant difference in 2D and 3D (time, frequency and space), effectively controlling for multiple comparisons. Clusters were defined as significant if the probability of observing larger effects from shuffled data was below 5%. The cluster-level test statistic is defined as the sum of the t statistics in 2D or 3D space in the respective cluster. For the identification of the probable neuronal generators of the observed sensor effects, statistical comparisons at the source level were computed using dependent-samples t-tests. Results from the source level were thresholded and corrected for multiple comparisons using AlphaSim (alpha-level = 0.01, critical cluster size = 915 voxel; http://afni.nimh.nih.gov/afni/).

Reaction tendencies were computed as an individual's predisposition towards perceiving the illusion. This relative proportion of "illusion" reactions (number of "illusion" trials divided by the number of all mismatching trials; high numbers indicated a greater tendency towards an "illusion" percept) in all mismatching trials was correlated with the individual differences (cortical activity or functional connectivity for the "illusion" trials versus "no illusion" trials) at the source level for the time-frequency analyses. This analysis indicated with which neuronal processes the individual's predisposition to perceiving the sound-induced flash illusion was associated.

If phase synchrony influences subsequent perception, an analysis of single-trial phase difference should yield additional information to the condition comparison. A repeated-measures ANOVA in R (Team, 2011) was used to evaluate the effects of the source phase differences, the Tukey-HSD test was used for the post-hoc analyses. A trend in the proportion of illusion trials per source phase difference quartile was evaluated with the Cochran-Armitage test.

All aspects of offline treatment of the MEG signals were accomplished using fieldtrip (Oostenveld et al., 2011), an open-source signal processing toolbox for Matlab (http://www.mathworks.com). Anatomical structures corresponding to the statistical effects are labelled according to the Talairach atlas.

3.3. Results:

We used the sound-induced flash illusion to elucidate the role of pre-stimulus oscillatory brain activity and connectivity on the changing perception of invariant stimuli as well as event-related activity associated with different perceptions. We analyzed cortical activity associated either with the perception of an illusory double flash (response ’2‘) or with the perception of only a single visual stimulus (response ’1‘).

3.3.1. Behavioural Data:

In the analysis of the subjects‘ behavioural responses, we found that participants reported an illusory double flash perception in 46% of the trials. This was not significantly different from the number of non-illusory trials (52%) as assessed with a paired t-test ($t=0.7$, $p=0.49$; figure 8B). Subjects correctly identified the number of visual stimuli in the control trials in which one visual and one auditory stimulus (92%) or when two visual and two auditory stimuli were presented (72%). The number of reports of a double flash was significantly larger in the control condition with two auditory and visual stimuli than in the critical trials with two auditory and one visual stimulus ($t=4.23$, $p<0.001$). This indicates that the subjects did not make an error when reporting having seen a second visual stimulus in the critical incongruent trials, but that both percepts were equally probable. There was no significant difference in reaction times between the two response categories as assessed with a paired t-test (714 ms vs. 730 ms, t=-0.46, p=0.64). As the reaction times within the incongruent trials do not differ and there was also no difference from the mean overall reaction time (724 ms), subjects were unlikely to have experienced a perceptual ambiguity or conflict, as suggested by Mishra and colleagues (Mishra et al., 2010). Please note that we introduced a 500-ms delay between stimulus offset and the response in order to avoid premature button presses.

3.3.2. Event-Related Activity:

In the analysis of the event-related activity of the two response categories, we found a significant difference between 265 ms and 280 ms after trial onset ($p<0.05$; figure 10A). Illusory perception produced a larger event-related field with a bilateral parietal topography (figure 10B). We wish to point out, however, that this effect was again derived from the RMS applying the Holms correction, in other words, an approach that considers all sensors together. The ERF effect did not survive the more conservative cluster-based correction for multiple comparisons, perhaps due to its spread onto two spatially rather circumscribed clusters. As we introduced a 500-ms delay between stimulus onset and the response screen, this period was not contaminated by motor responses. LCMV source analysis identified the cingulate gyrus as the source of this effect (figure 10C); this structure has been often associated with attention, control, error processing and performance monitoring (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Keil et al., 2010) but has also been identified as part of a salience network (Menon & Uddin, 2010) involved in the maintenance of task sets and goal-directed behavior (Dosenbach et al., 2007). Unlike earlier studies (Shams et al., 2005; Mishra et al., 2007; Mishra et al., 2010; Cappe et al., 2010), we did not find evidence for early audiovisual interactions. However, we did not focus on the contrast between combined audiovisual stimulation and separated auditory and visual stimulation, but rather on the effect of different perceptions of identical stimuli.

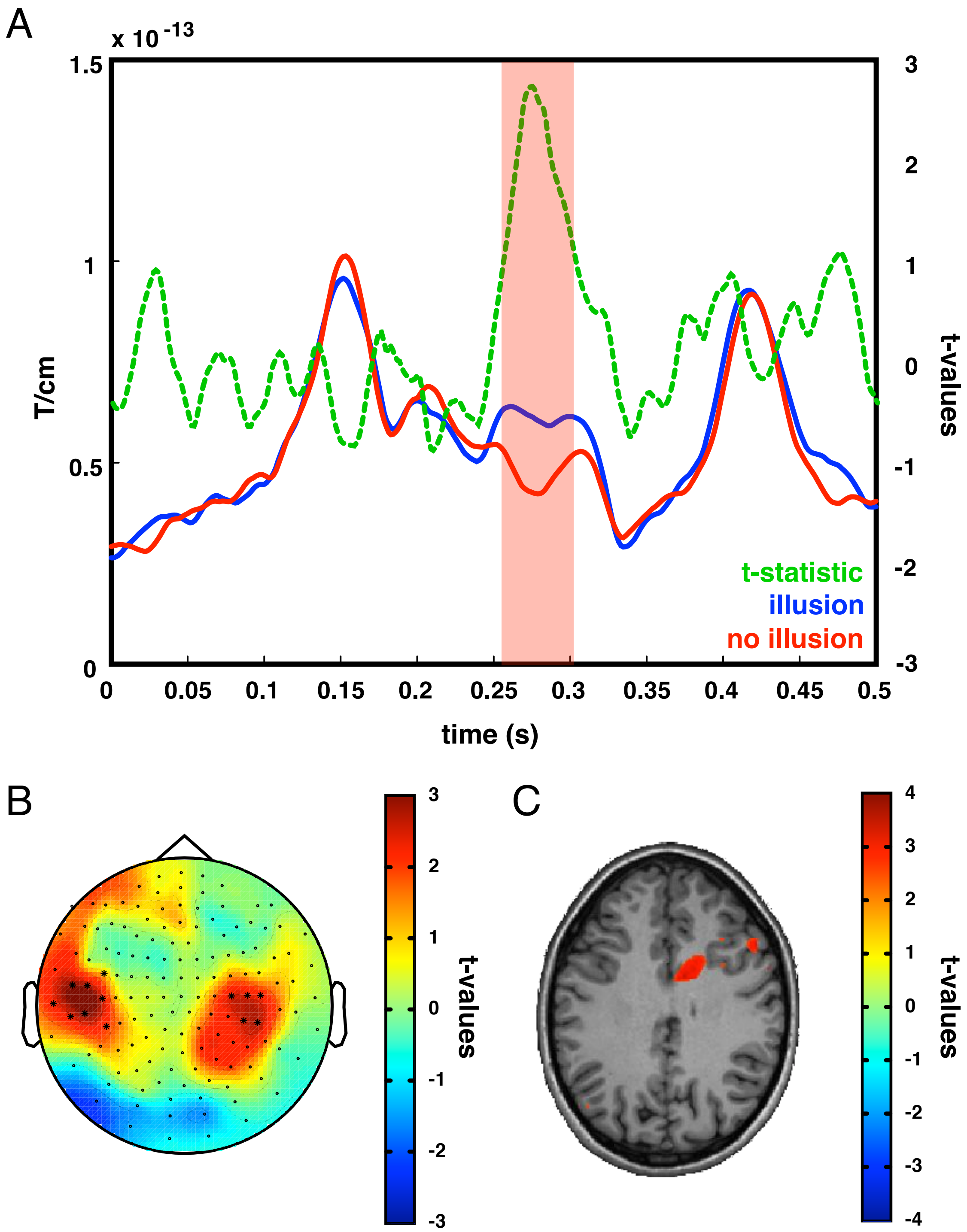

Figure 10:

(A) Root mean square of the event-related field for the channels showing a significant difference between the perceptual conditions as well as t-values for the comparison. The red bar marks the interval for yielding a significant difference. (B) Topography of the interval for yielding a significant difference between the illusion and non-illusion trials. Higher values (larger t-values, red) indicate greater field strength. (C) Source projection for the interval identified in the sensor-level analysis. The LCMV-beamformer identified the cingulate cortex as the source of this effect.

3.3.3. Pre-Stimulus Activity:

The focus of the present study was on the role of pre-stimulus activity. We therefore analysed oscillatory activity in the interval beginning 500 ms before and ending upon stimulus onset using a wavelet time-frequency analysis. Utilising a cluster-based permutation statistic, we identified a beta-band cluster (13-21 Hz, -500 ms until -100 ms), which significantly differentiated between subsequently perceived illusions and non-illusion trials ($p<0.05$; figure 11A). The topography associated with this effect comprised left temporal sensors (figure 11B). Due to the low spatial acuity of topographic sensor maps, a correct interpretation of the results required the identification of possible cortical generators. The Beamformer source analysis (DICS, Gross et al., 2001) suggested posterior portions of the left middle temporal gyrus (BA39, MNI coordinates [-40 -64 18], figure 11C) as the source for this effect. This underscores the role of the putatively multisensory (Calvert et al., 2000) left temporal areas in merging audiovisual information, as indicated by findings on the McGurk effect (Beauchamp et al., 2010; Keil et al., 2011) and by findings on ambiguous audiovisual stimuli (Hipp et al., 2011).

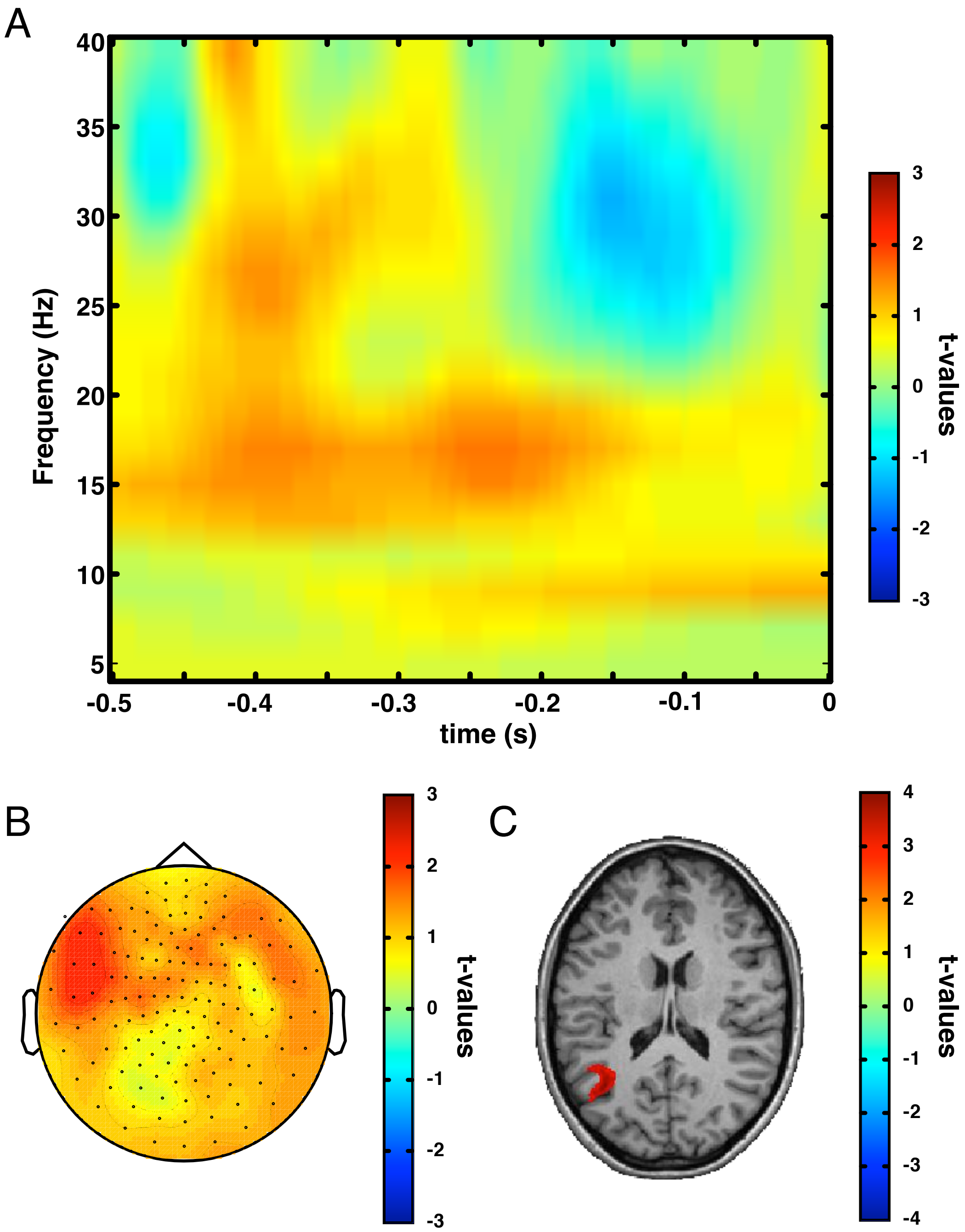

Figure 11:

(A) Wavelet time-frequency representation of the difference between illusion and non-illusion trials in the 500 ms interval before stimulus onset. Higher values (larger t-values, red) indicate relatively more power in the illusion trials. Topography of time and frequency range (-500 ms to - 100 ms, 13-21 Hz) yielding a significant difference between illusion and non-illusion trials. Higher values (larger t-values, red) indicate relatively more power in the illusion trials. (C) Source projection for the time-frequency range identified in the sensor-level analysis. The DICS-beamformer identified the left middle temporal gyrus (BA39) as the source of this effect.

A positive correlation between the reaction tendency towards an illusion and the voxel-wise beta power difference values for the comparison between illusion and non-illusion trials was found in the left middle frontal gyrus (BA9, MNI coordinates [-34 9 37], r~0.76, p<0.05; figure 12). Thus, processes at the level of multi-sensory areas might be insufficient for explaining an upcoming illusion. Top-down influences from frontal areas might thereby play an important role, as well as activity in a network spanning primary sensory, multi-sensory and higher-order areas.

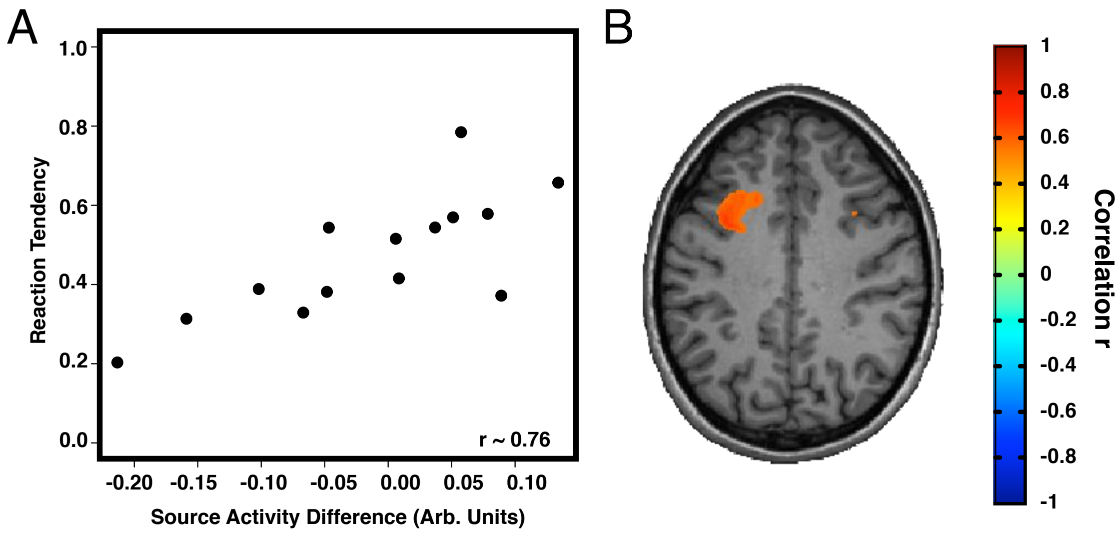

Figure 12:

(A) Correlation between an individual's reaction tendency to perceive the illusion and voxel-wise pre-stimulus beta power (13-21 Hz) difference between illusion and non-illusion trails. (B) This correlation was localised in the left middle frontal gyrus (BA9).

3.3.4. Connectivity:

In order to investigate the influence of network connectivity, we computed phase-locking values between the region of interest identified in the power analysis (i.e., BA39), the auditory and visual cortices identified via analysis of the N1-location and the whole brain volume. The statistical comparison of phase-locking values between the two illusion and non-illusion trials revealed a complex pattern of alpha (9-11 Hz) and beta (13-21 Hz) phase synchrony associated with varying perception of invariant stimuli (see figure 6 for details). In the alpha band (solid lines in figure 13), the right primary auditory cortex was found to be more strongly connected to visual areas in BA18 prior to the illusion trials. The primary visual cortex, however, was more strongly connected to medial frontal and parietal (BA4) areas and less connected to the inferior frontal cortex (BA44) prior to the illusion trials. This points to an important role of ongoing fluctuations in network connectivity in multi-sensory perception. The left middle temporal gyrus, the source of the beta-band power effect, was found to be relatively more phase locked in the beta band (dashed lines in figure 13) in illusion trials to auditory processing areas in the anterior temporal lobe (BA21) and relatively less phase-locked in illusion trials to visual processing areas in the occipital lobe (BA18). This indicates that, at the group level, auditory and multi-sensory areas are more strongly connected prior to audiovisual illusions, whereas visual and multi-sensory areas are more strongly connected prior to non-illusion trials.

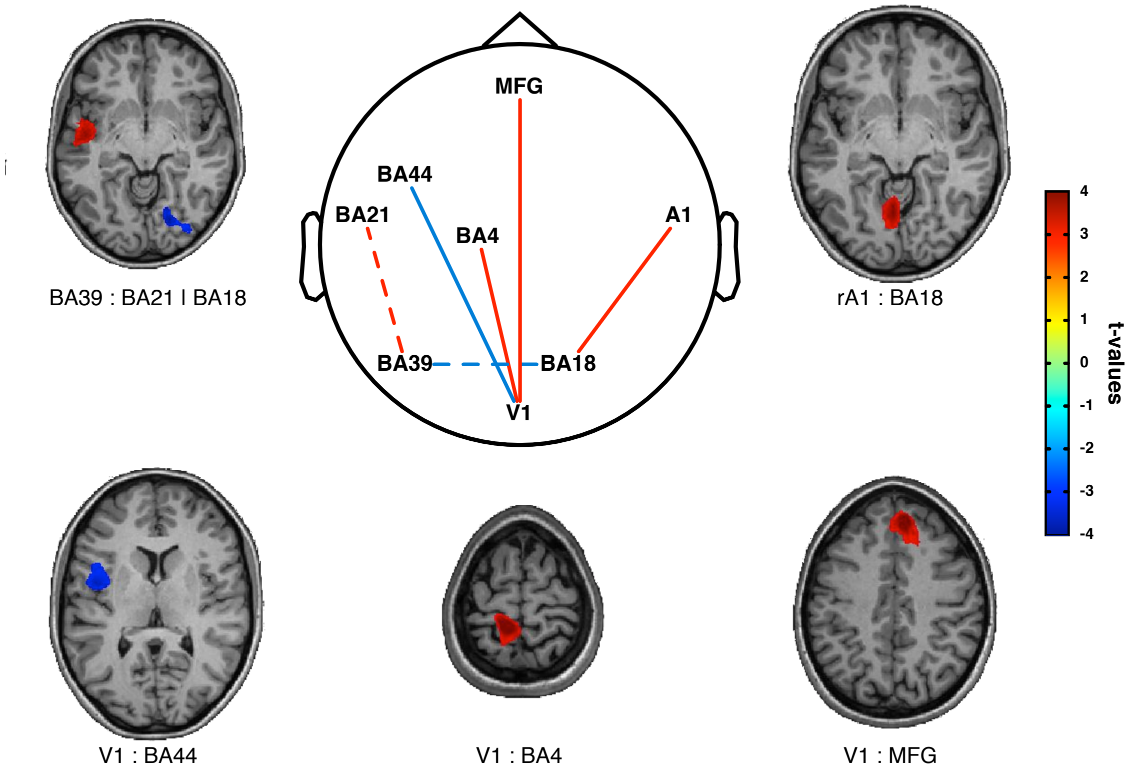

Figure 13:

Results of the source-level phase synchrony analysis. Positive t-values (red) indicate stronger phase-synchrony in the illusion trials, negative t-values indicate stronger phase synchrony in the non-illusion trials. In the beta band (dashed lines), BA39 was found to be more strongly phase-locked to anterior temporal area BA21 and less phase-locked to occipital area BA18 in illusion trials. In the alpha band (solid lines), the primary auditory cortex was found to be more strongly phase-locked to occipital area 18. The primary visual cortex was more strongly phase-locked to frontal (MFG) and parietal (BA4) areas, but less phase-locked to inferior frontal area BA44.

In order to assess the role of ongoing phase on single-trial perception, we computed the deviation from the mean phase difference between the cortical sources identified above. Small deviance values thus indicate a stronger connectedness (i.e., a fixed phase difference). For the connectivity between BA39 and BA21, we found a significant effect for the phase deviance on perception ($F(3,52)=6.41$, $p<0.001$, figure 14). For small phase deviance values (first quartile), the proportion of illusory trials was significantly above chance level and significantly larger than for the third and fourth quartile. For large phase deviance values (third and fourth quartile), this proportion was significantly below chance level. We found a significant trend

(Chi^2=6.54, $p<0.05$) in the data indicating a larger proportion of illusion trials for smaller phase differences and vice versa for large phase deviance values. This means that not only do phase-locking values generally differ between subsequent perceived illusions and non-illusions, but that the extent of synchronisation between BA39 and BA21 influences perception on a single trial level. To further support this finding, we split the single trial phase deviance data and used the first dataset to predict the effect of phase deviance on perception in the second data set. We found a significantly smaller phase deviance for the perception of the illusion ($F(1,26)=3.25$, $p<0.05$). The prediction for the effect of phase deviance on perception was not significantly different from the observed effect in the second dataset ($Chi^2=13.36$, $p=0.98$), thus indicating a correct prediction. One aspect, however, is that the left posterior middle temporal region (see Figure 11C) and BA21 are in relatively close proximity (6.2 cm), necessitating an exact scrutiny of whether the described effect could be due to volume conduction. Indeed, a correlation between beta power in these two regions is highly significant, even though it has to be emphasised that beta power in BA21 did not significantly differentiate between the perceptual categories. An argument against volume conduction based on plausibility assumptions is that, in this case, a maximum could be expected around the seeding region and dropping off linearly in all directions. Figure 13 shows that this is clearly not the case, with the peak-phase synchrony effect being well separated from the peak beta power effect. Another plausibility check requires the investigation of the angle of the phase differences (not to be confused with our previously described measure of phase deviance, in which the "raw" single-trial phase differences were subtracted from the mean phase difference), which assures that they do not equal 0 or 180 degrees (as in the case of volume conduction). We performed this analysis for all of the single trials in the aforementioned quantiles and were able to find that the phase difference between BA39 and BA21 was significantly larger in the first quartile than in the fourth. If stronger beta power would have lead to spurious phase synchronisation effects (i.e., due to volume conduction), an opposite pattern could have been expected (i.e., the first quantile being closer to 0 degrees). Furthermore, the absolute differences were significantly above 0 and less than π in all four quartiles, indicating that the activity measured here in fact represented locally independent source activity and that we could indeed reveal genuine synchronisation effects.

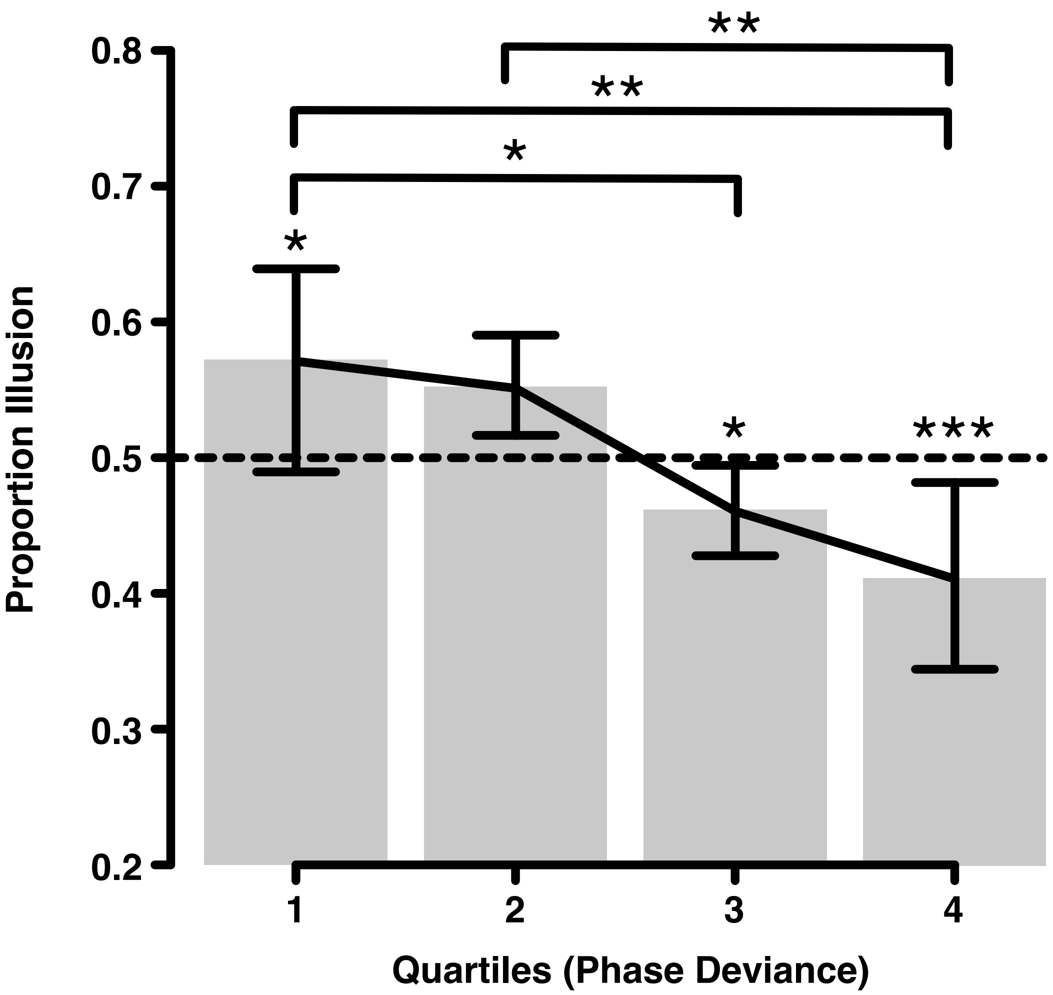

Figure 14:

Source-level phase difference between BA39 and BA21. We computed the beta-band phase deviance from the mean phase difference between the sources and binned it into quartiles. Displayed is the relative proportion of illusion trials per quartile. In the first quartile, the proportion of illusion trials was above chance level and larger than in the third and fourth quartile. Error bars indicate the 95% confidence interval.

3.4. Discussion:

The present study aimed to elucidate the role of cortical activity associated with varying perception upon invariant stimulation using MEG. The main findings are: 1) the perception of the SIFI is associated with elevated evoked activity in the cingulate cortex; 2) increased beta band activity in left temporal areas before the sound onset precedes the perception of the illusion; and 3) audiovisual integration as seen in the illusion is characterised by a complex pattern of alpha and beta-band phase synchrony, especially by increased connectivity between multi-sensory and secondary auditory areas.

Studies on the influence of ongoing cortical activity have mostly focused on alpha-band power (Van Dijk et al., 2008; Romei et al., 2010) and phase (Busch, Dubois, & Vanrullen, 2009; Mathewson et al., 2009) in the visual domain. The present study underscores the role of pre-stimulus activation patterns on upcoming perception and makes important additions. First, the previous studies reporting alpha effects focused on simple perceived-versus-not-perceived distinctions, making arousal fluctuations a difficult factor to exclude. In our study, participants always had a conscious perception, which however differed in its quality. We show that the qualitative difference of conscious percepts in our experiment originated outside primary sensory regions in areas likely involved in multi-sensory integration, the left BA39, the junction between the temporal, occipital and parietal cortices. As noted by Hein and Knight (Hein & Knight, 2008), the function of the multi-sensory superior temporal sulcus varies depending on the nature of network co-activation. The current findings are in line with this, as audiovisual information was either integrated in the case of an illusory percept or not depending on the connectivity pattern of this multi-sensory area. Furthermore, our study is one of the few (e.g., Ploner, Lee, Wiech, Bingel, & Tracey, 2010; Keil et al., 2011) also focusing on pre-stimulus functional connectivity and its role for perception. While Hanslmayr (Hanslmayr et al., 2007) reported also beta and gamma band phase coupling influences next to alpha band power influences on visual perception, the analysis was performed at an electrode level. Schoffelen and colleagues (Schoffelen & Gross, 2009) have demonstrated that problems of volume conduction can be greatly reduced by the approach we chose in this study.

3.4.1. The perception of the sound-induced flash illusion is associated with elevated evoked activity in the cingulate cortex

Studies analyzing audio-visual multisensory interactions (Shams et al., 2005; Mishra et al., 2007; Cappe et al., 2010; Mishra et al., 2010) have focused on the difference in activation between audiovisual stimuli and auditory and visual stimuli (AV-(A+V)). These studies show early interactions, as audiovisual stimuli engage distinct configurations of cortical sources. We compared the event-related activity within an identical AV stimulation, which resulted, however, in two distinctly different percepts. We found a differentiating cortical response 265 ms to 280 ms after sound onset in the cingulate cortex. Assuming a duration of 90 ms for the stimulation, this effect occurred 180 ms after stimulus offset. Given the difference in latency and projected source, it is unlikely that the effect found here is related to previously reported differences in activation. We introduced a 500-ms delay between stimulus onset and the response screen, thus the present effect is not contaminated by a motor response. Numerous reports (Botvinick et al., 2001; Keil et al., 2010) have associated this area and processes in this time interval with cognitive control, performance monitoring and error processing. The process reported here, however, is unlikely to be related to error processing as it occurs prior to the actual response. As the cingulate cortex has been associated with a salience network (Menon & Uddin, 2010) involved in monitoring internal and extra-personal events as well as directing behavior through task maintenance (Dosenbach et al., 2007), it is possible that the current results point to an ongoing monitoring process, especially given the functional connectivity to primary sensory areas as identified by Dosenbach.

3.4.2. Increased beta-band activity in left temporal areas before the sound onset precedes the perception of the illusion

A number of studies have been performed on the comparison between matching and mismatching multimodal information (Senkowski et al., 2008) and with regard to variations in perception of invariant multimodal stimuli (Lange et al., 2010). Little is known about the predictive value of pre-stimulus oscillatory activity on multimodal perception. Bulkin and Groh (Bulkin & Groh, 2006) suggested that the brain weighs sources of sensory information according to their assumed reliability when producing a unified percept . Thus, it should be possible to detect a signature of this top-down weighing mechanism in the pre-stimulus period and—depending on the current state of top-down processing—find predictive values for perception in this interval. Our recent work (Keil et al., 2011) has pointed to the importance of beta-band power and phase in the perception of the McGurk effect. Audiovisual fusion, as indexed by the McGurk illusion, depends on the current local activity in the left STG as well as the state of connectivity between this region and frontal and temporal regions. The current study supports the importance of local beta band activity in multimodal areas for the fusion between multimodal information. In line with tthis, we found increased beta band power prior to stimulation in the left BA39. This local activity differed significantly between subsequent audiovisual fusion and non-fusion. The source of this effect has also been implicated with multimodal processing in fMRI (Calvert, Hansen, Iversen, & Brammer, 2001; Watkins, Shams, Tanaka, Haynes, & Rees, 2006) and electrophysiological studies (Cappe et al., 2010; Mishra et al., 2010). The correlation of source power values with subsequent behavior indicated an involvement of BA9 in the middle frontal gyrus. Thus, not only does local activity in the middle temporal gyrus generally influence upcoming perception, but top-down influences from frontal areas also reflect an interindividual predisposition to the illusion. Based on effects found post-stimulus in superior temporal areas, Mishra et al. (Mishra et al., 2010) have argued that this locus provides the proximal trigger for perceiving the SIFI. We extend this view and argue that this is especially true for activity prior to stimulation, which sets the pathways for upcoming perception.

3.4.3. Audiovisual integration as seen in the sound-induced flash illusion is characterised by a complex pattern of alpha and beta-band phase synchrony

Empirical evidence suggests that perception involves a widespread neuronal network in addition to activations of sensory and association areas (Koch, 2004; Dehaene et al., 2006). It is therefore important to consider states of functional networks in addition to local cortical activity (Buzsáki, 2006; Senkowski et al., 2008). Phase synchronisation of oscillatory activity (Lachaux et al., 1999; Varela et al., 2001) has been proposed as a mechanism for large-scale integration. To test the involvement of a distributed network influencing subsequent perception, we analyzed source space phase-locking values. In line with Hipp (Hipp et al., 2011), we found beta band phase synchrony in a network comprising temporal and occipital areas. The perception of an illusion becomes more likely depending on the state of pre-stimulus connectivity between the multimodal area BA39 and auditory and visual areas. Moreover, single-trial phase difference between BA39 and the auditory area BA21 has predictive value for upcoming perception in individual participants: The stronger these sources are coupled the more likely an illusion will occur. The trend we observed in the single-trial phase difference data indicates that the stronger the interaction between these two areas, the stronger the influence of auditory information during multimodal perception gets. Aside from this integration of a multimodal area with sensory areas, which is in line with the notion of beta activity as a marker of top-down processing (Engel & Fries, 2010), we also found modulations in alpha band phase synchrony. If an illusion is subsequently perceived, the primary auditory cortex is phase locked to the visual area BA18. The primary visual cortex, however, is connected to medial frontal and parietal areas but disconnected from inferior frontal areas. Thus, the influence between auditory and visual areas is increased as well as the influence between the frontal and visual cortices. Mishra and colleagues (Mishra et al., 2010) have argued for the influence of attention on the perception of the sound-induced flash illusion. We argue that not only attention modulates upcoming perception but also the current network architecture, as indicated by alpha and beta-band phase synchrony.

3.4.4. Conclusion

The present study adds evidence to the importance of pre-stimulus local and network activity on upcoming perception. For the SIFI, two pre-stimulus features appear to be of great importance: relatively enhanced beta power in left temporal multi-sensory integration regions and the strength of coupling between this region and left secondary auditory regions. More research is needed to address the issue of directionality of the network activity. Studies involving active external perturbations of the current state are needed in order to evaluate the role of multimodal cortical areas.

4. Third Study: Pre-stimulus beta and gamma activity influence upcoming perception of the sound induced flash illusion: a combined EEG-TMS study.

4.1. Introduction:

Different cortical areas are specialised for detecting and processing different types of sensory signals. To be useful for multi-sensory perception, the resulting information must be combined. A number of perceptual phenomena show that one modality can thereby influence the other and also that this influence can lead to novel precepts (i.e., illusions). The incongruence of information from different modalities is the basis of audiovisual illusions that hint at the way in which sensory areas are interconnected (Eagleman, 2001).

Siegel et al. (Siegel et al., 2012) very recently put forward the idea that frequency-specific oscillations in distributed cortical networks may provide indices (termed ʼfingerprintsʻ) of network interactions that underlie cognitive processes. The idea of canonical neuronal computations underlying cognition is based on the notion by Crick and Koch (Crick & Koch, 2003) that these highly selective, integrative and flexible processes are achieved through the transient formation of large coalitions of neurons. Recently, a number of reports have suggested that beta-band activity could play an outstanding role in large-scale network processes. Historically, beta-band activity has been mainly related to motor cortex activity and the prediction of choice (Donner et al., 2009), which seems to reflect a local suppression of ongoing rhythmic activity via cortical activation (Pfurtscheller 1999). However, Buszaki (Buzsáki & Draguhn, 2004) as well as von Stein (von Stein & Sarnthein, 2000) have stated that relatively lower frequencies such as the beta band (12 -18 Hz) are well suited for inter-areal connectivity. This has also been proposed by Kopell et al. (Kopell & Ermentrout, 2000) based on computational model considerations. In a visual target detection task, Gross et al (Gross et al., 2004) could show that successful target detection was associated with enhanced beta-band coherence between frontal and parietal areas. Thus, fluctuations in attention that cause alterations in behaviour might be signalled by changes in beta-band coherence. Using a bistable audiovisual stimulus, Hipp et al. (Hipp et al., 2011) also found that fluctuations in beta-band coherence between frontal and parietal areas reflect fluctuations of attention and thus determine the perception of the bistable stimulus. In the same study, the authors found that enhanced gamma-band synchronisation was specifically associated with a cross-modally more integrated percept. We recently showed that pre-stimulus beta-band activity in the left superior temporal gyrus (STG) influences audiovisual integration, as seen in the McGurk effect (Keil et al., 2011) and in the sound induced flash illusion. Using a tactile visual double-flash paradigm, Lange et al (Lange et al., 2010) also reported pre-stimulus beta-band power influences. Despite an increasing amount of correlative evidence, the causal nature of the link between brain oscillations and cognitive functions remains difficult to isolate.

Following the literature reviewed above, we propose that, in the case of incongruent multi-sensory information, the strongest *pre-stimulus* coalition predisposes the percept. If the local activity in a multimodal cortical area is sufficiently strong, upcoming multi-sensory information will be likely integrated. In the case of incongruent information, this leads to a novel or illusory percept. By perturbing this local activity with TMS, it should thus be possible to change the fate of the audiovisual integration and the subsequent percept. We therefore used a virtual lesion approach based on single TMS (Silvanto & Muggleton, 2008; Chambers, Payne, Stokes, & Mattingley, 2004) pulses to directly interact with an MEG-identified local temporal beta-band oscillator associated with audiovisual integration and illusory fission perception, thereby following the experimental logic outlined by Beauchamp et al. (Beauchamp et al., 2010). We hypothesise that: 1) Illusory perception is preceded by an increase in beta-band power in the left BA39; and 2) TMS to the left BA39 interferes with beta-band activity and reduces the likelihood of an illusion. The influence of TMS should be at its highest when beta power at the time of stimulation is at its strongest.

4.2. Methods:

4.2.1. Subjects:

Data from eight subjects (five female and three male with a mean age of 23.6) were analysed in the present study. All participants were right-handed, had normal hearing and normal or corrected-to-normal vision as well as no history of epilepsy or head trauma. Prior to the experiment, participants received detailed instructions regarding the procedure of the experiment and subsequently gave their written informed consent. The procedures of the experiment were approved by the Ethics Committee of the University of Konstanz.

4.2.2. Experimental Design:

The experiment consisted of 900 trials in which we presented small dots and short tones in six blocks of 150 trials each. The stimuli were presented via Psyscope X (http://psy.ck.sissa.it/) on a MiniMac (Apple Inc.). 480 trials contained the critical mismatching stimuli (1 dot, 2 tones). We followed the description of Shams' (Shams, Kamitani, & Shimojo, 2002), experiment (2) in the presentation of stimuli, which we had already used in a previous study. In half of the trials, a TMS pulse was given. The site of stimulation was changed between the left and right BA39 in each block and the starting side was balanced across subjects. Thus, we presented 224 critical trials without TMS, 128 critical trials with TMS to the left BA39 and 128 critical trials with TMS to the right BA39. A fixation cross was displayed throughout the entire stimulus presentation. Visual stimuli were presented for 17 ms, auditory stimuli for 7 ms, and the second stimuli followed after an inter-stimulus interval of 50 ms (see figure 15). In order to make the onset of stimulation unpredictable, a random pause between 1700 ms and 2400 ms was inserted between the onset of the fixation cross and the presentation of stimuli. TMS was applied at a fixed latency of 500 ms prior to stimulus onset. Using a forced choice task with a 500-ms delay following stimulus offset, participants had to indicate whether they had perceived zero, one or two visual stimuli by pressing a button. The dependent variable in this investigation was thus the subjectively perceived content of the audiovisual sensation. The visual stimuli were presented on a computer monitor inside a chamber shielded for external and power line noise. The monitor was positioned 130 cm in front of the subject, the fixation cross had a size of 1.5 by 1.5 cm and visual stimuli were presented 5.5 cm below the fixation cross with a diameter of 2 cm. The auditory stimuli were 1000 Hz sine wave tones presented via in-ear headphones (Sennheiser CX 400-II).

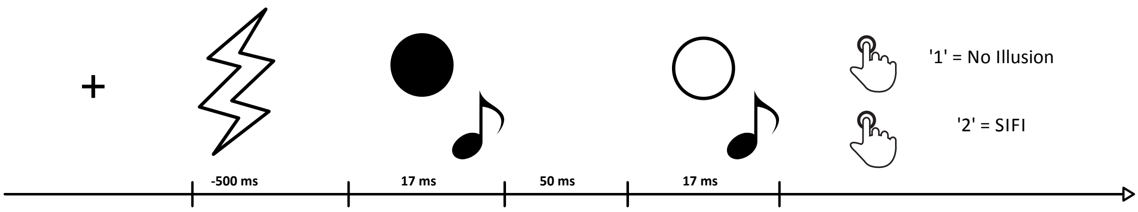

Figure 15:

Schematic description of an incongruent trial. In trials with TMS, a single TMS pulse was given either to the left or right BA39 500 ms prior to stimulus onset.

4.2.3. TMS Stimulation:

Based on a previous study on the pre-stimulus influence on the perception of the SIFI, we chose the left BA39 (MNI coordinates [-40 -64 18]), a multi-sensory area (Beauchamp, 2005) as the target location. We identified this region in subject-specific individual T1-weighted MR images and marked it for neuronavigation. An individual homologue site on the right hemisphere was marked by inverting the left-right axis and checking it using anatomical landmarks. A researcher was present throughout the experiment, holding and positioning the TMS coil at the marked location.

Neuronavigation was accomplished using an ANT (Enschede, NL) visor neuronavigation tool. TMS was applied with a biphasic Magstim (Rapid^2, MAGSTIM CO., Whitland, Dyfed, UK) system using a figure-eight coil. The intensity of stimulation was adjusted to 110% of the motor threshold, defined before the experiment as described by Hartmann et al (Hartmann, Schulz, & Weisz, 2011) in example 3, using the ConSole (http://console-kn.sf.net/) environment.

4.2.4. EEG Acquisition:

Electroencephalographic (EEG) recording was conducted using a 128-channel DC amplifier with equidistant layout ANT system with a ground electrode taped to the right cheek. Subjects were sitting comfortably and were instructed to remain still during the stimulation and to avoid eye movements and blinks as much as possible. Continuous data sets were recorded with a sampling rate of 2048 Hz. TMS-compatible sintered Ag/AgCl electrodes were used. Skin/electrode impedance was maintained below 5 kΩ. A video camera installed inside the EEG chamber allowed the monitoring of subjects' behaviour and compliance throughout the experiment.

4.2.5. Data Analysis:

Following data acquisition, epochs of four seconds (+/- 2s) encompassing stimulus onset were extracted from the raw data. Epochs were demeaned and detrended, TMS artefacts were removed using spline interpolation as described by Thut et al. (Thut et al., 2011). Subsequently, epochs were resampled to 300 Hz. A 1 Hz high-pass filter (Butterworth, filter order 4) was applied to remove remaining slow drifts in the data and line noise was removed using discrete fourier transform (DFT). Epochs were visually inspected for EOG or movement artefacts, excessive noise or channel jumps. Critical trials (one visual stimulus and two auditory stimuli) were grouped according to their response into two categories: 'no illusion' (response '1') and 'illusion' (response '2') as well as either without TMS ('No TMS'),

TMS to the left hemisphere ('TMS left') or TMS to the right hemisphere ('TMS right'). The number of trials across all categories was equalised for each subject using random omission in order to ensure comparable signal-to-noise ratios.

Single-trial activity was then projected into a common source space of 915 cortical sources based on the MNI standard brain. Sensor-level cross-spectral density was therefore computed between 5 and 40 Hz and 1 Hz resolution using a Hanning taper. Subsequently, this sensor-level activity (see below for the definition of the time windows) was projected into source space using a time domain beamformer (LCMV, Van Veen et al., 1997).

In the comparison of cortical activity, we first replicated the approach described in our previous work on the SIFI and compared pre-stimulus oscillatory power between the illusion and non-illusion trials in an interval between -400 ms and stimulus onset. In a second step, we compared the time interval between 1100 ms and 700 ms prior to stimulus onset for all conditions (i.e., 400-ms intervals of 600 ms until 200 ms before TMS) in order to ascertain identical baseline intervals for the TMS and No-TMS conditions. We then separately calculated relative signal change for the illusion and non-illusion trials in the No-TMS, TMS left and TMS right condition in t-values and further tested the signal change within and between conditions using t-tests based on Monte-Carlo randomisation with cluster correction for multiple comparisons (Maris & Oostenveld, 2007).

TMS effects differ significantly depending on the brain state at time of stimulation (Silvanto et al., 2008). Based on our previous work on the SIFI, we hypothesise that the beta-band might signal a brain state with an increased predisposition for audiovisual integration. In the analysis of illusion versus no illusion trials, we found that the gamma-band differentiated between trials with and without an upcoming illusion (see Results). In addition to comparing power for illusion versus non-illusion trials in the different conditions, we therefore split the TMS trials into strong and weak pre-TMS beta power (hypothesis driven) and pre-TMS gamma power (data driven) groups based foremost on the median split of the global average power between 15 and 25 Hz (beta-band) and 30 and 35 Hz (gamma-band) and secondly on the median split of the power at the sites of stimulation for the same frequency bands. This was done in order to elucidate the influence of the current brain state on TMS. In the statistical analysis, we followed the same steps as outlined above—that is, comparing the power for the different groups and time intervals as well as signal change between pre- and post-TMS intervals.

For illustrative purposes, we projected the results of the source space statistics onto an inflated brain. EEG data analysis was performed using the FieldTrip (Oostenveld et al., 2011) software package (http://fieldtrip.fcdonders.nl/) and a custom-made MATLAB (http://www.mathworks.com/) code.

Behavioural data were analysed using R (Team, 2011) in terms of the relative proportion of illusion trials in all incongruent trials. The relative number of trials per subject between the ’with-TMS‘ and ’without-TMS‘ as well as the ‘strong beta power’ and ‘weak beta power’ conditions were compared using an independent-samples T-test.

4.3. Results:

In the present study, we used the sound-induced flash illusion as a tool to study perceptual variability upon invariant stimulation. We analysed cortical activity associated either with the perception of an illusory double flash (response ’2’) or with the perception of only a single visual stimulus (response ’1’). We furthermore used single-pulse TMS to perturb ongoing local cortical activity.

4.3.1. Behavioural Results:

In the analysis of the subjects‘ behavioural responses, we found similar performance as compared to our previous MEG study on the sound-induced flash illusion. Participants reported an illusion in 52% of the trials without TMS. This was not significantly different from the number of non-illusory trials (48%), as assessed using an independent-samples t-test (t=0.35, p=0.72; figure 16). Similar results were obtained from the trials with TMS to the left BA39 (52% illusion vs. 48% non-illusion, t=0.37, p=0.72) and to the right homologue (47% illusion vs. 53% non-illusion, t=-0.67, p=0.5).

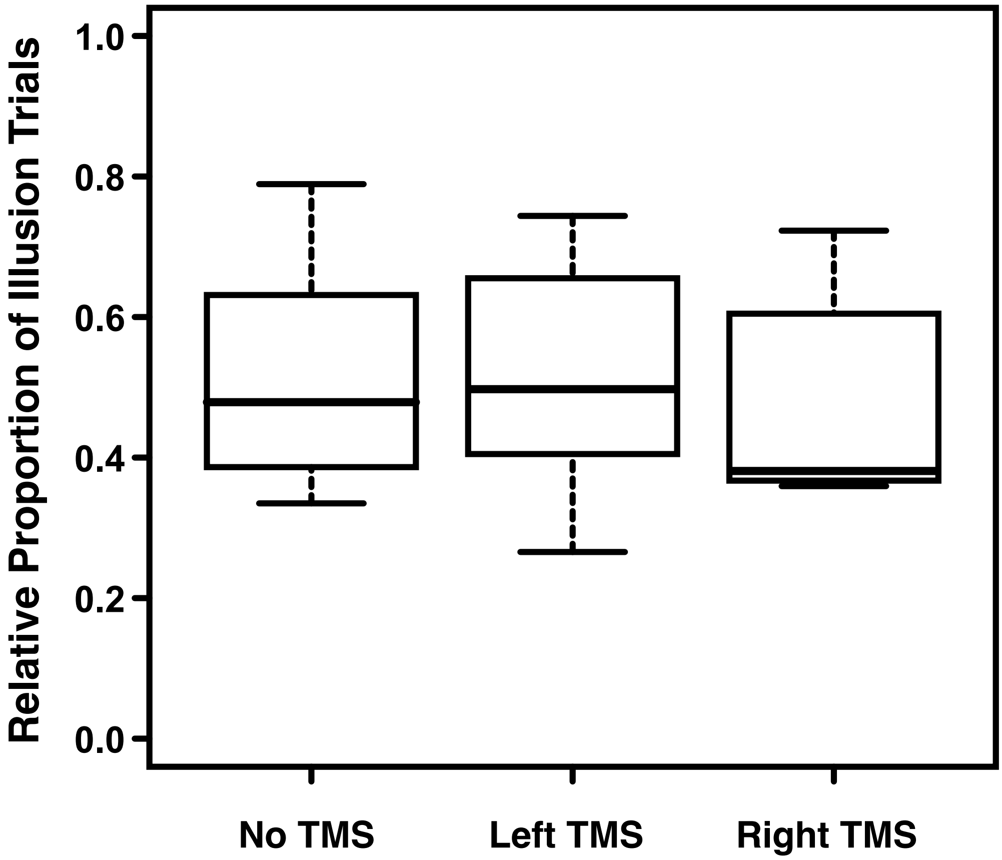

Figure 16:

Behavioural Results. Comparison of the relative proportion of illusion trials in all incongruent trials in the 'No TMS', 'Left TMS' and 'Right TMS' conditions. No significant differences between the conditions were found.

4.3.2. EEG Data:

We compared oscillatory power between the illusion and non-illusion trials within the pre-stimulus interval between -400 ms and stimulus onset as well as the signal change in cortical activity from a baseline interval 1100 ms to 700 ms prior to stimulus onset (i.e., before the TMS pulse) using fast Fourier transformation (FFT) for the No-TMS, TMS left and TMS right conditions. In addition to analysing the effect of oscillatory power on the upcoming perception, we examined the effect of oscillatory power on TMS-induced changes in cortical activity. We therefore split the TMS trials into strong and weak beta and gamma power subsets and compared oscillatory power in the pre-TMS and post-TMS intervals as well as in signal change.

4.3.3. Illusion versus Non-Illusion Trials:

One focus of the present study was the replication of findings about the influence of pre-stimulus power on upcoming perception. We therefore analysed pre-stimulus power (-400 to 0 ms with respect to stimulus onset) in the No TMS, TMS left and TMS right trials and initially without baseline correction. However, we did not find any pre-stimulus power differences that had survived the conservative cluster-based correction for multiple comparisons.

We then examined the signal change relative to the pre-TMS baseline (figure 17) and found a high beta/low gamma-band cluster (28 Hz - 40 Hz) in which the signal change differed significantly between subsequently perceived illusion and non-illusion trials in the No TMS condition ($p_{corr}<0.001$, corrected for multiple comparisons; figure 17A). The power in this frequency band increased relative to the baseline if subjects consequently reported an illusion. Since this condition did not involve an intervention during the pre-stimulus period, this result indicates that *transient* increases or decreases in gamma power precede illusions or non-illusions, respectively. The projection of this effect onto an inflated brain surface suggested the right temporal cortex as the source of this effect. This right temporal effect was abolished in the TMS left as well as TMS right trials. For these conditions, we found an increase in a partially overlapping frequency band (~30-35 Hz) in the left temporal cortex, albeit at an uncorrected level ($p_{unc}<0.05$, not corrected for multiple comparisons; figure 17B). Additionally, we found an increase in gamma-band power in the left anterior temporal and inferior frontal cortex in the TMS right trials ($p_{unc}<0.05$, not corrected for multiple comparisons; figure 17C). The left temporal effect in the two TMS conditions are in spatial proximity to our previous MEG study (Keil et al, submitted), although at a higher frequency band, thus partially confirming our hypothesis of an involvement of the left temporal cortex in the perception of the illusion. Most noteworthy in this analysis is the right hemispheric dominance of the high beta/low gamma effect in the No-TMS condition, which disappears following TMS. It is possible that we recorded different aspects of the same process of audiovisual information integration in our MEG and EEG studies. Siegel et al. (Siegel, Engel, & Donner, 2011) have summarised that high and low beta frequencies have separate underlying circuit mechanisms, thus representing distinct yet related aspects of perception.

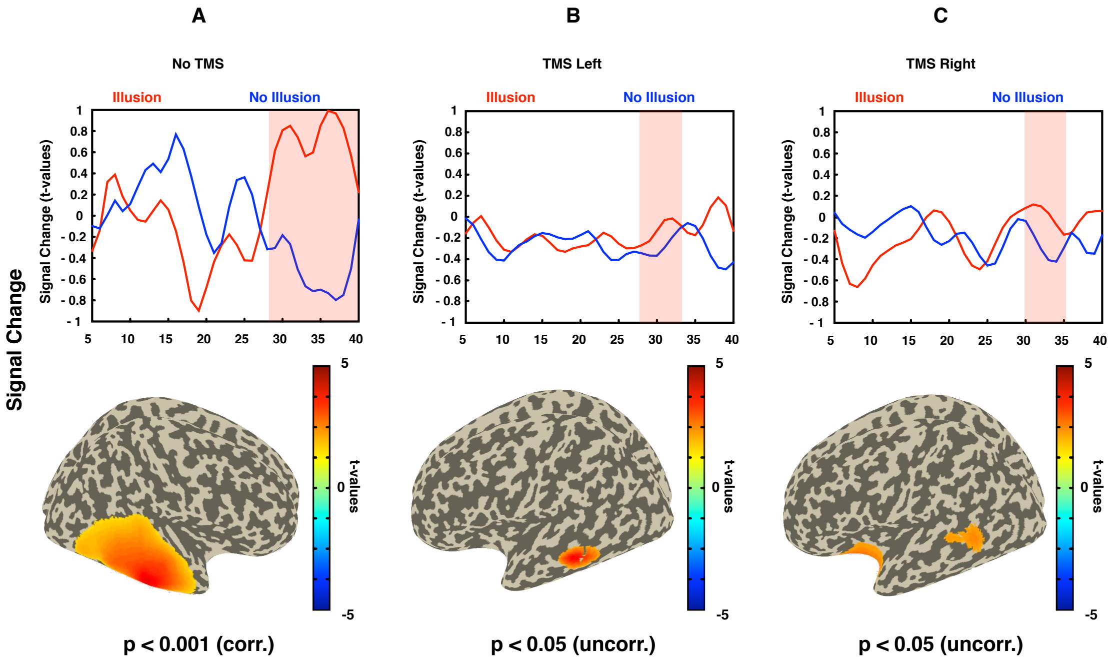

Figure 17:

Comparison of illusion versus non-illusion trials. Comparison of signal change (t-values) between illusion and non-illusion trials for the No-TMS (A), TMS left (B) and TMS right (C) conditions. Illusion trials are consistently marked by an increase in pre-stimulus gamma power relative to baseline.

4.3.4. Pre-TMS State-Dependent Effects on Behaviour:

The second focus of the present study was to elucidate the influence of the pre-TMS brain state on the effect of TMS and subsequent illusory perception. In the comparison of *all* illusion versus non-illusion trials, we found that TMS did not have an effect on perception. However, when splitting the TMS trials into strong and weak pre-TMS beta-band power based on the global power (see Introduction), we found a significant modulation of perception following TMS to the right BA39, indicating that participants had perceived an illusion in 55% of strong beta trials compared to 44% of illusion trials in weak beta trials ($t=2.23$, $p<0.05$; figure 18A). Contrary to our hypothesis, TMS to the left BA39 did not modulate the perception (52% of illusion trials in the strong beta trials vs. 48% of illusion trials in the weak beta trials, $t=0.9$, $p=0.38$). We found a similar effect when splitting the trials based on the pre-TMS beta power at the site of stimulation. TMS to the right BA39 lead to a perception of the illusion in 54% of strong beta trials compared to 45% of illusion trials in the weak beta trials (t=4.26, p<0.01; figure 18B). Here again, TMS to the left BA39 did not modulate the perception (49% of illusion trials in the strong beta group vs. 51% of illusion trials in the weak beta group, t=0.08, p=0.93). Moreover, in the split based on the global power as well as on the local power at stimulation site, we only found this effect for the beta-band and not for the gamma-band. This indicates that beta-band modulations have a stronger influence on subsequent perception than gamma-band effects. In the analysis of illusion versus non-illusion trials, we found stronger gamma-band power preceding an illusion. However, it appears that this effect depends on the TMS and is not related to the pre-TMS brain state. It instead relies on the pre-stimulus brain state as seen in our previous MEG study.

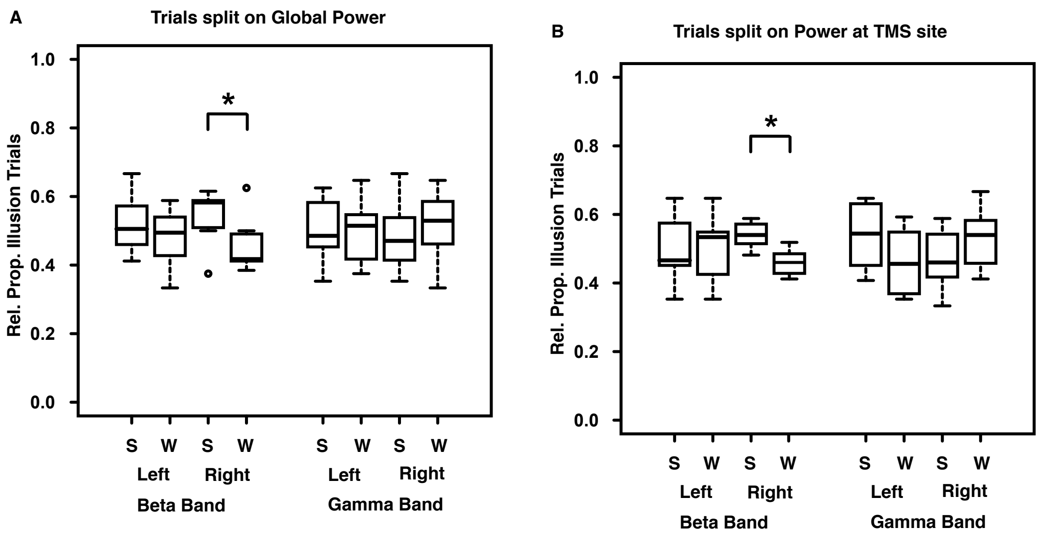

Figure 18:

Comparison of the relative proportion of illusion trials in all incongruent trials with TMS either to the left or right BA39. A significant difference in the likelihood of an illusion between trials with strong and weak pre-TMS beta power was found for the 'Right TMS' condition. This was found for trials sorted by global power (A) as well as for trials sorted by local power at the site of stimulation (B).

4.3.5. Pre-TMS State-Dependent-Effects on Oscillatory Power:

In order to elucidate the influence of brain state on the effect of TMS, we split the single trials in strong and weak beta-band and gamma-band based on the pre-TMS global power between 15 Hz and 25 Hz (beta-band) and 30 Hz and 35 Hz (gamma-band) as well as on local power at the respective sites of stimulation. In both split conditions, we identified a robust modulation depending on pre-TMS power in the beta as well as gamma-band sorted trials. Beta-band power decreased relative to baseline in the case of high pre-TMS beta-band power and, inversely, increased in the case of low pre-TMS power.

When comparing global pre-TMS power differences, the strongest disparities can be found in the precuneus within the longitudinal fissure and parietal areas ($p_{corr}<0.001$, corrected for multiple comparisons; see supplementary figure 1). These areas have been implicated as central hubs in small-world networks integrating different cortical areas (Bullmore & Sporns, 2009). In the analysis of signal change between the post and pre-TMS intervals for the strong vs. weak beta-band trials based on global power, we found a differential modulation in the beta-band (15 Hz - 25 Hz) in the inferior frontal and anterior temporal cortices following left as well as right hemispheric TMS. As mentioned above, beta-band power increased relative to low pre-TMS beta-band power but decreased relative to high pre-TMS beta-band power ($p_{corr}<0.001$, corrected for multiple comparisons; figure 19A). This could be an explanation for the large variance in signal change in the comparison between illusion and non-illusion trials. Taken together with the behavioural effect of how TMS differentially influences subsequent perception depending on the pre-TMS brain state, these results underline the important role of the current brain state in upcoming perception and stimulation. They also support recent findings of the state-dependency of TMS (Silvanto et al., 2008; Siebner et al., 2004; Weisz et al., 2012). It is noteworthy that the modulation of global power did not include the site of stimulation. This hints at a modulation of connectivity to remote areas depending on or varying with the global beta-band state and underlines the findings of Siebner et al. (Siebner et al., 2009) of the influences of TMS on distant cortical areas.

A similar pattern of power modulation depending on the pre-TMS power was found in the analysis of trials sorted according to the global gamma-band power. Again, gamma-band power decreased relative to baseline in the case of high pre-TMS gamma-band power and, as seen before, increased in the case of low pre-TMS power. Additionally, we again found here the strongest pre-TMS differences in the precuneus within the longitudinal fissure and parietal, but also frontal areas (see supplementary figure 2). In the analysis of signal change, we found a differential modulation of gamma-band power (28 Hz - 38 Hz) following TMS to the left as well as right BA39 in the prefrontal and inferior frontal cortex ($p_{corr}<0.001$, corrected for multiple comparisons; figure 19B). Again, none of the stimulated areas exhibited consistent modulation, although parietal and frontal cortical areas did, thus indicating a modulation of connectivity to higher level areas with gamma-band state.

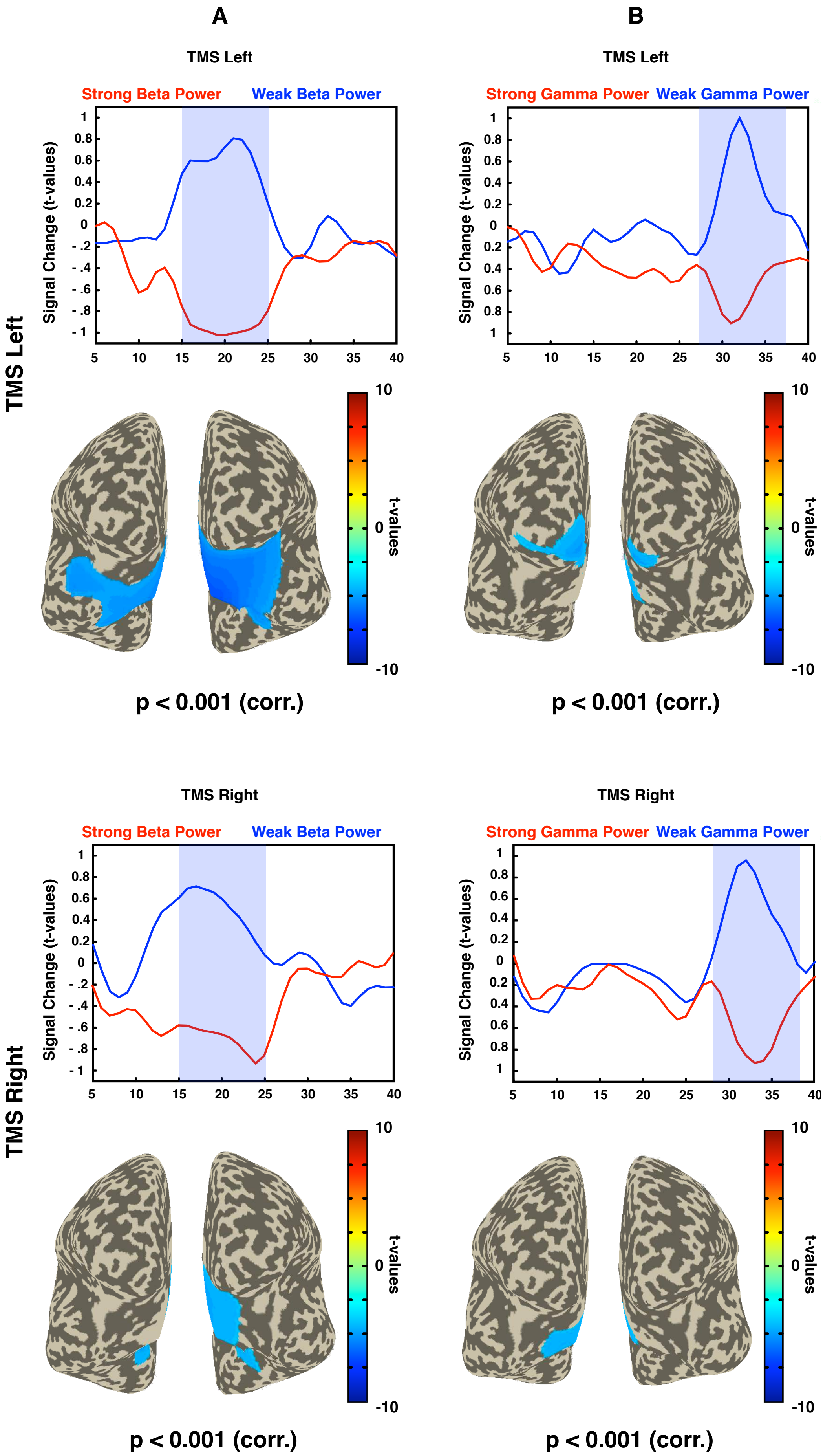
A
B
TMS Left
Strong Beta Power
Weak Beta Power
Strong Gamma Power
Weak Gamma Power
Signal Change (t-values)
t-values
p < 0.001 (corr.)
TMS Right

Figure 19:

Trials sorted by global pre-TMS power. (A) Comparison of signal change (t-values) between strong and weak pre-TMS beta-band power trials. Strong pre-TMS beta power trials are marked by a decrease in beta-band power after bilateral TMS stimulation whereas a beta-band power increase is found following weak pre-TMS beta-band power. (B) Comparison of signal change (t-values) between strong and weak pre-TMS gamma-band power trials. Strong pre-TMS gamma power trials are marked by a decrease in gamma-band power following bilateral TMS stimulation, whereas a gamma-band power increase is found following weak pre-TMS beta-band power.

In the comparison of trials sorted for the local power at the respective stimulation sites, we found the same pattern of a decrease in both strong and weak power in the beta as well as the gamma-band (figure 20). With respect to the cortical location, these modulations were circumscribed to the sites of stimulation; however, we also found that a larger frequency range was modulated. In the beta-band sorted trials, the frequency range identified in the cluster-based permutation analysis ranged from 13 Hz to 27 Hz, thus comprising the beta and low gamma range ($p_{corr}<0.001$, corrected for multiple comparisons; figure 20A). In the gamma-band sorted trials, the cluster analysis identified a large gamma-band range from 27 Hz to 35 Hz ($p_{corr}<0.001$, corrected for multiple comparisons; figure 20B). It is worth noting that power modulation following TMS to the left BA39 displayed two peaks: one in the beta range and one in the gamma range. Taken together, these results indicate that TMS has a different mode of action depending on the local and the global state of activation. Local power at the site of stimulation as well as activity in connected regions is modulated depending on the brain state at the time of stimulation.

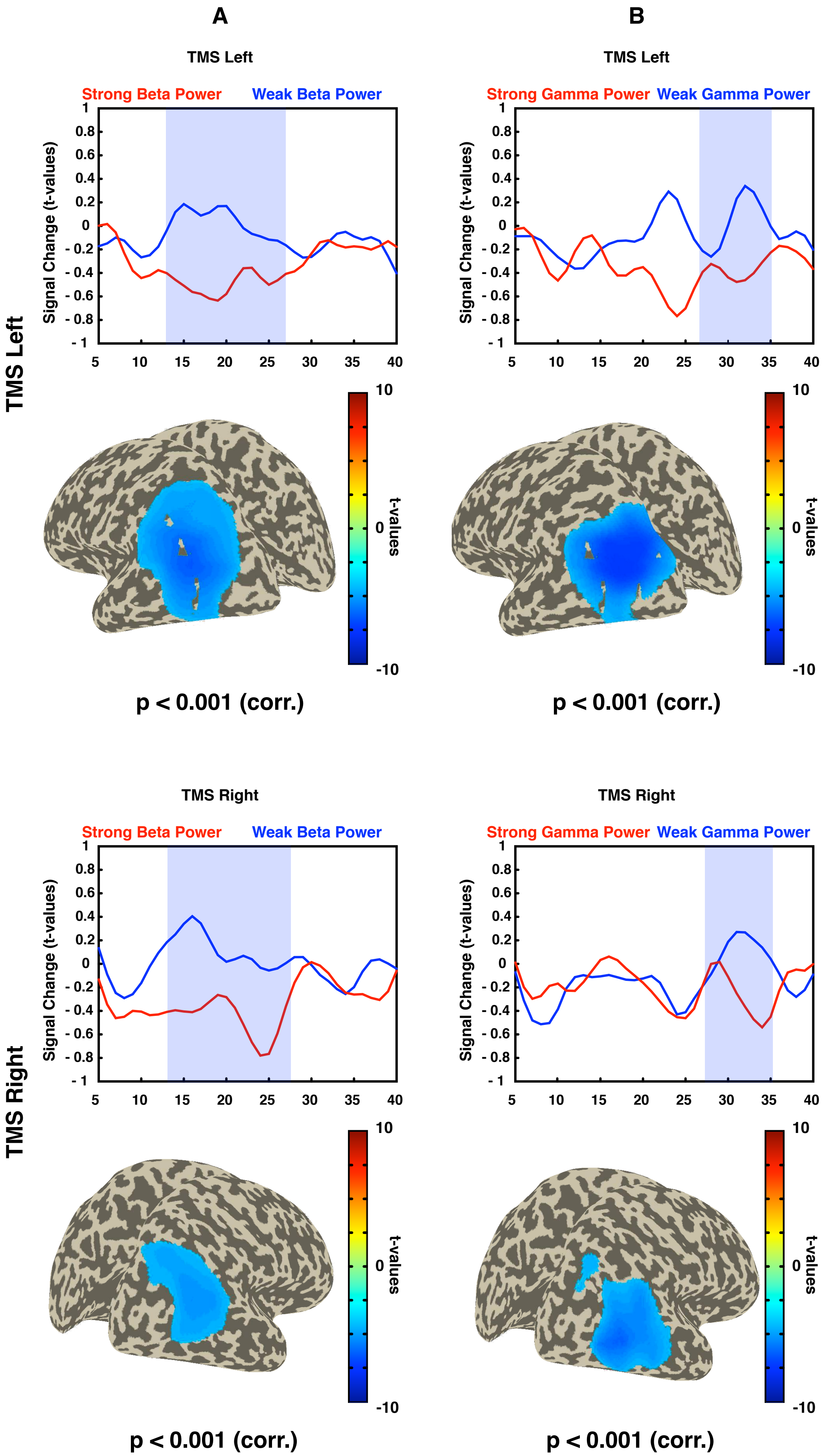
A
B
TMS Left
TMS Left
Strong Beta Power
Weak Beta Power
Strong Gamma Power
Weak Gamma Power
Signal Change (t-values)
t-values
p < 0.001 (corr.)
p < 0.001 (corr.)
TMS Right
TMS Right
Strong Beta Power
Weak Beta Power
Strong Gamma Power
Weak Gamma Power
p < 0.001 (corr.)
p < 0.001 (corr.)

Figure 20:

Trials sorted by local pre-TMS power at the site of stimulation. (A) Comparison of signal change (t-values) between strong and weak pre-TMS beta-band power trials. Strong pre-TMS beta power trials are marked by a decrease in beta-band power following bilateral TMS stimulation, whereas a beta-band power increase is found following weak pre-TMS beta-band power. (B) Comparison of signal change (t-values) between strong and weak pre-TMS gamma-band power trials. Strong pre-TMS gamma power trials are marked by a decrease in gamma-band power following bilateral TMS stimulation, whereas a gamma-band power increase is found following weak pre-TMS beta-band power.

4.4. Discussion:

In the present study, we used EEG analysis of the sound-induced flash illusion as a tool to investigate the influence of ongoing oscillatory activity on variable perception of invariant stimuli and tried to influence this perception using bilateral single pulse TMS to the multi-sensory BA39 in the temporo-parietal cortex.

We demonstrate that ongoing oscillatory activity has a wide range of effects on the fate of audiovisual stimulation and upcoming perception as well as on the outcome of external TMS perturbation. The first main finding is that ongoing oscillatory power influences upcoming perception. Low gamma power is significantly increased in the right temporal cortex if an illusion is subsequently perceived. Secondly, albeit to a weaker extent, increases in high beta/ low gamma power in left temporal areas following single-pulse TMS predispose an upcoming illusory perception, thus partially confirming our previous MEG results. The third main finding is that ongoing pre-TMS oscillatory power influences the effect of single-pulse TMS at the level of brain activation as well as behaviour. As a general pattern, strong oscillatory power is decreased whereas weak power is increased by TMS in brain regions remote to as well as at the site of stimulation.

4.4.1. Ongoing Oscillatory Power Influences Upcoming Perception:

Audiovisual integration has been localised a number of times in the superior temporal gyrus (Calvert et al., 2000; Barraclough et al., 2005) and we could recently show that pre-stimulus beta-band power in the left STG also influences upcoming audiovisual integration as seen in the McGurk effect (Keil et al., 2011) as well as in the sound-induced flash illusion. In contrast to our hypothesis and our previous results indicating that beta-band power in left temporal and temporo-parietal cortex influences upcoming perception, we found in the present study that high beta/low gamma-band activity in the right temporal cortex predisposes variable perception of an invariant stimulus in the trials *without TMS*. In the analysis of trials *with TMS*, we found that single-pulse TMS to the left and right temporo-parietal cortex abolishes these right temporal gamma power differences and that power differences between the illusion and non-illusion trials are seen in the left temporal cortex. This underlines the important influence of the state of the left temporal cortex prior to audiovisual stimulation on upcoming perception. Additionally, the stronger gamma-band power preceding an illusion in the trials with TMS that we found in the present study appears to be dependent on the TMS and not to be related to the pre-TMS brain state, as the pre-TMS gamma-band power did not influence the perception. Taken together, these results partially confirm our first hypothesis. They overlap with our previous findings that the brain state prior to audiovisual stimulation influences upcoming perception. However, aside from beta-band activity in the left temporo-parietal cortex, high beta/low gamma-band power in the left and right temporal cortices also critically influence perception.

Given that we used EEG in present study in contrast to MEG in our previous work, it is possible that we tapped into two different processes of the same mechanism. Hipp et al. (Hipp et al., 2011) also recently reported that pre-stimulus beta as well as gamma-band activity predict upcoming perception of a bistable stimulus. The authors attributed the beta-frequency activity to a general mechanism mediating large-scale interactions across a larger network of frontal, parietal and sensory areas, whereas the strength of gamma-frequency activity influenced the local audiovisual integration. This view is also shared by Siegel et al. (Siegel et al., 2012), who attribute spectral fingerprints to network processes underlying cognition. In this review, the authors assign the beta frequency range a role in the top-down control of attention via a larger network, and the gamma frequency range a role in local bottom-up processes. These roles are also supported by considerations of the spatial distance between network nodes. Longer distances and therefore longer conduction delays between distant brain regions might limit the frequency of network oscillations (Kopell & Ermentrout, 2000; von Stein & Sarnthein, 2000). The beta-band power and phase effects reported in our previous MEG studies could be seen as the fingerprint of a larger top-down attentional process, whereas the local gamma-band power increase prior to an audiovisual illusion could index a local integration of auditory and visual patches in the temporal cortex (Beauchamp, 2005) and may provide the necessary spatial and temporal links that bind together the processing to build a coherent percept (Tallon-Baudry & Bertrand, 1999). Moreover, Beauchamp et al. (Beauchamp, 2005) identified multi-sensory cortical areas in both hemispheres in the superior temporal and temporo-parietal cortex. Our results of a right temporal pre-stimulus effect in the present study and, on the other hand, a left temporal pre-stimulus effect in our previous work, support this. It is noteworthy that the right temporal cortex shows strong modulations, which underlines the importance of the right hemisphere in addition to our previous findings for the left temporal cortex. Although TMS did not lead to an overall change in perception, it modulated the global brain state, so that the location of the largest differences in local power shifted hemispheres.

Moreover, the current finding of an influence of TMS on perception depending on the *pre-TMS* beta-band power but not on the gamma-band power supports the relevance of beta-band activity for multi-sensory perception despite the lack of a significant beta-band power modulation in absence of TMS.

4.4.2. Ongoing Oscillatory Power Influences the Effect of Single-Pulse TMS:

Contrary to our hypothesis, we did not find a significant difference in the comparison of the likelihood of an audiovisual illusion between trials with TMS and without TMS in the present study. The results of a recent TMS study on the McGurk effect by Beauchamp et al. (Beauchamp et al., 2010) might serve as an explanation for the weak influence of TMS on perception. Although a reduction in the likelihood of an illusion following pre-stimulus TMS was reported, a significant reduction could only be achieved as early as 120 ms before the stimulus onset. It is therefore possible that the cortex had already recovered from the perturbation 500 ms beforehand, as in the current experimental setup. An alternative explanation for the small influence of TMS on the behaviour could be the suboptimal orientation of the coil to the target area, as TMS-effects have been shown to be highly dependent on coil orientation (Mills, Boniface, & Schubert, 1992; Thut et al., 2011). We only identified the individual location of the targeted BA39 in the structural MR image based on a previous MEG study and did not identify the individual orientation of the target gyrus, but placed the TMS coil in the assumed perpendicular orientation. Thut et al. (Thut et al., 2011) report findings with rhythmic alpha TMS, in which 90°-rotated TMS had similar—albeit significantly smaller—effects as optimally oriented TMS.

A different line of explanation may be the considerable amount of state-dependent TMS effects. It has been shown by others (Siebner et al., 2004; Silvanto et al., 2008), Weisz et al. 2012) that TMS effects are dependent on the pre-TMS brain state. The question thus remains whether the pre-TMS state in terms of oscillatory power can help untangle the TMS effects. As hypothesised, the influence of TMS on perception varied with the strength of local beta-band power prior to stimulation. In the present study we looked at signal change influencing upcoming perception and found increased high beta and gamma-band power prior to an upcoming illusion throughout the analysis. However, perception of the illusion was significantly influenced depending on the modulation of pre-TMS beta-band power by TMS. In fact, after splitting the trials with TMS into trials with strong and weak pre-TMS beta power, it emerged that TMS modulates perception in a state-dependent fashion. An audiovisual illusion was significantly more likely following right hemisphere TMS in the strong pre-TMS beta-band trials than in the weak pre-TMS beta-band trials, supporting the findings of Beauchamp et al. (Beauchamp et al., 2010), which indicate that TMS to the temporal cortex can influence audiovisual integration. This was found for trials sorted by local power at the site of stimulation and for trials sorted by global power. It is crucial to note, however, that although strong power decreased, it was still significantly stronger than the increased power in the weak-power trials (see supplementary figures 1, 2, 3 and 4), thus supporting the findings from the trials without TMS that increased (i.e., stronger local power abets an illusion). Importantly, the same pattern emerged following TMS in both hemispheres: the perturbation of a state of strong beta-band power led to a reduction in beta-band power, whereas, conversely, the perturbation of a state of weak beta-band power led to an increase in beta-band power. This supports the view (Silvanto et al., 2008; Weisz et al., 2012) that the current brain state influences the effect of TMS and is a further hint at the importance of the brain state in the reaction to external stimulation. The idea that differential modulation of cortical activity could lead to a modulation of perception was also addressed by Bolognini et al. (Bolognini et al., 2011). The authors show that the perception of the sound-induced flash illusion increased following anodal tDCS (transcranial direct current stimulation) of the temporal cortex and decreased following anodal stimulation of the occipital cortex; additionally, this effect was reversed with a reversal of polarity. A similar effect was found in the perception of TMS-induced visual phosphenes (Romei et al., 2008; Hartmann et al., 2011). These authors found that, depending on the alpha-band power in the visual cortex, TMS can elicit a phosphene. This indicates that TMS has different effects depending on the current state of the brain— in these cases indexed by alpha power. A highly important aspect of the present results—and going beyond currently discussed notions in the TMS state-dependency literature—is that TMS induced a strong modulation of oscillatory power at the site of stimulation but also in supposedly connected regions in the inferior frontal and anterior temporal cortex. This supports the interpretation that different pre-TMS power levels reflect non-identical brain connectivity configurations that are then probed via TMS. If TMS were only to affect the cortical area at the site of stimulation, we would not find a consistent modulation of power in distant brain regions. This builds upon previous findings of the brain state dependency of TMS and adds more evidence to the importance of network processes prior to stimulation as well as the long-distance effect of local stimulation. This is in line with the findings by Siebner et al. (Siebner et al., 2009) that the spread of neuronal excitation throughout a neuronal network depends on the network state. Presumably, active connections produce a more disruptive effect on the functional interplay between the stimulated areas and connected brain regions. The global and local states of activation lead to a different mode of action of single-pulse TMS.

4.4.3. Conclusion:

The current brain state influences the perception as well as impact of external perturbation. An increase in local high beta/low gamma-band power in the right temporal cortex significantly influences the fate of an upcoming audiovisual stimulus. Similarly, beta and gamma-band power prior to TMS stimulation significantly influence the fate of oscillatory power at the site of stimulation and also presumably connected regions. The present study adds evidence to the importance of pre-stimulus local and network activity on upcoming perception and external stimulation. Further research is needed to closely examine the role of

TMS on oscillatory activity in areas outside the motor cortex. The combination of EEG and TMS promises to help disentangle the influence of global brain state.

5. General Discussion

The current work started with the notion that identical stimuli can elicit different cortical responses, a notion that - although not new - has received a lot of attention in the last decade.

The goal of the three studies presented here was to elucidate the role of pre-stimulus activity in the reaction to stimulation. This pre-stimulus activity has often been regarded as irrelevant noise, however I argued based on empirical and theoretical considerations that it carries valuable and decisive information for the reception and perception of external stimuli. Local activity characterised by the power of an oscillatory frequency, but also activity in larger networks spanning distant cortical regions - signalled by phase coherence of oscillatory activity between regions - significantly influences how our brain reacts to stimulation, how we perceive events and ultimately what we become conscious of.

In the *first study*, pre-stimulus beta-band power in the left superior temporal gyrus was found to be stronger if an audiovisual fusion in the McGurk illusion was subsequently perceived. Moreover, increased phase coupling with fronto-parietal areas but decreased coupling with inferior temporal cortex prior to stimulus onset facilitated the fusion between mismatching auditory and visual information. This fusion thus influenced the perception of the subjectively congruent illusion.

This finding was replicated with a much simpler audiovisual illusion in the *second study.* Increased pre-stimulus beta-band power in a left multi-sensory cortical area preceded the subjective perception of multiple visual stimuli in the sound induced flash illusion. Beta-band phase coupling between the multi-sensory left temporo-parietal cortical area showing the power modulation and the left auditory cortex could predict the upcoming perception in each trial. Stronger local activity and stronger coupling between multi-sensory and uni-sensory areas furthered the fusion between auditory and visual information. And again: the fusion influenced the illusory subjective perception of multiple visual stimuli aside the multiple auditory stimuli.

The repetition of the second study in the EEG instead of the MEG in the *third study* revealed that not only beta-band power but also modulations of gamma-band power influence the perception of the sound induced flash illusion. Additionally, the pre-stimulus state of cortical activity was found to influence the effect of an electrical stimulus delivered via TMS. The pattern of cortical activity changed depending on local and global power prior to stimulation and had different effects on the subsequent perception of the illusion. Stronger local and global beta-band power preceded the fusion between auditory and visual information. As in the previous two studies, this fusion influenced the subjective perception of incongruent audiovisual stimuli.

5.1. Conclusion:

The state of cortical activity prior to stimulation as described by local oscillatory power and phase coupling between distant areas influences how stimuli of different modalities are integrated. We however only become aware of the *result* of the integration. In the introduction, I cited the analogy to politics by Siegel et al. (Siegel et al., 2012): One coalition governs. Based on the current findings, it can be argued that one coalition of sensory inputs governs the subjective perception. The content of the percept changes depending on the constitution of the coalition. In case of mismatching sensory input, the percept can thus be either a fusion between the single inputs or a shift to one of the modalities. One key to understanding how we become conscious of the world around us thus is to understand how different modalities are integrated and how specific cortical properties influence the integration but also sensation of the single sensory inputs.

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Figures:

Figure 1:

Trial and timing overview with relative responses. (A) Example trial with two video frames from a video used in this experiment (top row), the audio trace of the syllable "aba" presented simultaneously to the video (middle row). Mouth movement and audio onset occur at time 0 ms. The interval prior to this is referred to as "pre-stimulus". (B) Box plot with responses relative to the total number of trials per category. On average, congruent trials were correctly identified in 96.19 % of cases. A "fusion" percept was reported in 41.61% of incongruent trials, whereas a unimodal percept was reported 48.02% of the time.

Figure 2:

Summarised results of the timecourse-analysis. (A) Event-related field trace of the positive sensor cluster for the "fusion" (red), and "unimodal" (blue) trials as well as the t-values for the comparison between the two conditions (green). (B) Topography (t-values, "fusion" vs. "unimodal" trials) of the positive sensor cluster (masked for statistical significance) found in the statistical analysis between 550 ms and 650 ms after sound onset. (C) Source projection (t-values, "fusion" vs. "unimodal" trials) of the effect found in the ERF analysis based on the LCMV analysis masked for statistical significance.

Figure 3:

Summarised results of the pre-stimulus time-frequency-analysis. (A) Time-frequency representation of the pre-stimulus interval at sensor level for the comparison between "fusion" and "unimodal" trials. Time 0 ms indicates the onset of mouth movement and audio stream. (B) Topography (14-30 Hz, -380 to -80 ms) of the positive beta band cluster found in the pre-stimulus interval at sensor level for the comparison between "fusion" and "unimodal" trials. (C) DICS source projection of the beta band effect found at sensor level. Left superior temporal gyrus (left), precuneus (middle) and right middle frontal gyrus (right) were identified as possible generators of the beta band effect. Displayed are t-values of the comparison between trials with a "fusion" percept versus a "unimodal" percept masked for statistical significance.

Figure 4:

Correlation between the tendency towards a "fusion" percept and the voxel-wise power difference values for the comparison between "fusion" and "unimodal" trials. Right inferior frontal gyrus (A) displayed a high positive correlation (B) with the "fusion" versus "unimodal" power difference. Displayed are correlation indices r masked for statistical significance. Positive reaction tendency indicates a high tendency towards a “fusion” percept.

Figure 5:

Phase synchrony between the seed region in left superior temporal gyrus (far left) and the whole brain volume as well as correlation with the tendency towards a “fusion“ percept. (A) Displayed are t-values of the comparison between trials with a “fusion” percept versus a “unimodal” percept masked for statistical significance. Right middle temporal gyrus (top left) and left middle frontal gyrus (top right) were found to be functionally coupled to the lSTG. Bilateral superior temporal gyrus (bottom left), medial frontal gyrus (bottom middle) and left fusiform gyrus (bottom right) were found to be functionally decoupled from the lSTG. (B) Correlation between the tendency towards a “fusion” percept and the voxel-wise difference values for the comparison between “fusion” and “unimodal” trials for the phase synchrony with the lSTG. Displayed are correlation indices r masked for statistical significance. Anterior right superior temporal gyrus (top left) and right inferior temporal gyrus (bottom left) displayed high negative correlations. Bilateral superior parietal lobule (top right), cingulum (top middle), posterior right superior temporal gyrus (bottom middle) and left middle occipital gyrus (bottom right) displayed high positive correlations.

Figure 6:

Summarised results of the post-stimulus time-frequency-analysis. (A) Time-frequency representation of the post-stimulus interval at sensor level for the comparison between “fusion” and “unimodal” trials. Time 0 ms indicates the onset of mouth movement and audio stream. (B) Topography (3-7 Hz, 200 to 600 ms) of the negative theta band cluster found in the post-stimulus interval at sensor level for the comparison between “fusion” and “unimodal” trials. (C) DICS source projection of the theta band effect found at sensor level. Left superior frontal gyrus (left), precuneus (middle) and cuneus (right) were identified as possible generators of the theta band effect. Displayed are t-values of the comparison between trials with a “fusion” percept versus a “unimodal” percept masked for statistical significance.

Figure 7:

Correlation between the tendency towards a “fusion” percept and the voxel-wise power difference values for the comparison between “fusion” and “unimodal” trials. Right inferior frontal gyrus (A and B) displayed a high negative correlation. Right superior frontal gyrus (C and D) displayed a high positive correlation with the “fusion” versus “unimodal” power difference. Displayed are correlation indices r masked for statistical significance. Positive reaction tendency indicates a high tendency towards a “fusion” percept.

Figure 8:

(A) Schematic representation of a critical trial in the present study. The presentation of the fixation cross was followed by that of a short visual stimulus accompanied by a short auditory stimulus. After an interval of 50 ms, the second auditory stimulus was presented. (B) Behavioral results in the present study. Subjects perceived a sound-induced flash illusion (response „2“) in 46% of critical trials.

Figure 9:

Schematic description of the source phase difference analysis procedure. In a first step, phase difference (Δ phase) between cortical sources for every trial and the mean Δ phase were computed. In a second step, the difference between the mean Δ phase and each individual Δ phase was computed. These differences between Δ phase values were binned into subject-individual quartiles and the relative proportion of illusion trials per quartile was counted.

Figure 10:

(A) Root mean square of the event-related field for the channels showing a significant difference between the perceptual conditions as well as t-values for the comparison. The red bar marks the interval for yielding a significant difference. (B) Topography of the interval for yielding a significant difference between the illusion and non-illusion trials. Higher values (larger t-values, red) indicate greater field strength. (C) Source projection for the interval identified in the sensor-level analysis. The LCMV-beamformer identified the cingulate cortex as the source of this effect.

Figure 11:

(A) Wavelet time-frequency representation of the difference between illusion and non-illusion trials in the 500 ms interval before stimulus onset. Higher values (larger t-values, red) indicate relatively more power in the illusion trials. Topography of time and frequency range (-500 ms to - 100 ms, 13-21 Hz) yielding a significant difference between illusion and non-illusion trials. Higher values (larger t-values, red) indicate relatively more power in the illusion trials. (C) Source projection for the time-frequency range identified in the sensor-level analysis. The DICS-beamformer identified the left middle temporal gyrus (BA39) as the source of this effect.

Figure 12:

(A) Correlation between an individual's reaction tendency to perceive the illusion and voxel-wise pre-stimulus beta power (13-21 Hz) difference between illusion and non-illusion trails. (B) This correlation was localised in the left middle frontal gyrus (BA9).

Figure 13:

Results of the source-level phase synchrony analysis. Positive t-values (red) indicate stronger phase-synchrony in the illusion trials, negative t-values indicate stronger phase synchrony in the non-illusion trials. In the beta band (dashed lines), BA39 was found to be more strongly phase-locked to anterior temporal area BA21 and less phase-locked to occipital area BA18 in illusion trials. In the alpha band (solid lines), the primary auditory cortex was found to be more strongly phase-locked to occipital area 18. The primary visual cortex was more strongly phase-locked to frontal (MFG) and parietal (BA4) areas, but less phase-locked to inferior frontal area BA44.

Figure 14:

Source-level phase difference between BA39 and BA21. We computed the beta-band phase deviance from the mean phase difference between the sources and binned it into quartiles. Displayed is the relative proportion of illusion trials per quartile. In the first quartile, the proportion of illusion trials was above chance level and larger than in the third and fourth quartile. Error bars indicate the 95% confidence interval.

Figure 15:

Schematic description of an incongruent trial. In trials with TMS, a single TMS pulse was given either to the left or right BA39 500 ms prior to stimulus onset.

Figure 16:

Behavioural Results. Comparison of the relative proportion of illusion trials in all incongruent trials in the 'No TMS', 'Left TMS' and 'Right TMS' conditions. No significant differences between the conditions were found.

Figure 17:

Comparison of illusion versus non-illusion trials. Comparison of signal change (t-values) between illusion and non-illusion trials for the No-TMS (A), TMS left (B) and TMS right (C) conditions. Illusion trials are consistently marked by an increase in pre-stimulus gamma power relative to baseline.

Figure 18:

Comparison of the relative proportion of illusion trials in all incongruent trials with TMS either to the left or right BA39. A significant difference in the likelihood of an illusion between trials with strong and weak pre-TMS beta power was found for the 'Right TMS' condition. This was found for trials sorted by global power (A) as well as for trials sorted by local power at the site of stimulation (B).

Figure 19:

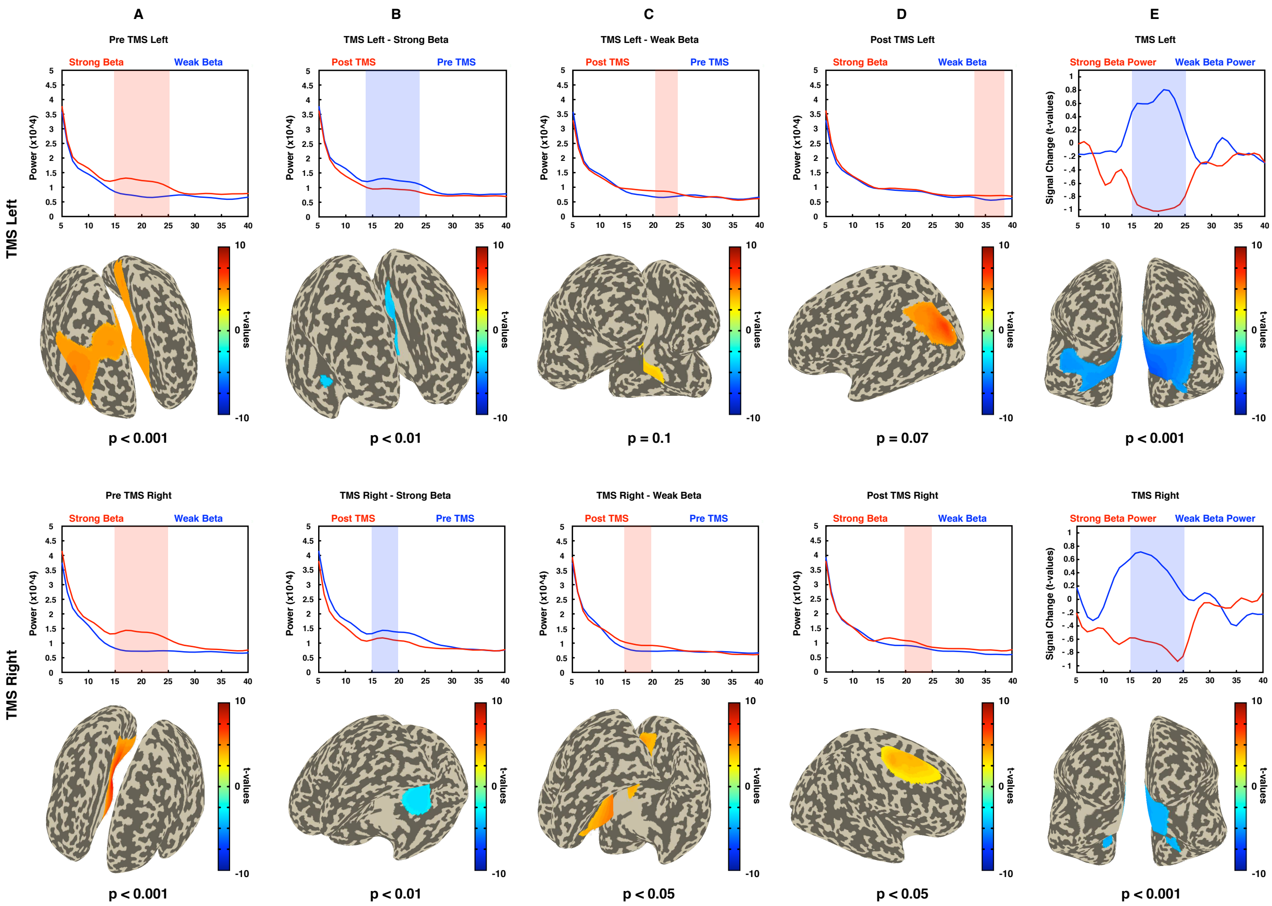
Trials sorted by global pre-TMS power. (A) Comparison of signal change (t-values) between strong and weak pre-TMS beta-band power trials. Strong pre-TMS beta power trials are marked by a decrease in beta-band power after bilateral TMS stimulation whereas a beta-band power increase is found following weak pre-TMS beta-band power. (B) Comparison of signal change (t-values) between strong and weak pre-TMS gamma-band power trials. Strong pre-TMS gamma power trials are marked by a decrease in gamma-band power following bilateral TMS stimulation, whereas a gamma-band power increase is found following weak pre-TMS beta-band power.

Figure 20:

Trials sorted by local pre-TMS power at the site of stimulation. (A) Comparison of signal change (t-values) between strong and weak pre-TMS beta-band power trials. Strong pre-TMS beta power trials are marked by a decrease in beta-band power following bilateral TMS stimulation, whereas a beta-band power increase is found following weak pre-TMS beta-band power. (B) Comparison of signal change (t-values) between strong and weak pre-TMS gamma-band power trials. Strong pre-TMS gamma power trials are marked by a decrease in gamma-band power following bilateral TMS stimulation, whereas a gamma-band power increase is found following weak pre-TMS beta-band power.

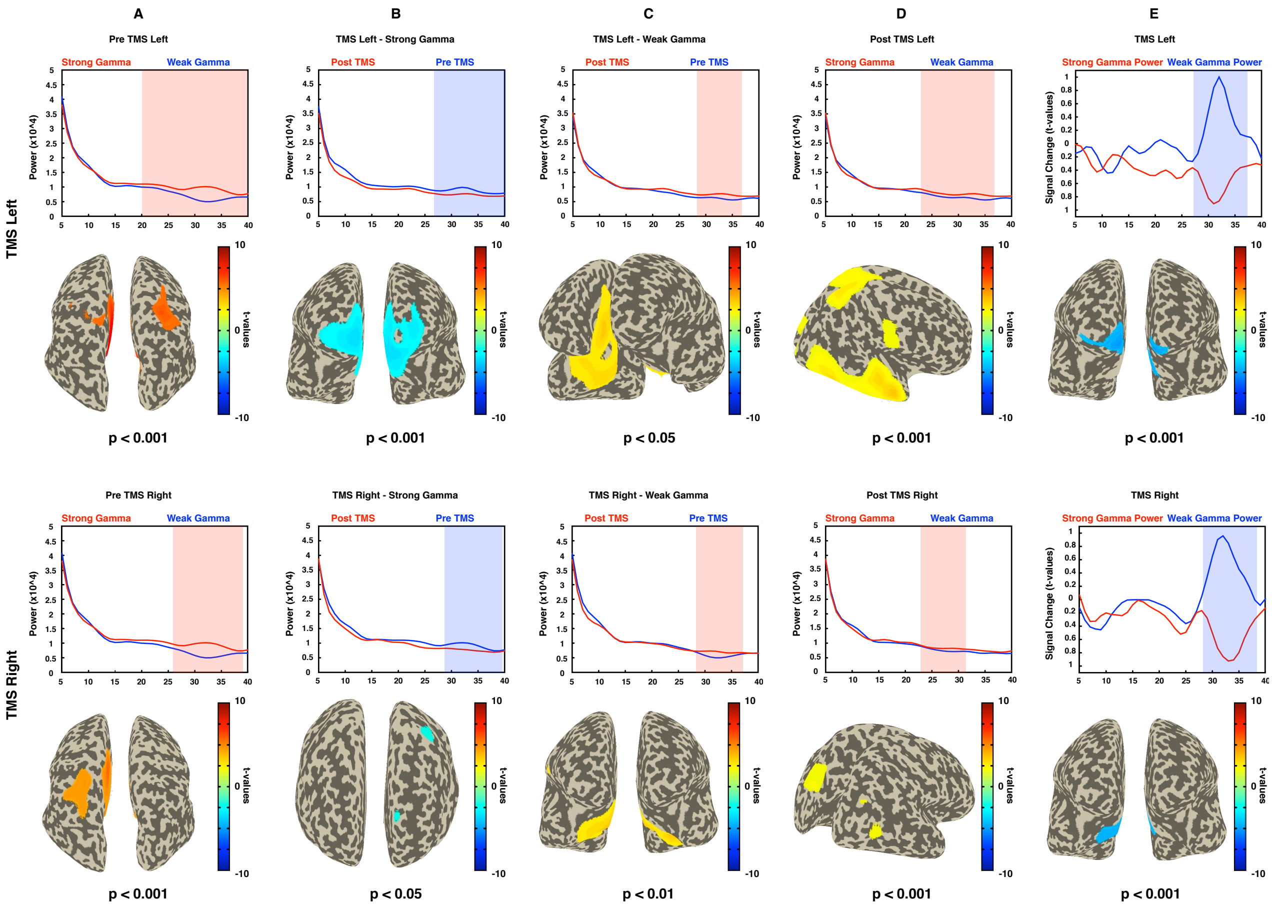
Supplementary Material:

Supplementary Figure 1:



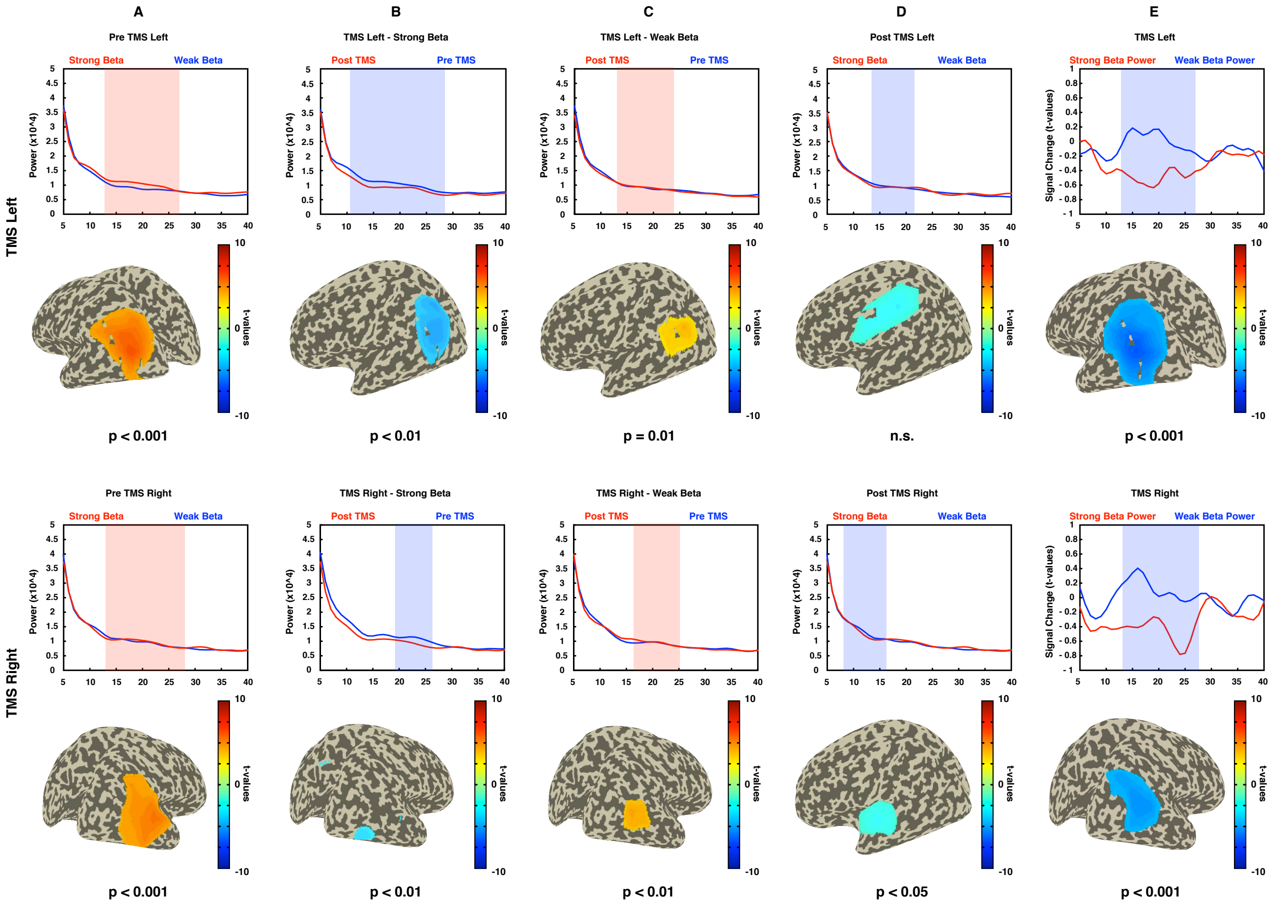
Trials sorted by global pre-TMS beta-band power. Comparison of power and signal change (t-values) between strong and weak beta-band trials. (A) Pre-TMS beta power differences between strong and weak pre-TMS power trials. Note that trials were selected based on strong or weak pre-stimulus beta power. (B) Signal change for the strong pre-TMS beta power trials. Left and right TMS were followed by a decrease in beta-band power. (C) Signal change for the weak pre-TMS beta power trials. Right TMS was followed by an increase in beta-band power, the power increase following left TMS was not significant. (D) Post-TMS power differences between strong and weak pre-TMS power trials. Strong pre-TMS power trials were marked by higher gamma-band power in the left occipito-parietal cortex following left hemisphere stimulation and higher beta-band power over right parietal cortex following right hemisphere stimulation. (E) Comparison of signal change (t-values) between strong and weak pre-TMS power trials. Strong pre-TMS beta power trials are marked by a decrease in beta-band power following bilateral TMS stimulation.

Supplementary Figure 2:



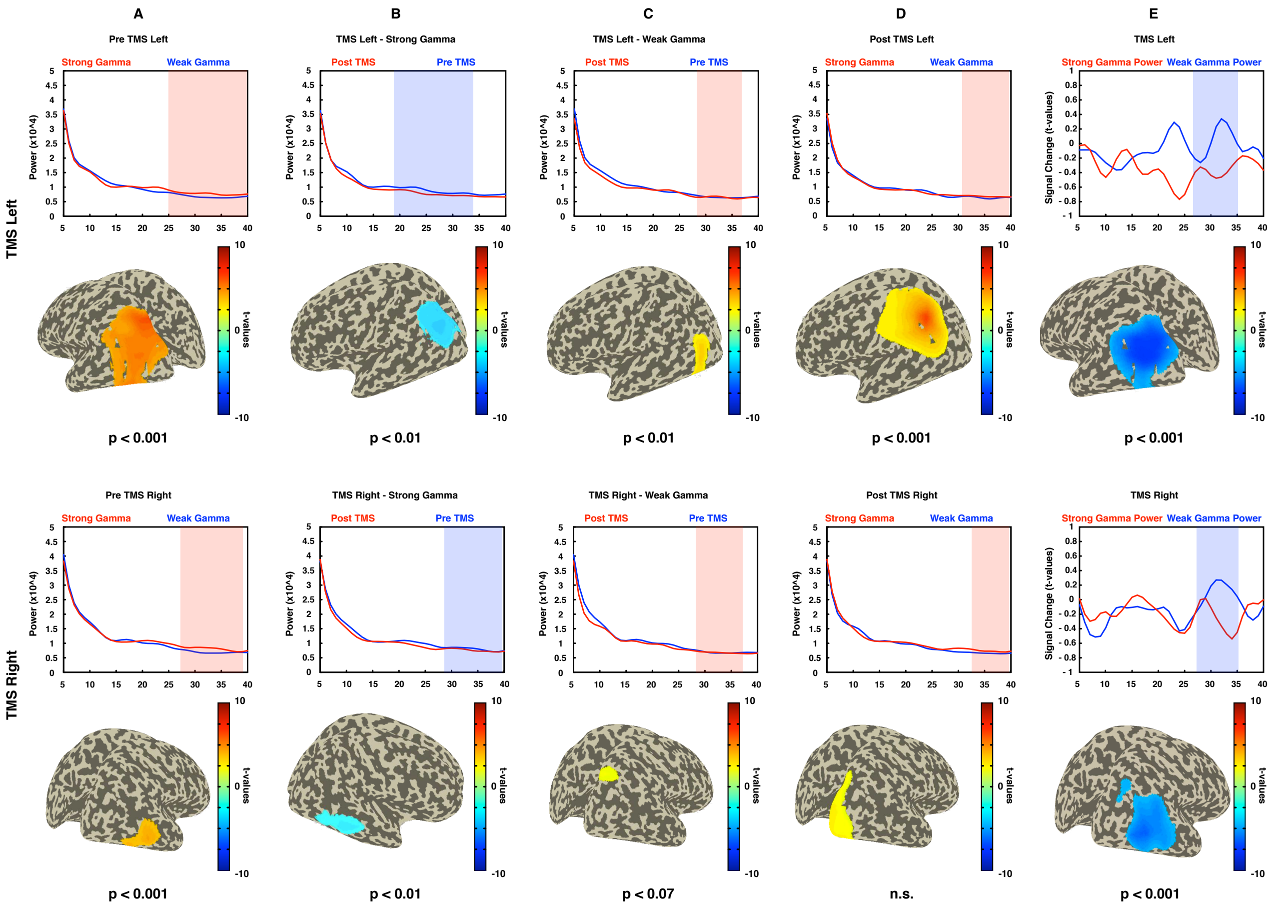
Trials sorted by global pre-TMS gamma-band power. Comparison of power and signal change (t-values) between strong and weak gamma-band trials. (A) Pre-TMS gamma power differences between strong and weak pre-TMS power trials. Note that trials were selected based on strong or weak pre-stimulus gamma power. (B) Signal change for the strong pre-TMS gamma power trials. Left and right TMS were followed by a decrease in gamma-band power. (C) Signal change for the weak pre-TMS gamma power trials. Left and right TMS were followed by an increase in gamma-band power. (D) Post-TMS power differences between strong and weak pre-TMS power trials. Strong pre-TMS power trials were marked by higher gamma-band power in the left temporal cortex and precuneus following TMS. (E) Comparison of signal change (t-values) between strong and weak pre-TMS power trials. Strong pre-TMS gamma power trials are marked by a decrease in gamma-band power following bilateral TMS stimulation.

Supplementary Figure 3:



Trials sorted by pre-TMS beta-band power at the respective site of stimulation. Comparison of power and signal change (t-values) between strong and weak beta-band trials. (A) Pre-TMS beta power differences between strong and weak pre-TMS power trials. Note that trials were selected based on strong or weak pre-stimulus beta power. (B) Signal change for the strong pre-TMS beta power trials. Left TMS was followed by a decrease in a wide frequency range spanning from the alpha to the gamma-band. Right TMS was followed by a decrease in beta-band power. (C) Signal change for the weak pre-TMS beta power trials. Left and right TMS were followed by an increase in beta-band power. (D) Post-TMS power differences between strong and weak pre-TMS power trials. The beta-band difference between strong and weak beta-band trials in left parietal cortex following left TMS failed to reach significance. Following right hemisphere TMS, we found stronger alpha power in the left anterior temporal cortex in the weak beta trials. (E) Comparison of signal change (t-values) between strong and weak pre-TMS power trials. Strong pre-TMS beta power trials are marked by a decrease in beta-band power after bilateral TMS stimulation.

Supplementary Figure 4:



Trials sorted by pre-TMS gamma-band power at the respective site of stimulation. Comparison of power and signal change (t-values) between strong and weak gamma-band trials. (A) Pre-TMS gamma power differences between strong and weak pre-TMS power trials. Note that trials were selected based on strong or weak pre-stimulus gamma power. (B) Signal change for the strong pre-TMS gamma power trials. Left and right TMS were followed by a decrease in gamma-band power. (C) Signal change for the weak pre-TMS gamma power trials. Left and right TMS were followed by an increase in gamma-band power. (D) Post-TMS power differences between strong and weak pre-TMS power trials. Strong pre-TMS gamma-band trials were marked by an increase in left parietal gamma power following left TMS. Following right TMS, the stronger gamma-band power in the occipital lobe failed to reach significance. (E) Comparison of signal change (t-values) between strong and weak pre-TMS power trials. Strong pre-TMS gamma power trials were marked by a decrease in gamma-band power following bilateral TMS stimulation.