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Impact of ongoing alpha oscillations on visual perception and neurophysiological response: an integration with a psychophysical approach

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ABSTRACT

Neural oscillations are considered to be the building blocks of cognitive functioning, and in the last decades neuroscientists have developed fundamental theories on their role in brain dynamics. Recently, a growing body of evidences has shown that ongoing oscillatory activity can account for a considerable amount of variability in behavioral performance and in neurophysiological response. In the domain of visual perception, a crucial role is played by neural oscillations within alpha frequency range. Alpha activity is believed to exert an inhibitory function on stimulus processing and to reflect cortical excitability, both when it fluctuates spontaneously as well as when it is modulated, by top-down or bottom-up mechanisms. It has been recently suggested that alpha rhythm may not be considered as a unitary phenomenon; however, still little is known about the neural mechanisms associated with alpha activity as measured by non-invasive recordings. Furthermore, up to now most of the studies on the effects of ongoing alpha activity on visual perception focused on a special class of stimuli, i.e., with a near-threshold intensity, and much less is known about what happens in the response beyond sensory threshold.

In the present work, we aimed at addressing these issues by studying the effects of ongoing alpha oscillations on perceptual and neurophysiological outcome in the visual domain. The first goal was to replicate recent findings on the effects of spontaneous fluctuations of pre-stimulus alpha power and phase on a visual detection task, by using near-threshold stimuli. In addition to the original study, the use of magnetoencephalography allowed us to reconstruct brain sources of pre-stimulus and evoked activity. In a second study, we aimed at modulating ongoing alpha activity by using a sensory deprivation paradigm, and tested the effects of such modulation by means

of a wide range of stimulation intensities. The use of transcranial magnetic stimulation (TMS) with concurrent electroencephalography allowed to directly assess the neurophysiological and perceptual response to TMS, by means of TMS-evoked potentials and phosphene perception. Finally, in a third study we developed a formal model of the effects of ongoing alpha activity on visual perception, with the aim of disentangling possible neural mechanisms which cannot be discerned non-invasively. The model is based on cross-frequency interactions between alpha functional inhibition and gamma activity of sensory neurons and highlights the advantages of presenting a wide range of stimulus intensities in the study of the effects of pre-stimulus oscillatory activity, using a psychophysical approach.

Taken together, our results are consistent with current literature about the inhibitory function played by ongoing alpha activity on visual perception. Indeed, both perceptual and neurophysiological response to an external stimulus were affected by pre-stimulus alpha activity, when it fluctuated spontaneously as well as when it was modulated by a sensory deprivation paradigm. Moreover, the present findings support the hypothesis that alpha oscillations subtend distinct mechanisms, and highlighted that new insights may arise from applying a psychophysical approach to the study of ongoing activity on perception.

By using different methodological approaches, the present work provides novel advances in the field of non-invasive investigation of ongoing oscillations on behavior, specifically on alpha inhibition of visual perception.

1. INTRODUCTION

1.1 Ongoing brain activity impacts behavior

The brain is never at rest: it is always involved in a metabolically demanding, endogenously driven neural activity (Raichle, 2011). Neuroscientists have been interested not only in the study of spontaneous activity *per se*, which led to the fruitful field of research on resting state dynamics (Cabral, Kringelbach, and Deco, 2014), but also in the impact of ongoing activity on behavior.

Furthermore, the brain's response does not depend entirely on external input: indeed, the repeated presentation of the same stimulus gives rise to highly variable response, in terms of behavioral performance as well as at the neural level (Vogels, Spileers, and Orban, 1989), a phenomenon that interestingly has been observed also in anesthetized animals (Tomko and Crapper, 1974). The traditional approach to neural evoked responses assumes that the actual response to an external stimulus is superimposed to some unrelated noise, which is believed to explain the observed variability. Ongoing activity is therefore obscured by averaging over trials or by normalization to pre-stimulus baseline, with the aim of improving signal-to-noise ratio (Picton, 2000). More recently, however, a consistent amount of evidence from several methodological perspectives has shown that ongoing neural activity contributes to the way the brain responds to sensory stimuli (Arieli, Sterkin, Grinvald, and Aertsen, 1996; Hesselmann, Kell, Eger, and Kleinschmidt, 2008; Kayser, McNair, and Kayser, 2016; Martin, Barnes, and Stevens, 2012; Schölvinck, Friston, and Rees, 2012; Weisz et al., 2014).

Since ongoing activity has been shown to account for a considerable portion of response variability, it cannot be deemed just as noise. Rather, it is a crucial aspect for signal

processing, and the study of its functional meaning represents an intriguing thread in neuroscience (Britz and Michel 2011; Sadaghiani and Kleinschmidt 2013; Ruhnau, Hauswald, and Weisz, 2014).

1.2 Neural oscillations in the study of brain dynamics

For a long time, from lesion studies to the spreading of modern neuroimaging techniques (e.g., functional magnetic resonance – fMRI, above all), cognitive neuroscience has been greatly interested in localization and segregation of brain functions, highlighting the importance of space dimension at the expense of time (Cohen, 2011). However, the limitations of stationarity assumption (i.e., considering brain activity to be constant in a given time-window) became increasingly clear, and time has regained increasing scientific consideration compared to space in neurocognitive research (Cohen, 2011). In this context, the high temporal resolution of electrophysiological recordings (e.g., magneto/electro-encephalography – M/EEG – for non-invasive investigation in humans) proved to be extremely valuable in the study of time-frequency patterns, especially in the study of the effects of ongoing activity on perception.

1.2.1 The role of alpha band

Alpha-band (8-13 Hz) oscillatory activity is dominant in the human brain: it represents the strongest electrophysiological signal measured non-invasively and it can be observed transversely across cognitive domains (Berger, 1929; Klimesch, 2012). The original interpretation of alpha rhythm as reflecting cortical "idling" (Pfurtscheller, Stancák, and Neuper, 1996) is not accepted anymore, because a large number of studies convincingly demonstrated its active role in task implementation, especially in top-down control processes (e.g., spatial attention; Banerjee, Snyder, Molholm, and Foxe, 2011). One of

the most widespread interpretation considers alpha activity as playing an inhibitory role in cortical areas not involved in the task: the larger the EEG alpha power, the stronger the inhibition (Klimesch, Sauseng, and Hanslmayr, 2007; Jensen and Mazaheri, 2010; but see Palva and Palva 2007). Moreover, inhibition appears to be cyclic, depending on the phase of alpha oscillations (referred to as "pulsed inhibition"; Mathewson et al., 2009).

1.2.2 Alpha-gamma cross-frequency interactions

At the neurophysiological level, the effects of top-down alpha inhibition are commonly described in terms of changes in neural excitability, which in turn affect signal processing (Klimesch, Sauseng, and Hanslmayr, 2007). In this context, a clear evidence has been reported by Haegens and colleagues (2011), who showed a decrease of firing rate during periods of high alpha power in monkeys. On the same line, recent hypotheses emphasize the involvement of cross-frequency interactions between alpha activity and gamma power (>30 Hz), the latter as a measure of neural processing (Fries, Nikolić, and Singer, 2007). It is worth noting that alpha and gamma are not the only frequency bands involved in cross-frequency interactions. In turn, alpha power appears to interact with slower rhythms, for example with delta and theta activity, in neurophysiological recordings as well as in behavioral time courses (Helfrich, Huang, Wilson, and Knight, 2017; Song et al., 2014).

Alpha-gamma interactions have been observed not only during stimulus processing but also during rest and in the pre-stimulus window. It has been suggested that at least two cross-frequency mechanisms characterize alpha-gamma relationship: gamma power not only is inversely correlated with alpha power, namely amplitude-amplitude coupling (AAC), but it also appears to be nested within the phase of alpha, i.e., phase-amplitude coupling (PAC; Spaak, de Lange, and Jensen, 2014). Intriguingly, PAC and AAC appear

to be linked, with stronger alpha power increasing PAC (Osipova, Hermes and Jensen, 2008).

1.2.3 Fundamental theories on neural oscillations

In the last decades, neuroscientists have developed fundamental theories on the role of neural oscillations in brain dynamics, which have been supported by a number of experimental findings: among the others, Communication Through Coherence (Fries, 2005) and Gating By Inhibition (Jensen and Mazaheri, 2010).

Communication Through Coherence (CTC)

According to CTC theory, neural oscillations play a crucial role in establishing communication among brain areas. The main concept of CTC theory states that neural communication, i.e., effective connectivity, is subserved by neural synchronization in the gamma rhythms, especially for bottom-up processes (Fries, 2005; Fries, 2015; Fries, Nikolić, and Singer, 2007). Synchronization occurs when excitability fluctuations of neural groups are coherent: for example, neural communication between two brain regions is enabled when they show the same oscillatory frequency (i.e., gamma band) with a constant phase difference over time. Within the CTC framework, synchronization ensures that temporal windows for input and output are concurrently open, thus enabling communication among neurons (**Figure 1.1**).

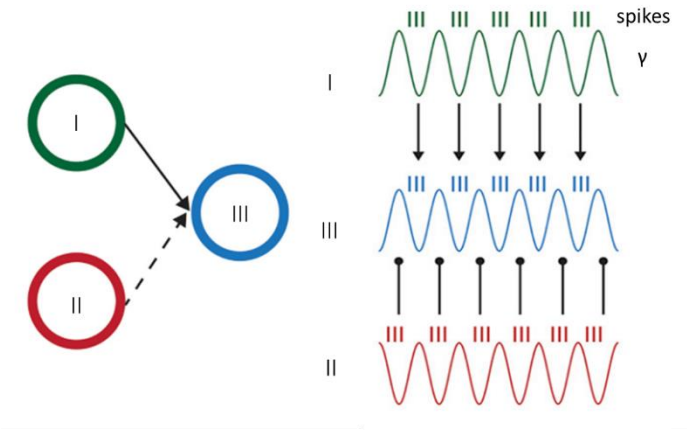


Figure 1.1 Schematic representation of the CTC framework (adapted from Bonnefond, Kastner, and Jensen, 2017). I, II and III represent three neural assemblies oscillating in the gamma band. Gamma synchronization between I and III ensures information flow from one neural assembly to the other, while communication between II and III is prevented by gamma desynchronization (II and III are shown in antiphase).

Gating By Inhibition (GBI)

The GBI framework (Jensen and Mazaheri, 2010) focused on the need of inhibiting task-irrelevant brain areas for optimal functioning, more than on how task-relevant ones are engaged. The main hypothesis is that, during task execution, neural pathways which are irrelevant for that specific task have to be functionally blocked, and this mechanism is provided by means of alpha power (**Figure 1.2-A**). Specifically, GBI predicts a positive correlation between task performance and alpha activity in brain areas which are irrelevant for such task. In the meantime, active processing in task-relevant areas is provided by oscillatory activity in the gamma band, in the presence of low alpha power (i.e., AAC). A central aspect for the GBI framework is that alpha activity is phasic, and thus gives rise to a pulsed inhibition: task-irrelevant brain regions are not continuously inhibited, but there are short time-windows in which gamma activity is present allowing neural processing (i.e., PAC). This concept is referred to as “duty-cycle”: the stronger the

alpha power the shorter the window of gamma bursts; thus, gamma activity occurs mainly during low alpha power and at the trough of alpha oscillations (**Figure 1.2-B**).

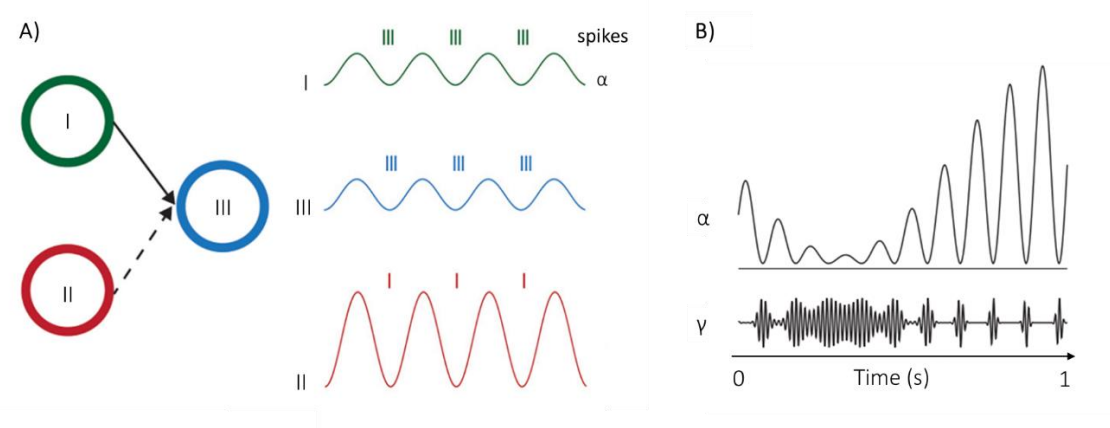


Figure 1.2 Concepts related to the GBI framework. **A)** Schematic representation of the GBI framework, adapted from Bonnefond, Kastner, and Jensen (2017). Communication between I and III is ensured by low alpha power in the two assemblies and by an increase alpha power in II, which blocks neural processing of a task-unrelated area. **B)** Concept of "duty cycle": the stronger the alpha power the shorter the time window of gamma bursts; gamma activity occurs when alpha power is low and at the through of alpha oscillations. Adapted from Osipova et al. (2008) and Jensen and Mazaheri (2010).

CTC and GBI: A unified framework

A recent proposal (Bonnefond, Kastner, and Jensen, 2017) aimed at unifying GBI (Jensen and Mazaheri, 2010) with CTC (Fries, 2005; Fries, 2015). According with the unified framework, two mechanisms act in a complementary way to ensure (and to block) the information flow, i.e. synchronization between regions and local power (**Figure 1.3**). Synchronization enables the interareal communication, and it has been suggested to occur in lower-frequencies (e.g., alpha band). Furthermore, the power of such low-frequency oscillations shapes the length of excitability windows within each cycle (**Figure 1.2-B**), thus determining the amount of information which can be transferred by means of feed-forward gamma oscillations.

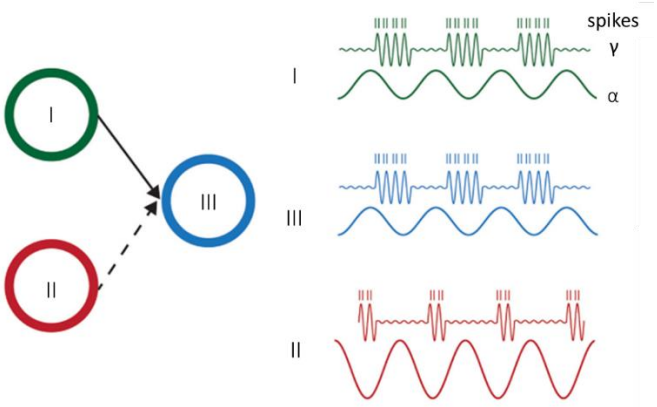


Figure 1.3 Schematic representation of the integration between CTC and GBI, adapted from Bonnefond, Kastner, and Jensen (2017). Communication between I and III is ensured by low alpha power and synchronization in the alpha band, which enables feed-forward gamma activity to flow from one region to the other one to ensure information transfer. High alpha power in II, together with phase asynchrony between II and III, blocks inter-areal communication.

1.3 M/EEG ongoing alpha activity affects visual perception

A growing body of evidence has shown that a considerable portion of the variability in visual tasks can be accounted by ongoing M/EEG alpha oscillations. The effects of pre-stimulus alpha activity on visual perception are commonly assessed by presenting stimuli at the individual sensory threshold intensity (i.e., the so-called "near-threshold stimuli", by definition detected in half of the trials; for a review see Ruhnau, Hauswald, and Weisz, 2014). In this context, single-trial analysis is crucial, since it allows to assess variance within-subjects, thus providing a richer data description (Pernet, Sajda, and Rousselet, 2011).

1.3.1 Effects of spontaneous trial-by-trial fluctuations

Visual perception has been shown to be influenced by spontaneous fluctuations in M/EEG alpha activity; specifically, parameters of both ongoing power and phase have been shown to have an effect on perceptual performance.

The effect of spontaneous variations in M/EEG power is well established: typically, trials with low levels of EEG alpha power preceding the stimulus (also known as anticipatory event-related desynchronization; Klimesch, Sauseng, and Hanslmayr, 2007) have higher probability of detection and/or discrimination, both between and within subjects (**Figure 1.4-A**; Busch and VanRullen, 2010; Hanslmayr et al., 2007; van Dijk, Schoeffelen, Oostenveld, and Jensen, 2008). Ongoing oscillatory activity can be described not only in terms of power, but also of phase: visual detection rate differs between opposite phases of 7-10 Hz oscillations (**Figure 1.4-B**; Busch, Dubois, and VanRullen, 2009; Busch and VanRullen, 2010; Mathewson et al., 2009).

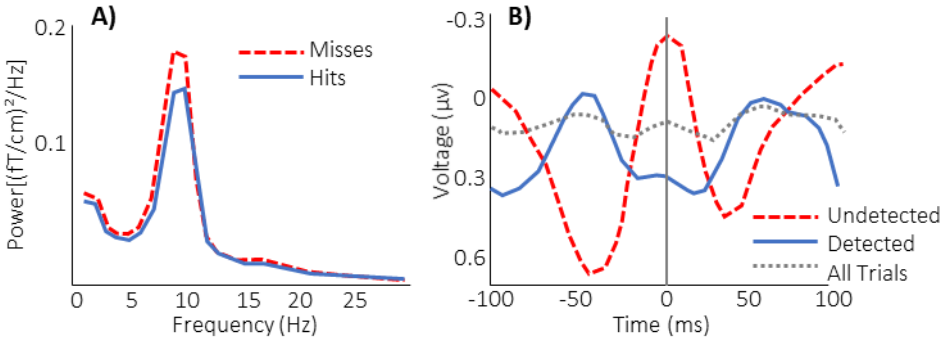


Figure 1.4. Effects of pre-stimulus alpha oscillations on visual detection. **A)** Alpha power: lower alpha power preceding the stimulus leads to a higher proportion of hits (grand average of the spectra calculated in 1 s before target onset in occipital MEG channels; adapted from van Dijk, Schoeffelen, Oostenveld, and Jensen, 2008). **B)** Alpha phase: opposite phases of alpha at target onset for detected and undetected targets (grand average ERP at EEG channel Pz; adapted from Mathewson et al., 2009).

Consistently with the literature on near-threshold stimuli, pre-stimulus M/EEG alpha power and phase are relevant factors also in predicting phosphene perception, a stand-alone phenomenon within the visual domain in which flashes of light are elicited by the stimulation of the visual cortex by means of transcranial magnetic stimulation (TMS; Dugué, Marque, and VanRullen, 2011; Romei et al., 2008). The study of phosphene

perception represents a valuable measure in research on spontaneous activity, as it allows to directly link ongoing oscillations with excitability of the visual cortex.

1.3.2 On the causal role of alpha oscillations

By definition, the effects of spontaneous oscillatory activity are investigated by means of correlations, based on *post-hoc* trial sorting (Romei et al., 2008; Mathewson et al., 2009; Dugué, Marque, and VanRullen, 2011). Nonetheless, studies which aimed to modulate alpha rhythm proved evidence of a causal role of pre-stimulus alpha oscillations on perception.

A traditional way to modulate alpha activity is by means of spatial attention: it has been shown that alpha power is lower for the attended compared to the unattended visual hemifield (Worden, Foxe, Wang, and Simpson, 2000; Sauseng et al., 2005). More recently, alpha oscillations have been modulated by entrainment mechanisms, which induce the phase alignment of brain's oscillatory activity to an external rhythmic stimulation. Entrainment may be achieved by directly stimulating the cortex with non-invasive brain stimulation techniques (Thut et al., 2017; Romei, Thut and Silvanto, 2016), such as TMS (Thut et al., 2011) or transcranial alternated current stimulation (Helfrich, Hermann, Engel, and Schneider, 2016), or by sensory stimulation (e.g., visual or auditory rhythmic stimuli; Spaak, de Lange, and Jensen, 2014; Henry and Obleser, 2012). Entrainment of endogenous alpha rhythm results in enhanced EEG power and phase-locking, and, in turn, the entrained EEG alpha rhythm modulates perception: short trains of rhythmic TMS at alpha frequency delivered on occipital or parietal areas affect visual detection in a lateralized way, consistently with correlative studies (Romei, Gross, and Thut, 2010). In order to specifically investigate the causal role of phase, the delay between the entraining stimulation and the presentation of the target stimulus has been varied,

revealing a cyclic modulation of visual perception (Landau and Fries, 2012; Mathewson et al., 2012; Spaak, de Lange, and Jensen, 2014). Additionally, the role of alpha phase has been investigated by means of phase reset induced by cross-modal stimuli (Romei, Gross, and Thut, 2012): phosphene perception was influenced by the time interval occurring between an auditory stimulus and the subsequent TMS pulse, giving rise to a periodic pattern cycling at 10 Hz phase-locked to the sound.

To summarize, the dominance of the alpha rhythm in the human brain is widely accepted and its functional role in behavior has been deeply investigated since the early stages of EEG studies. Current literature on near-threshold stimuli and phosphene perception provides compelling evidence that pre-stimulus EEG oscillations in the alpha-band play a causal role in modulating visual perception, and, at the neurophysiological level, important progresses have been made in addressing the role of alpha in cross-frequency interactions, as shown both by experimental evidence (Helfrich, Hermann, Engel, and Schneider, 2016; Osipova, Hermes, and Jensen, 2008; Song et al., 2014; Spaak et al., 2012) and theoretical frameworks (Bonnefond, Kastner, and Jensen, 2017; Jensen and Mazaheri, 2010; Schalk, 2015).

1.4 Open issue: does alpha rhythm subtend distinct mechanisms?

Whether alpha activity represents a unitary phenomenon is still a matter of debate. Indeed, the general relation between M/EEG features and micro-level mechanisms is likely to be few to some, rather than one to one: the same M/EEG oscillatory feature may subtend several functions, as well as being generated by distinct mechanisms (Cohen, 2017). For example, distinct neural mechanisms give rise to M/EEG power, but in non-invasive recordings their relative contribution cannot be discerned. Simultaneous EEG and

invasive local field potentials recordings have shown that EEG power can be explained by a linear combination of amplitude and synchronization, and that the two mechanisms may act independently from each other (Musall et al., 2014). Interestingly, this effect has been observed both in stimulus-present and stimulus-absent conditions and especially in the gamma band (Musall et al., 2014).

Regarding the alpha band, evidence that it may not be a unitary phenomenon arise when considering specific aspects of the oscillation. For example, it has been suggested that different functions may be subtended by different frequencies, with 10 Hz enabling functional deactivation in unattended visual scenes and 7 Hz involved in periodic visual sampling when attention is focused (Zoefel and VanRullen 2017). Moreover, alpha activity appears to be generated by distinct networks: cingulo-opercular for tonic alertness, frontoparietal for phasic adaptive control and dorsal parieto-frontal for selective attention (Sadaghiani and Kleinschmidt, 2016). The understanding of the neural mechanisms that regulate cross-frequency interactions with the gamma band may be helpful in addressing this open issue about alpha (Cohen, 2017; Hyafil, Giraud, Fontolan, and Gutkin, 2015; Sadaghiani and Kleinschmidt, 2016; Spaak et al., 2012).

1.4.1 Alpha power *versus* alpha phase

As described in previous sections, cortical excitability is related both to M/EEG alpha power and phase, and up to now it is still unclear whether or not they belong to the same mechanism and/or how they may be related (Hanslmayr, Gross, Klimesch, and Shapiro, 2011; Zoefel and VanRullen 2017). Indeed, the effects of alpha power and phase do not always coexist or interact (Benwell et al., 2017a; Benwell et al., 2017b), suggesting they may be associated with different mechanisms.

Beyond the clear discrepancy in time course, M/EEG power and phase show differences both in the topography of the effects (posterior for power, Hanslmayr et al., 2007; fronto-central for phase, Busch, Dubois, and VanRullen 2009) and in the frequency band which mostly affects the perceptual outcome, which appear to be lower for phase (~7Hz; Busch, Dubois, and VanRullen, 2009; Busch and VanRullen, 2010; Zoefel and VanRullen, 2017; **Figure 1.5**). It has been suggested that alpha power may be related to the subject's tonic state of attention and arousal, while alpha phase may be involved in actual coding of visual processing (Busch, Dubois, and VanRullen, 2009).

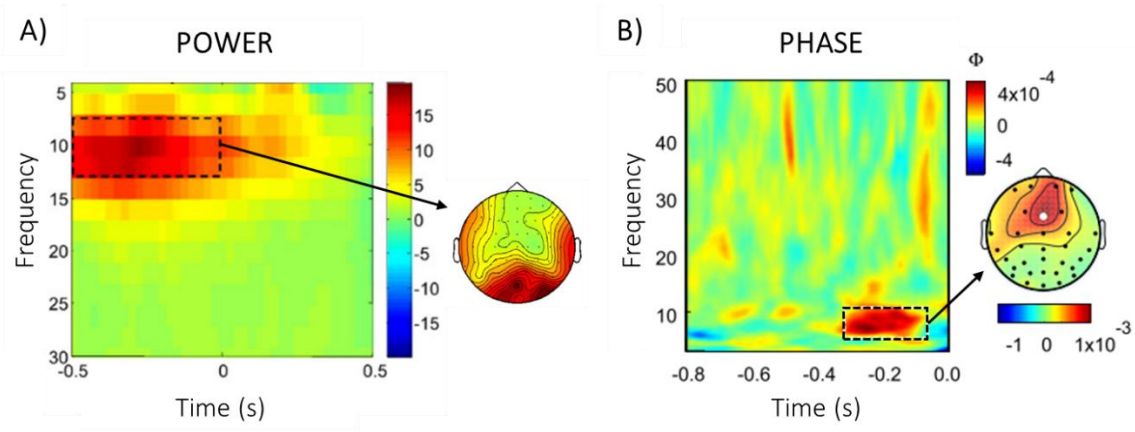


Figure 1.5 Effects of pre-stimulus alpha activity on visual perception. **A)** Power difference between perceivers and non-perceivers in a visual perception task. Time-frequency plot as recorded from channel Oz, and topographical activation averaging over frequencies and time points as indicated by the rectangle; adapted from Hanslmayr et al., 2007. **B)** Phase difference between hits and misses in a visual detection task. Time-frequency plot of Phase Bifurcation Index (Φ) averaged across channels; adapted from Busch, Dubois, and VanRullen, 2009.

Conversely, Hanslmayr and colleagues (2011) argued that EEG alpha power and phase reflect the same mechanism and share a common origin: they both indicate fluctuations between externally and internally oriented brain states and are generated by thalamo-cortical loops. Indeed, according to this perspective, it appears unclear the reason why cortical excitability would be related to two mathematically independent measures (i.e.,

power and phase). A recent account, namely the Function through Biased Oscillations (FBO; Schalk, 2015) addressed this issue suggesting a more parsimonious view about the role of neural oscillations in general, comprising the alpha band. FBO suggests that cortical excitability is better reflected by instantaneous voltage amplitude of oscillations, which provides a more complete interpretation of the power and phase effects described in literature (**Figure 1.6**). According to this framework, the effects of oscillatory power and phase are by-products of biased oscillations, resulting in the phase of an oscillation being relevant at high power levels only. A recent study provides experimental evidence supporting the FBO hypothesis (Schalk, Marple, Knight, and Coon, 2017). Importantly, the FBO account allowed to reconcile time-locked findings, such as ERPs and pre-stimulus slow task-related activity (e.g., readiness potential or contingent negative variation) with observations from time-frequency analyses. Moreover, the FBO framework may explain the interaction observed between the two measures of oscillatory activity, namely an effect of alpha phase on performance in trials with high alpha power only (Cohen and Van Gaal, 2013; Mathewson et al., 2009).

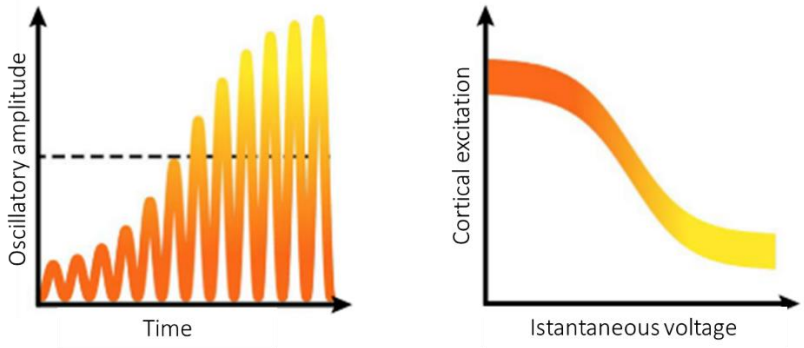


Figure 1.6 Schematic representation of the FBO framework, adapted from Shalk et al., 2017. Color gradient indicate the relationship to cortical excitability, with dark corresponding to high cortical excitability and light to low cortical excitability. Excitation is high when instantaneous amplitude is low.

Finally, some authors argued that the effect of pre-stimulus EEG alpha phase is even stronger than the one of power, accounting for 16% of performance variability in a visual detection task, compared to 12% observed for EEG power (Busch, Dubois, and VanRullen, 2009). However, while a few studies in literature observed the effect of pre-stimulus M/EEG alpha phase (Busch, Dubois, and VanRullen, 2009; Mathewson et al., 2009), others reported null results (Benwell et al., 2017a; Benwell et al., 2017b). Future research is needed to rule out the influence of technical limitations and experimental factors, such as stimulus duration, in order to establish the effective contribution of M/EEG phase in the pre-stimulus window.

1.4.2 Sensitivity *versus* response criterion

Another issue that has been recently raised concerns the effects of alpha activity on perceptual performance. For a long time, the effects of ongoing alpha oscillations on visual perception (i.e., low pre-stimulus power as well as the trough of alpha waves leading to a higher probability of stimulus detection) have been interpreted as mediated by changes in perceptual acuity (Ergenoglu et al., 2004; Romei et al., 2008a). However, an increase in hit rate (i.e., the proportion of detected targets) does not necessarily corresponds to an improved sensory sensitivity; it may also reflect a stronger tendency to report the presence of a stimulus even when it is absent, i.e., a change in the response criterion towards a more liberal one. Therefore, by considering the hit rate only it is not possible to evaluate the sensitivity of the sensory system. The signal detection theory (Green and Swets, 1966) takes into account all possible responses to the stimulus-present and the stimulus-absent trials (false alarms and correct rejections in addition to hits and misses), allowing to disentangle the relative contribution of sensitivity and response criterion.

Recently, several works claimed that the better performance associated to lower pre-stimulus alpha power is not due to an improved perceptual acuity, but rather to a more liberal criterion (Iemi, Chaumon, Crouzet, and Busch, 2017; Limbach and Corballis, 2016). Furthermore, a recent finding suggested that the nature of this biased response is perceptual and not decisional in nature (Iemi and Busch, 2018).

Future studies are needed in order to establish whether the effects of ongoing alpha oscillations on visual perception are always due to a change in response criterion, for example if this mechanism could explain also the effects of alpha phase or of alpha power when it is externally modulated besides when it fluctuates spontaneously.

1.5 Beyond near-threshold stimuli

Most of the studies reported so far investigated the effects of ongoing oscillations on visual perception by means of near-threshold stimuli, in order to maximize variability in the response. Nonetheless, when measuring perceptual abilities, experimental conditions may be compared by means of the psychometric function fitting, a data modelling technique in which an observer's performance in a detection or discrimination perceptual task is related to the physical quantity of a stimulus, e.g., its intensity (Wichmann and Hill, 2001). The psychometric function has the advantage of providing a large amount of information about performance, since several measures beyond the sensory threshold can be derived from it. To this respect, near-threshold stimuli used in most of the studies published in the field of pre-stimulus activity are just a special case obtained from the psychometric curve. Therefore, restricting the range of stimulus intensity around sensory threshold may represent a limitation in the study of underlying functional mechanisms.

1.5.1 The psychometric function

The psychometric function typically shows a sigmoid shape and is defined by four parameters. The choice of a two-parameter (α and β) sigmoid function (e.g., logistic, Weibull, cumulative Gaussian) determines the shape of the curve, defining its position along the abscissa and its steepness. Along the y axis, the function's boundaries are expressed by two additional parameters, namely γ and λ, which specify the lower and the upper asymptote, respectively. In a detection task, the lower bound of the function is usually set to 0, and it describes to the base rate of performance in the absence of a stimulus. The upper bound is determined by the so called "lapse rate", expressed by λ, which can be defined as the probability of responding incorrectly regardless of stimulus intensity. Like γ, also λ is often set to 0, resulting in an upper asymptote approaching 1 (i.e., performance of 100% at high stimulus levels). However, it is worth noting that not considering the lapse rate may bias the slope and threshold estimation (Wichmann and Hill, 2001).

The most common measure derived from the psychometric function is the sensory threshold, i.e., the stimulus intensity needed to perform with an accuracy of 50%. A change in threshold results from a shift of the psychometric function and indicates a variation in the global performance level (**Figure 1.7-A**). Another parameter used to evaluate variations in performance is given by the slope, which indicates the increase rate in performance as a function of stimulus intensity, with a steeper slope indicating a reduced variability around threshold (Parker and Newsome, 1998; **Figure 1.7-B**). Finally, a further modification of the psychometric function concerns the upper asymptote, indicating that experimental manipulations mainly affect performance in response to high

intensity stimuli, possibly due to an altered lapse rate (Wichmann and Hill, 2001; **Figure 1.7-C**).

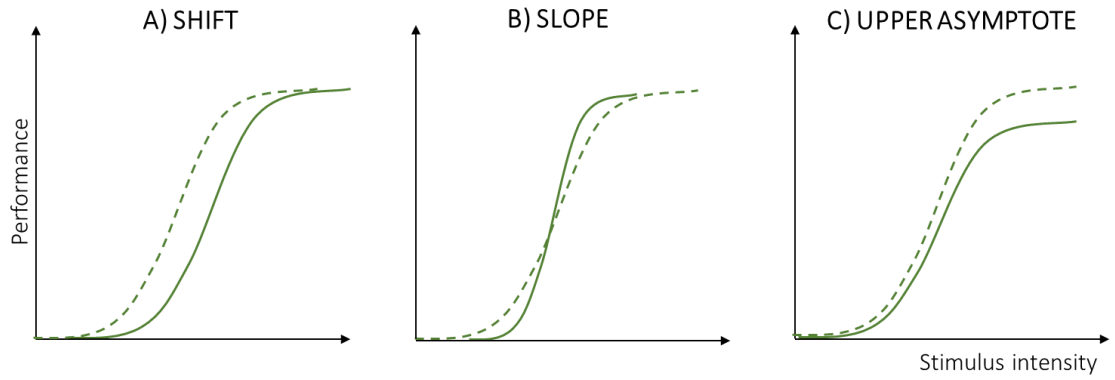


Figure 1.7 Selective modifications of the psychometric function. Hypothetical performance in a visual detection task as a function of stimulus intensity. Different experimental conditions may selectively affect the psychometric function, by altering: **A)** the threshold (i.e., by determining a shift of the curve), **B)** the slope, or **C)** the upper asymptote.

One of the benefits of fitting the psychometric function to psychophysical data relies in making hypotheses on functional mechanisms underlying cognitive or perceptual processes, which are associated with specific changes in the psychometric curve. For example, contrast and response gain are two mechanisms studied in the visual domain, which act at the input and at the output level of the system, respectively. The contrast gain mechanism is represented by a shift of the psychometric function and, consequently, by a change in sensory threshold and sensitivity; the response gain is associated with a modification in the upper bound. As an example, in the framework of visual perception, it has been shown that while the effects of sustained attention are consistent with a contrast gain model (i.e., reduction of threshold), transient attention can be better explained as a mixture of contrast gain and response gain mechanisms (threshold reduction and increase of the upper asymptote; Ling and Carrasco, 2006). Likewise, both visual attention and adaptation affect contrast sensitivity, but their effects are due to

different non-interacting mechanisms, with attention affecting the upper asymptote and adaptation determining a shift of the psychometric function (Pestilli, Viera, and Carrasco, 2007).

1.5.2 A psychophysical approach to the study of pre-stimulus oscillations

We suggest that valuable insights about the involvement of different mechanisms associated with ongoing alpha activity may arise from a psychophysical approach, i.e., by using a wide range of stimulus intensities and fitting the psychometric function. To our knowledge, two studies have addressed this issue so far, and in both cases changes in the psychometric function have been related with pre-stimulus alpha power. Chaumon and Busch (2014) reported evidence in favour of a response gain mechanism (i.e., a reduction of the upper asymptote in trials with high alpha power), while Benwell and others, (2017a) showed that pre-stimulus alpha power predicts visuospatial bias, but not discrimination sensitivity. It is worth noting that in the study by Benwell and co-workers, the proportion of correct responses is not represented as a function of stimulus intensity, but of visuospatial bias instead; therefore, the two studies are not comparable on the psychometric curve's parameters.

1.6 The present work

In this project we aimed at further investigate the effects of ongoing alpha activity in the visual domain, by studying its effects on both perceptual and neurophysiological outcome by means of different methodological approaches.

In the next sections, we present three main studies.

1) Study 1: Spontaneous fluctuations. *Effects of MEG pre-stimulus activity on visual detection and event-related fields*. Our first aim was to replicate a previous work on the effects of spontaneous pre-stimulus alpha activity on a near-threshold visual detection task. While the original study was run by using EEG, in the present one MEG recording allowed us to investigate the role of pre-stimulus alpha power and phase, as well as the evoked response, not only at the sensor level but also by reconstructing brain sources.

2) Study 2: Modulation of pre-stimulus oscillations. *Effects of a dark adaptation paradigm on phosphene perception and TMS-evoked potentials.* Here we aimed at experimentally modulating pre-stimulus oscillatory activity, by means of a dark adaptation paradigm. The effects of the experimental modulation were evaluated through a TMS-EEG protocol, by assessing phosphene perception and TMS-evoked potentials and gaining insights from the full psychometric function estimation.

3) Study 3: Neural mechanisms. *A formal model for the effects of ongoing M/EEG oscillations on visual perception.* Finally, we developed a formal model with the aim of addressing the demanding issue of how pre-stimulus oscillations contribute to visual perception, in terms of neural mechanisms. Starting from the psychometric function observed at the behavioral level, the model allows to make predictions on specific cross-frequency mechanisms which may be associated with the effects of pre-stimulus alpha oscillations.

1.6.1 Technique of Study 1: MEG

Among neuroimaging techniques, MEG is considered an extremely powerful tool to non-invasively investigate brain functioning, characterized by a unique combination of high temporal and spatial resolution (Baillet, 2017; Paetau and Mohamed, 2013; Pizzella et al., 2014; Proudfoot, Woolrich, Nobre, and Turner, 2014; Stefan, Nakasato, and Papanicolaou, 2012). MEG signal is obtained by recording the magnetic fields produced by electrical currents of neurons' post-synaptic potentials, and thus represents a direct measure of neural activity. MEG presents several advantages compared to other techniques, such as EEG and fMRI, in which the high resolution in one dimension (i.e., temporal in EEG, spatial in fMRI) comes at the expense of the other one (i.e., spatial in EEG, temporal in fMRI). By enabling a sampling rate of thousands per second, MEG allows a fine measurement of neural oscillations, which are believed to play a fundamental role in brain functioning, as highlighted in previous sections (Proudfoot, Woolrich, Nobre, and Turner, 2014). Moreover, the magnetic fields produced by neural assemblies and recorded by MEG sensors do not suffer from distortion when passing through the layers of head tissues, allowing a more precise source localization of neural activity, especially for superficial sources (since the magnetic field decreases rapidly with distance). Importantly, MEG contributed to overcome the idea of segregated brain areas towards the study of the whole brain as a network, revealing real-time interactions among distant regions (Baillet, 2017). Taken together, the characteristics of MEG make it a unique and promising technique in the study of brain dynamics.

1.6.2 Technique of Study 2: TMS-EEG

The combination of TMS with simultaneous EEG (TMS-EEG) is a highly promising tool in the study of brain functional dynamics (Ilmoniemi and Kičić, 2010; Kitajo, Hanakawa, Ilmoniemi, and Miniussi, 2015). Indeed, TMS allows to establish causal relationships between brain areas and cognitive functions by inducing neural depolarization in the cortex beneath the area of stimulation (Barker, Freeston, Jalinous, and Jarratt, 1987; Barker, Jalinous, and Freeston, 1985), while EEG enables the direct recording of neural activity with an excellent temporal resolution (Berger, 1929; Sejnowski, Churchland, and Movshon, 2014). Therefore, TMS-EEG represents a unique opportunity to non-invasively measure the instantaneous cortical response to a focal perturbation with a high temporal and spatial resolution, providing information on the brain's excitability and connectivity (Bortoletto, Veniero, Thut, and Miniussi, 2015; Ferreri and Rossini, 2013).

EEG response to TMS may be investigated by means of TEPs, an equivalent of event-related potentials in EEG (Chung, Rogasch, Hoy, and Fitzgerald, 2015). TEPs represent a reliable measure of cortical excitability: they change depending on site, intensity and angle of TMS stimulation (i.e., they are sensitive), while they have been shown to be stable over time (i.e., they are reproducible; Casarotto et al., 2010, Lioumis, 2009). So far, most of the research focused on motor areas (for a review see Ferreri and Rossini, 2013), and only a few studies recorded TEPs by stimulating the visual cortex (Bagattini, Mazzi, and Savazzi, 2015; Herring, Thut, Jensen, and Bergmann, 2015; Rosanova et al., 2009; Taylor, Walsh, and Eimer, 2010).

2. Study 1: SPONTANEOUS FLUCTUATIONS

Effects of MEG pre-stimulus activity on visual detection and event-related fields

2.1 Background and aim

Current literature provides compelling evidence that spontaneous fluctuations in ongoing oscillatory activity, as measured by magneto/electrophysiological (M/EEG) recordings, contribute to the way the brain responds to an incoming stimulus (**Section 1.3;** Ai and Ro, 2014; Arieli, Sterkin, Grinvald, and Aertsen, 1996; Baumgarten, Schnitzler, and Lange, 2016; Haegens et al., 2011; Iemi and Busch, 2018; Iemi, Chaumon, Crouzet, and Busch, 2017; Kayser, McNair, and Kayser, 2016; Leske et al., 2015; Limbach and Corballis, 2016; Linkenkaer-Hansen, 2004; Mazaheri, Nieuwenhuis, Van Dijk, and Jensen, 2009; Samaha, Iemi, and Postle, 2017; Schubert, Haufe, Blankenburg, Villringer, and Curio, 2008; van Dijk, Schoffelen, Oostenveld, and Jensen, 2008).

A large number of studies focused on the effects of ongoing oscillations on perception, and especially on detection tasks, by presenting so-called "near-threshold" stimuli. In a near-threshold stimulus, for each participant the intensity is set at the individual sensory threshold, such that, when it is repeatedly presented, it can be detected in half of the trials. In the visual domain, findings converged in showing that hits (i.e., target-detected trials) and misses (i.e., target-undetected trials) differ not only in the neurophysiological response evoked by the stimulus, but also in ongoing activity in the alpha band, with stronger power in the time-window preceding misses compared to hits (Busch, Dubois, and VanRullen, 2009; Iemi and Busch, 2018; Iemi, Chaumon, Crouzet, and Busch, 2017;

Lange et al., 2014; Mathewson et al., 2009; van Dijk, Schoeffelen, Oostenveld, and Jensen, 2008).

In this field, the study by Busch and colleagues (Busch, Dubois, and VanRullen, 2009) is particularly interesting. Indeed, not only they replicated previous findings on the role of the power of spontaneous pre-stimulus fluctuations in EEG alpha band, but they also showed for the first time that the phase of ongoing alpha oscillations accounts for a considerable portion of variability in performance as well. It is worth noting that the study by Mathewson et al., 2009 on pre-stimulus alpha phase was published in the same year with similar results.

The effect of ongoing alpha power has been further confirmed in following studies (Busch and VanRullen, 2010; Iemi, Chaumon, Crouzet, and Busch, 2017; Limbach and Corballis, 2016; Samaha, Iemi, and Postle, 2017). Differently, the effect of pre-stimulus alpha phase appears to be not well established yet, with variable results in terms of frequency (Mathewson et al., 2009; Busch and VanRullen 2010) and recent studies reporting null results (Benwell et al., 2017a; Benwell et al., 2017b). Moreover, up to now still little is known about cortical sources of the effects of pre-stimulus activity on perception (Busch, Dubois, and VanRullen, 2009; Iemi, Chaumon, Crouzet, and Busch, 2017).

Here, we aimed at replicating findings by Busch and colleagues (2009) on the effects of spontaneous fluctuations in alpha rhythm on visual perception. Specifically, we investigated the effects of pre-stimulus alpha power and phase on behavioral outcome and neurophysiological response (i.e., event-related fields, ERFs) in a near-threshold visual detection task. In the present study, the use of MEG may allow not only to corroborate previous findings, but also to extend the investigation of the effects of pre-stimulus alpha power and phase at the source level.

2.2 Materials and methods

2.2.1 Participants

Twenty young healthy volunteers took part in the study after giving written informed consent (12 females, mean age ± SD: 26 ± 4 years, all right handed). All participants had normal or corrected-to-normal vision and no history of neurological disorders. The study was conducted in accordance of the declaration of Helsinki and approved by the local ethics committee of University of Trento.

2.2.2 Experimental procedure

Participants were comfortably seated in a dimly lit, sound attenuated and magnetically shielded room. The visual detection task was comparable to the one described in Busch, Dubois and VanRullen (2009), shown in **Figure 2.1**. A fixation cross was always present in the center of the screen, while two lateral markers on its right side (7° of visual angle) indicated the location in which the target could appear. Participants were asked to maintain the fixation, while covertly attending the lateral site indicated by the markers. After a variable interval between 1 and 2 s, the target was presented in 80% of the trials. The target was a small dot (7' of visual angle) briefly presented (8.3 ms) at individual luminance threshold. A question mark appeared 1.5 s after target presentation, and participants were asked to report by a button press whether they detected the target or not. A new trial began after the response, or after 2 s if no response was recorded. Participants performed 6 blocks of 150 trials each (due to technical reasons, two participants only completed 4 blocks of the experiment). The experiment was created in MATLAB 2012b (The MathWorks, Natick, MA, USA) and Psychophysics Toolbox 3 (Brainard, 1997). Visual stimuli were presented on a translucent screen placed 1.5 m from participants, by

means of a DLP projector at a refresh rate of 120 Hz (PROPixx, VPixx Technologies Inc., Saint-Bruno, QC, Canada). A photo diode was used to set the trigger for stimulus onset.

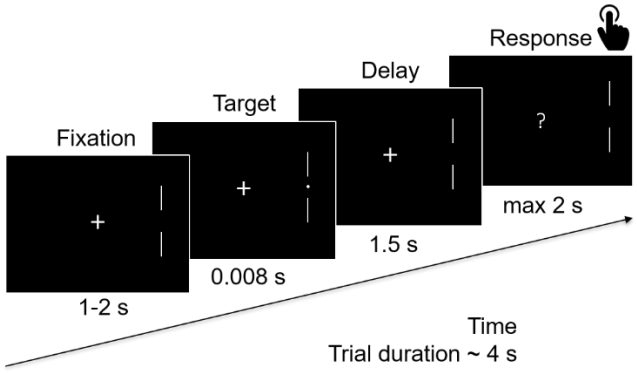


Figure 2.1 Trial structure of visual detection task in Study 1. While keeping the fixation on the central cross, participants were asked to detect a small dot that could briefly appear in 80% of the trials between two markers on the right side of the screen.

2.2.3 MEG recording

Whole-head MEG was continuously recorded with a sampling rate of 1 kHz (Neuromag306 system; Elekta, Stockholm, Sweden), placed in a magnetically shielded room. MEG data was recorded by 306 sensors (one magnetometer and two orthogonal planar gradiometers for each of 102 positions). A Polhemus Fastrack digitizer (Polhemus, VT, USA) was used to acquire for each participants the location of a set of landmarks: nasion and left/right periauricular points, five head position indicator (HPI) coils to track the position of the participants' head during the experiment, and more than 200 headshape samples, needed for offline head modelling.

2.3 Analysis: behavioral outcome

Detection performance was evaluated in terms of hit rate (i.e., correct detections on the total of presented targets) and false alarm rate (i.e., false alarms on the total number target-absent trials).

2.4 Analyses: MEG data

At sensor level as well as in source space, we aimed at comparing hits and misses in ERFs, pre-stimulus power and pre-stimulus phase. MEG data analysis was performed in MATLAB 2016b (The MathWorks, Natick, MA, USA) and Fieldtrip toolbox (Oostenveld, Fries, Maris, and Schoffelen, 2011).

2.4.1 Preprocessing

Sensor level

The MEG signal was high-pass filtered at 1 Hz and a notch filter at 50 Hz and 100 Hz was applied to avoid line noise. Data was downsampled at 256 Hz and epoched from 2 s before and 2 s after stimulus onset. The data was visually inspected to identify trials containing noise, eye movements and muscular artefacts, as well as noisy channels. On average (mean ± SD), 10 ± 2 % of the trials was discarded and 4 ± 2 channels were subsequently interpolated. Data from planar gradient pairs were combined using vector addition, but the reported analyses focused on magnetometers only. Target-absent trials were excluded, and the number of trials for hits and misses was equalized by randomly selecting a subset of trials from the condition with more trials.

Source-projection

To project sensor data obtained from preprocessing into source space, for each participant we first performed the coregistration between anatomical and MEG data, by using the individual MRI (or a standard MRI for 5 out of 20 participants who did not have the individual scan) and the landmarks recorded prior to acquisition, in order to align the two imaging modalities. A single shell head model (Nolte, 2003) was used to represent the geometrical and electro-magnetic properties of the head. Subsequently, we construct the source model by using a spatial grid of 899 points with a resolution of 15 mm in Montreal Neurological Institute (MNI) space, which was warped into individual head model. In this way, the data from each subject was mapped onto a common space. Finally, we calculated the forward model and applied a Linearly Constrained Minimum Variance (LCMV) beamformer filter (Van Veen, van Drongelen, Yuchtman, and Suzuki, 1997) to single-trial data, using a covariance window from -0.3 s to -0.1 s with respect to stimulus onset.

Time-frequency

We performed a single-trial time-frequency analysis by applying a Hanning taper with a time window of a frequency-dependent length (5 cycles per frequency), sliding in steps of 10 ms. In sensor level the time-frequency analysis was performed for frequencies from 1 to 50 Hz, while at source level it was restricted to the pre-stimulus window and to a frequency range from 1 to 30 Hz, due to higher computational demands. Power was given by the squared absolute value of the Fourier estimates.

2.4.2 Statistical analysis

If not otherwise specified, MEG data for hits and misses were compared by performing non-parametric cluster-based permutation tests for dependent samples (two-tailed *t* statistics; Maris and Oostenveld, 2007). This procedure allows to control for the multiple comparisons problem (type I error), arising when performing statistical tests at multiple time, frequency and sensors. First, it identifies significant spatio-temporal-spectral adjacent clusters, summing *t* values within each cluster to reveal a cluster level test statistic. Then, it performs random permutations by exchanging the data between hits and misses, within participants. After each permutation run, the maximum cluster level statistic was recorded to obtain a reference distribution of cluster-level statistics (approximated with Monte Carlo procedure of 1000 permutations). Finally, cluster-level *p*-values were estimated as the proportion of values in the reference distribution exceeding the cluster-statistics obtained in the real data. The level of significance was set at $p < 0.05$.

2.4.3 ERFs

At sensor level as well in source space, we computed ERFs by low-pass filtering the signal at 20 Hz and averaging over trials for hits and misses. Statistical testing was performed over all channels and time points from 0.2 s before to 0.8 s after stimulus onset.

2.4.4 Pre-stimulus power

Since we were interested in the effect of pre-stimulus alpha power (Busch, Dubois, and VanRullen, 2009; Hanslmayr et al., 2007; Iemi, Chaumon, Crouzet, and Busch, 2017; Zoefel and VanRullen, 2017), we performed the statistical analysis by averaging over frequencies in the alpha band (8-13 Hz). Pre-stimulus power in hits and misses was then

compared across spatial and temporal dimensions in 1 s before stimulus onset at sensor level, and in 0.5 s before stimulus onset in source space.

2.4.5 Pre-stimulus phase

To analyse the contribution of pre-stimulus phase on trial outcome, we computed the inter-trial coherence (ITC; Lachaux, Rodriguez, Martinerie, and Varela, 1999), i.e., phase coherence across trials, for hits (ITC_{hits}), misses (ITC_{misses}) and comprising hits and misses together (ITC_{all}), as follows. First, to control for difference in amplitude among trials and extract only the information about phase, the length of the complex vectors resulting from Hanning tapering and Fourier transform was normalized to 1 in all trials. Then, ITC was calculated as the length if the resultant complex Fourier vectors across trials along a unit circle. The range of ITC values is between 0 and 1, with 0 representing random phase angle distribution and 1 perfect phase-locking across trials. Among several existing measures to compare the phase opposition between trial groups, we applied the Phase Opposition Sum (POS), which has been shown to be more reliable compared to other measures (e.g., Phase Biphurcation Index, the one used in the original study; VanRullen, 2016), defined in (2.1).

(2.1)

$$POS = ITC_{hits} + ITC_{misses} - 2*ITC_{all}$$

POS values are positive only when both hits and misses are phase locked and have opposite phase angles; in all other cases (i.e., only one condition presents high ITC, both conditions present low ITC, or both conditions present high ITC but with similar phase angles), POS values are close to 0 (**Figure 2.2**).

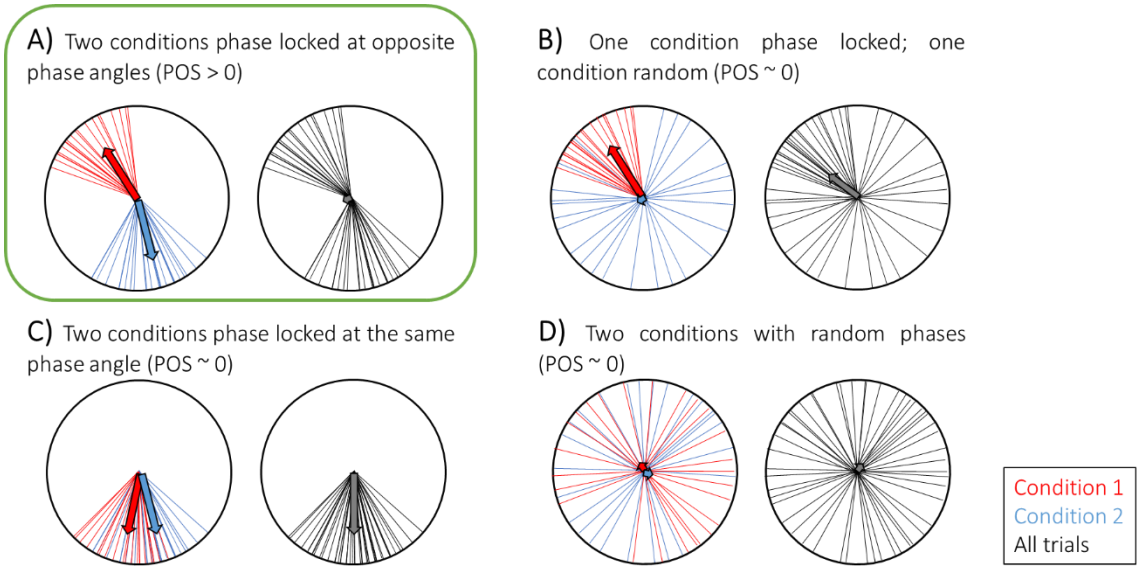


Figure 2.2. Schematic illustration of the Phase Opposition Sum (POS) on hypothetical data from two experimental conditions (Condition 1 and Condition 2), in different situations. Circles indicate possible phase angles between 0 and 2π; circles on the left represent the two conditions separately, while right circles show the global phase distribution. Each line represents one trial (red: Condition 1; blue: Condition 2; black: all conditions together); the angle represents the phase at a certain time and frequency of interest after amplitude normalization (i.e., each trial has equal length) and the arrows represent the ITC. **A)** Two conditions are phase-locked at opposite phase angles: ITC_1 and ITC_2 are both high, while ITC_{all} is low; this is the only case in which POS assumes positive values. **B)** Only one condition is phase-locked: ITC_1 is high, ITC_2 is low, and ITC_{all} is moderate, leading POS close to zero. **C)** Both conditions are phase-locked to the same angle: not only ITC_1 and ITC_2, but also ITC_{all} is high, therefore POS is close to zero. **D)** The phase of both conditions is randomly distributed, resulting in a POS close to zero. Adapted from Busch et al. (2009).

Statistical analysis of POS between hits and misses was performed by random permutations, applying a similar procedure to the one reported by Busch and colleagues (2009). For each subject, single trial data for hits and misses were merged together and new subsets for "pseudo-hits" and "pseudo-misses" were created by randomly selecting trials from the merged pool, and POS relative to the two subsets was computed. Importantly, the same trials were considered in the computation of the real and the shuffled data. This procedure was repeated 500 times, giving rise to a shuffled POS

distribution under the null hypothesis for each subject. In a second step, we randomly selected one permutation out of the 500 POS, and computed the grand-average among subjects. The second step was performed 10000 times. Finally, we computed as a *p* value the proportion of shuffled POS grand-averages that exceeded the observed POS grand average. The false discovery rate (FDR) procedure (Benjamini and Hochberg, 1995) was applied to the obtained *p* values in order to correct for multiple comparisons.

Since the effect of pre-stimulus phase on visual perception is still debated (Benwell et al., 2017a; Benwell et al., 2017b), and it is not clear whether it involves frequencies beyond the alpha band (Busch, Dubois, and VanRullen, 2009; Mathewson et al., 2009), we decided to not confine the analysis on the alpha frequency range. However, because of the high computational demands of phase calculation, we reduced the number of comparisons by averaging over 4 magnetometers of interest in fronto-central position (similarly to the procedure described in Busch, Dubois, and VanRullen, 2009; **Figure 2.5**). In source space, we restricted the statistical analysis of POS on a time-frequency-range of interest, based on the effects observed at sensor level, i.e., from -0.25 s to -0.1 s and within 10-12 Hz. This procedure allowed us to obtain a *p* value for each point in source space.

2.5 Results

2.5.1 Behavioral outcome

As expected, on average participants detected half of the targets (hit rate, mean ± SE: 46.91% ± 1.19), while false alarm rate was very low (mean ± SE: 2.74% ± 0.69).

2.5.2 ERFs

The hits *versus* misses comparison revealed larger responses for hits compared to misses, both on sensors and in source space.

Sensor level

In the ERFs at sensor level we observed two significant clusters, a first positive one from 0.29 s to 0.52 s and a later negative one from 0.47 s to 0.67 s. The difference between hits and misses was strongest in right central sensors for both time windows, as shown in **Figure 2.3**.

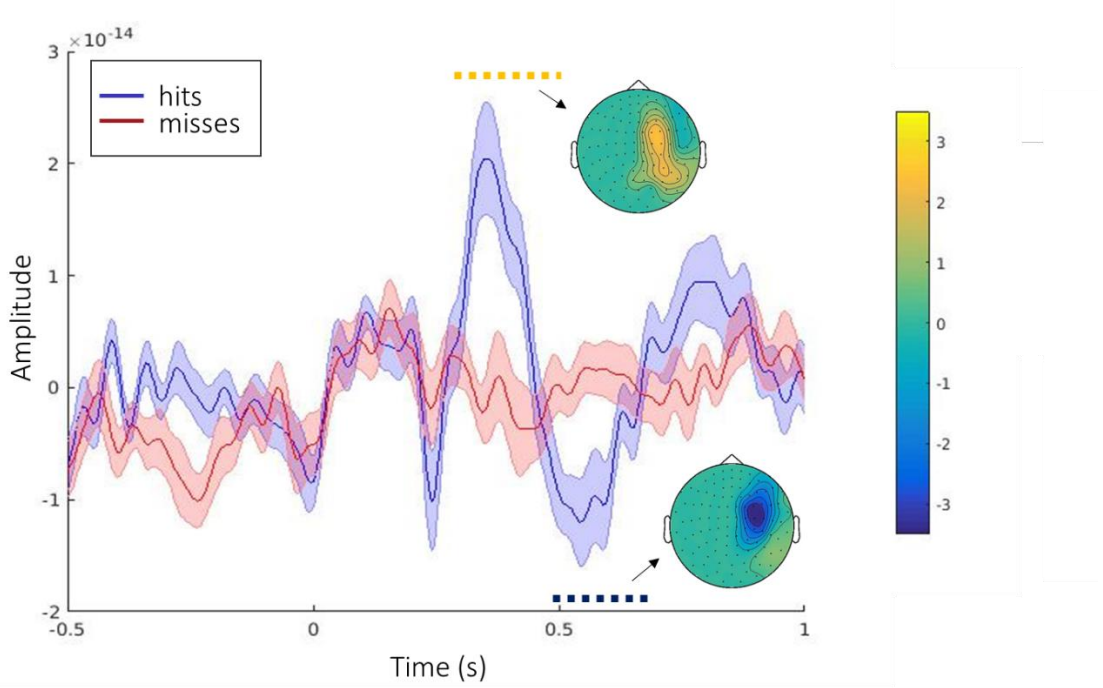
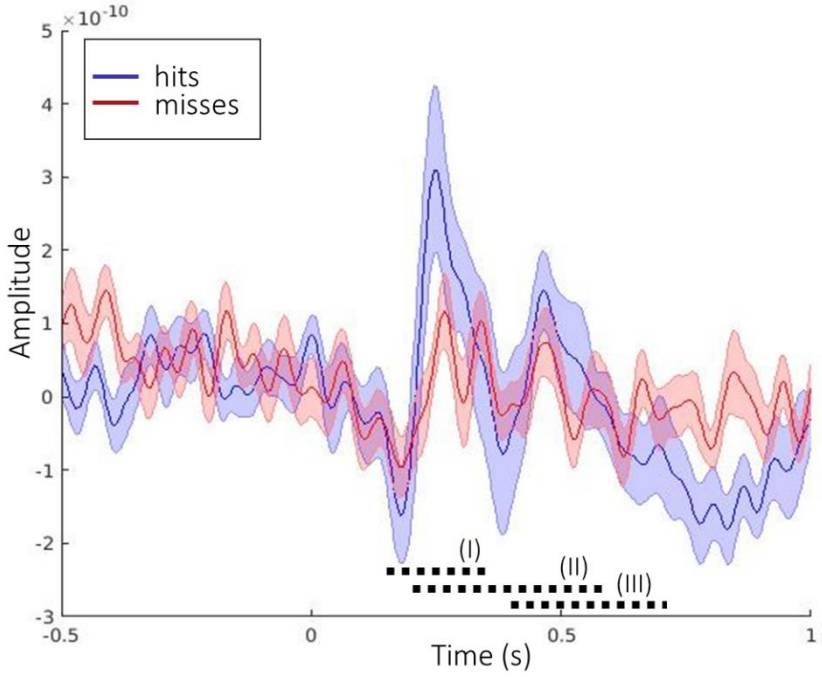


Figure 2.3 ERFs in sensor space. ERFs for hits (blue) and misses (red; SE in shaded error bars), averaged over sensors which showed a significant difference between hits and misses in at least one of the two clusters. Dashed lines indicate time-range of significant clusters: one positive (yellow) peaking at 0.34 s and one negative (blue) peaking at 0.54 s, whose *t* values are shown in topographical maps (range in colorbar).

Source level

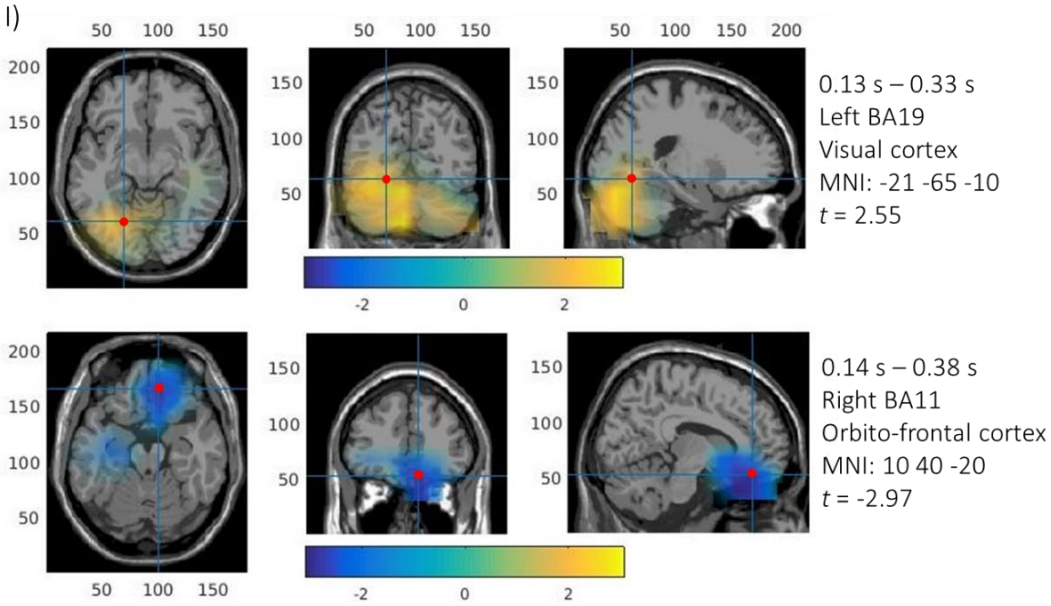
Statistical testing on ERFs in source space revealed three positive and three negative significant clusters; for each cluster we identified the location of the maximum *t* value in the cortex (**Figure 2.4**). Within the first 40 ms, we observed a positive cluster from 0.13 s to 0.33 s ($p = 0.002$) and a negative cluster from 0.14 s to 0.38 s ($p = 0.006$). The first positive cluster peaked in left Brodmann Area (BA) 19 (BA19; visual cortex, MNI coordinates: -21 -65 -10; $t = 2.55$), while maximum *t* value for the first negative cluster ($t = -2.97$) was located in right BA11, in the orbital gyrus (MNI coordinates: 10 40 -20). The second positive cluster ($p = 0.002$) ranged from 0.23 s to 0.47 s, whereas the second negative cluster ($p = 0.002$) occurred between 0.24 to 0.7 s. The second positive cluster showed the highest *t*-value ($t = 2.66$) in the left BA32, in the anterior cingulate cortex (MNI coordinates: -5 25 25), whereas the negative one peaked in the right BA20, in the inferior temporal gyrus ($t = -0.53$; MNI coordinates: 40 -12 -34). Finally, starting from 0.42 s we observed a positive cluster lasting up to 0.69 s ($p = 0.002$) and a negative cluster until 0.67 s ($p = 0.002$). The last positive cluster peaked in the left BA11, in orbitofrontal area ($t = 3.62$, MNI coordinates: 10 27 -14), while the negative one in left BA32, in anterior cingulate cortex ($t = -2.55$, MNI coordinates: -5 26 31).

A)


×10-10
hits
misses
Amplitude
(I)
(II)
(III)
Time (s)

B)

I)


0.13 s – 0.33 s
Left BA19
Visual cortex
MNI: -21 -65 -10
t = 2.55
0.14 s – 0.38 s
Right BA11
Orbito-frontal cortex
MNI: 10 40 -20
t = -2.97

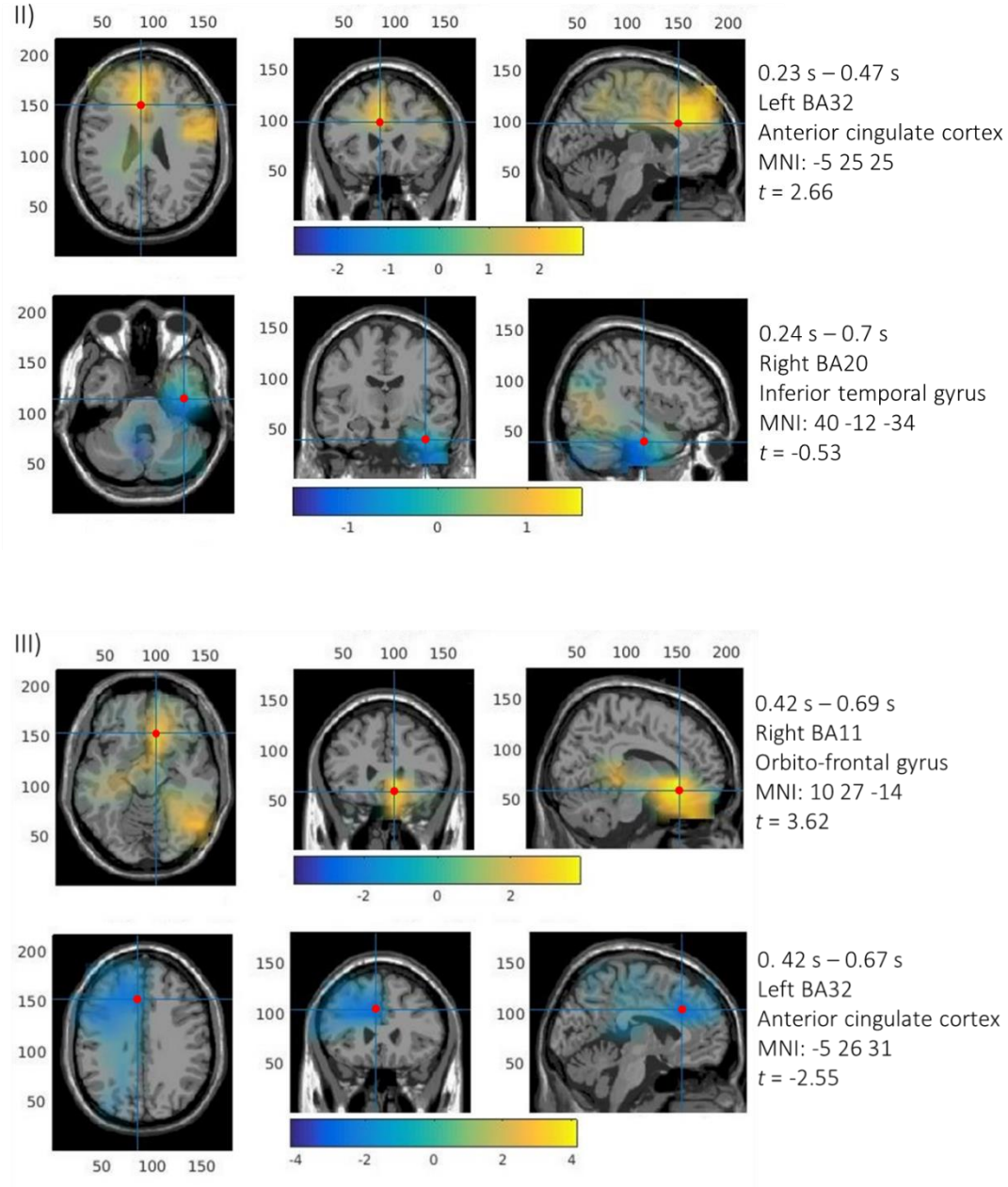


Figure 2.4 ERFs in source space. **A)** ERFs for hits (blue) and misses (red; SE in shaded error bars), averaged over points in source space which showed a significant difference between hits and misses; dashed lines indicate time-windows for significant clusters: I) clusters from 0.13 s to 0.38 s; II) clusters from 0.23 s to 0.7 s; III) clusters from 0.42 s to 0.69 s. **B)** From left to right: axial, coronal and sagittal MRI sections in neurological convention, showing *t* values for each significant cluster in ERFs from 0.2 s before to 0.8 s after stimulus onset (range in colorbar). The red dot indicates maximum *t* value in the cortex.

2.5.3 Pre-stimulus power

We observed a significant effect of pre-stimulus alpha power in source space, but no significant clusters emerged from the analysis on sensors.

Sensor level

Although at a descriptive level we observed higher power levels preceding misses compared to hits (**Figure 2.5**), on sensors no significant effects emerged from the cluster-based permutation test over channels and time-points in the alpha band.

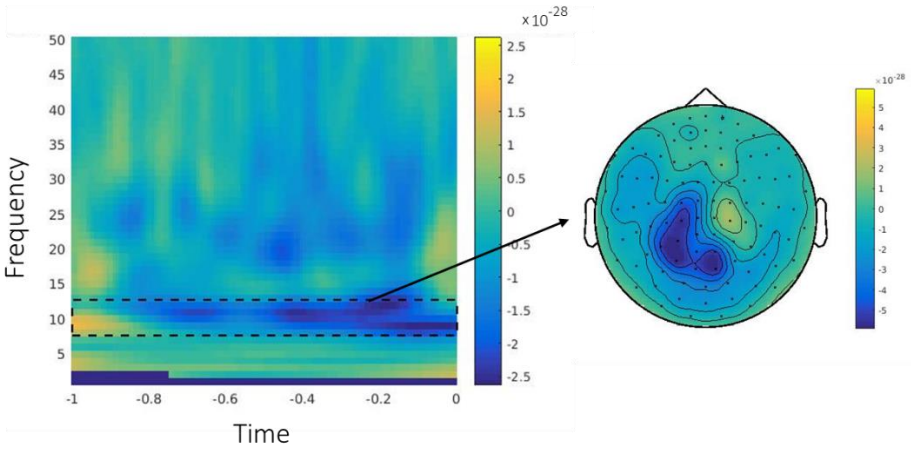


Figure 2.5 Pre-stimulus alpha power at sensor level. Left: time-frequency plot of spectral power averaged across all sensors; the rectangle highlights alpha frequency range (i.e., 8-13 Hz). Right: topographical map of the difference between hits and misses in the alpha band, averaged over time in 1 s before stimulus onset). Power range as shown in colorbars.

Source level

In source space, the cluster-based permutation test on pre-stimulus power in the alpha band revealed one significant negative cluster in the pre-stimulus window (p = 0.042), peaking between -0.45 s and -0.3 s. The strongest effect (t = -3.51) was located in left BA19, in the visual cortex (MNI coordinates: -49 -65 10).

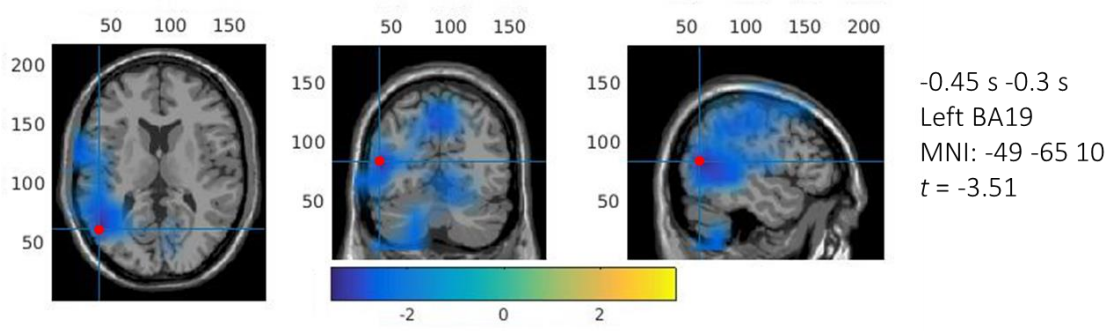


Figure 2.6 Pre-stimulus alpha power in source space. From left to right: axial, coronal and sagittal MRI sections in neurological convention, showing *t* values of the negative significant cluster in pre-stimulus power (range in colorbar). The red dot indicates highest *t* value in the cortex.

2.5.4 Pre-stimulus phase

Sensor level

The analysis on POS between hits and misses revealed a significant pre-stimulus effect at 11 Hz, from -0.2 s to -0.16 s in the pre-stimulus window (range of *p* values: from $p = 0.019$ to $p = 0.03$; **Figure 2.7**).

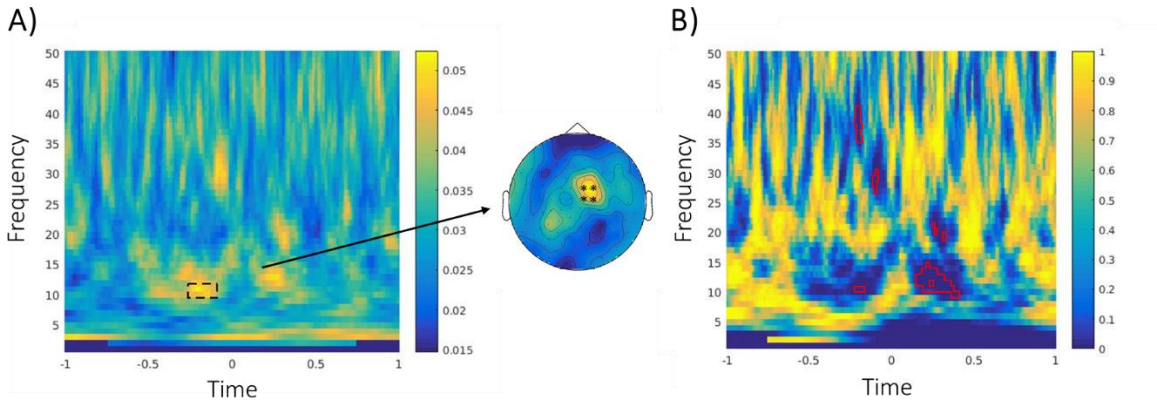


Figure 2.7 POS effect at sensor level. **A)** Time-frequency plot of POS values averaged across 4 sensors (as indicated by asterisks in the topographical map), and topographical activation averaged over frequencies and time-points as indicated by the rectangle. **B)** Uncorrected *p* values from statistical analysis on POS; areas within red boundaries indicate time-frequency points with significant POS satisfying an FDR of 5%. Range in colorbars.

Source level

Statistical analysis revealed 96 points in source space showing significant *p* values, after FDR correction for multiple comparisons (Benjamini and Hochberg, 1995). Significant *p* values mainly involved frontal areas, and the largest significant area was located in the left dorso-lateral pre-frontal cortex (**Figure 2.8**). In **Table 2.1** we described other brain regions which showed significant *p* values.

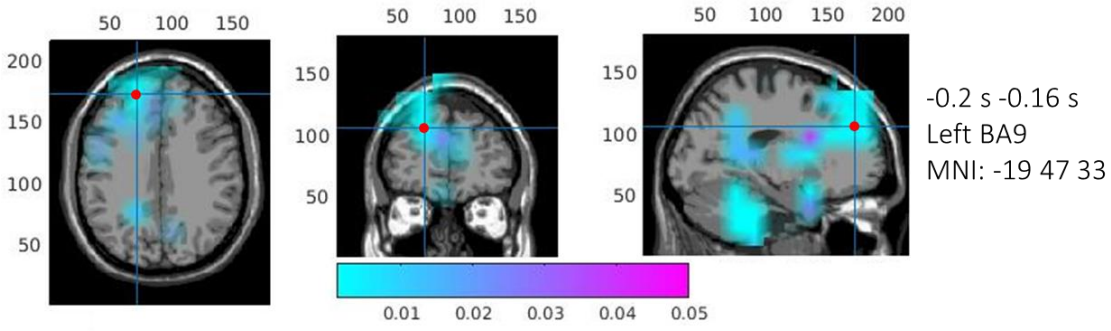


Figure 2.8 POS effect in source space. Points in source space showing significant *p* values in the cortex after FDR correction from statistical analysis on POS; range in colorbar.

Hemisphere	Brain region	Brodmann Area	MNI coordinates
Left	Dorso-lateral pre-frontal cortex	9	-19 47 33
Right	Anterior pre-frontal cortex	10	12 60 11
Left	Orbito-frontal cortex	11	-19 -11 -21
Right	Primary visual cortex	17	12 -67 11
Left	Inferior frontal gyrus	44	-51 11 11

Table 2.1 POS effect in source space. Main areas showing significant *p* values in the cortex after FDR correction from statistical analysis on POS.

2.6 Discussion

In the present study we aimed at replicating previous evidence (Busch, Dubois, and VanRullen, 2009) on the role of spontaneous pre-stimulus alpha activity on behavioral and neurophysiological outcome in a visual detection task, and at providing novel advances by exploring such effects also at the source level, by using MEG.

Our results were consistent with most findings from Busch and colleagues (2009). As expected, we observed a detection performance around 50%, indicating that the luminance threshold of visual stimuli was successfully set at individual sensory threshold. Furthermore, the neurophysiological response to stimuli (i.e., ERFs) was larger for hits compared to misses, both at the sensor level and in source space. The analyses on pre-stimulus window revealed a significant effect of alpha power in source space, with stronger power preceding misses compared to hits. Finally, we observed a significant effect of pre-stimulus alpha phase both on sensors and at source level, showing that pre-stimulus activity before hits and misses was phase-locked and pointing in different phase angles.

Results on ERFs are consistent with findings from Busch and colleagues (2009): while the neurophysiological outcome to undetected stimuli was virtually absent, detected stimuli gave rise to a clear evoked response compared to baseline. In sensor-level analysis we observed two significant clusters peaking around 0.4 s and 0.55 s, while analysis in source space revealed also a difference between hits and misses at earlier latencies. Specifically, the left visual cortex was involved in the earliest response. Since visual stimuli were always presented in the right hemifield, this result suggests that the difference between hits and misses in ERFs reflects sensory processing. Moreover, we observed a subsequent effect located in the inferior temporal gyrus. This brain region is

historically known to be crucial for the ventral stream of the visual pathway (Mishkin, Ungerleider, & Macko, 1983) and it has recently been found to be involved in conscious perception (Bisenius, Trapp, Neumann, & Schroeter, 2015). Finally, beside the effects in occipital and temporal cortex, we detected also frontal sources which were present along the time course of the ERFs. Frontal activations in response to hits may be involved in higher level functions, such as top-down modulation of visual processing (Gazzaley et al., 2015; Zanto, Rubens, Thangavel, & Gazzaley, 2011). Taken together, results from ERFs analysis in source space suggests that visual detection may not be considered a local phenomenon restricted to sensory regions (i.e., the visual cortex), but it is likely to involve connections with high-order associative cortices.

The analysis on pre-stimulus alpha power revealed a significant effect in source space. Consistently with the original paper and findings in literature (Busch, Dubois, and VanRullen, 2009; Iemi, Chaumon, Crouzet, and Busch, 2017; Limbach and Corballis, 2016; Samaha, Iemi, and Postle, 2017), we observed significantly stronger pre-stimulus alpha power preceding misses compared to hits. This result supports the interpretation of ongoing alpha power as playing an inhibitory role and reflecting cortical excitability (Klimesch, Sauseng, and Hanslmayr, 2007). The effect of alpha power in the pre-stimulus window was strongest between -0.45 s and -0.3 s before stimulus presentation in the left visual cortex. Interestingly, this result is consistent with EEG studies reporting the effect of alpha power in posterior electrodes and referring to pre-stimulus alpha power in terms of "occipital alpha" (Hanslmayr et al., 2007; Lange, Oostenveld, & Fries, 2013; Zoefel & VanRullen, 2017). Nonetheless, our data on sensors did not replicate the present result. It is worth noting that in the original work the number of comparisons over the spatial-spectral-temporal dimensions was significantly reduced by performing statistical tests on one selected channel only (i.e., Fz). Crucially, Fz was selected because it showed the

strongest difference between hits and misses. Since the effect of pre-stimulus alpha power on visual perception has been replicated in several studies (for a review see Ruhnau et al., 2014), we speculate that our non-significant result may arise from the characteristics of the detection task we used. Indeed, visual stimuli were always presented in the same hemifield (i.e., on the right). Therefore, spatial attention was not expected to fluctuate between the two hemifields, thus reducing the variability of alpha power fluctuations.

The effect of alpha phase that we observed in the present data in the pre-stimulus window is comparable with the one described by Busch and colleagues (2009) in terms of latency. Indeed, we both found a significant phase opposition between hits and misses around 200 ms before stimulus presentation. However, our results are slightly different from the original ones in terms of frequency. Indeed, while Busch et al., (2009) reported an effect peaking around 7 Hz, the one we observed here was around 11 Hz. Since the peak of alpha frequency is known to vary among participants (Başar, 2012; Haegens et al., 2014), the higher frequency in the phase effect observed here compared to the one by Busch and colleagues (2009) may be due to the fact that on average the two groups of participants may differ in the individual alpha frequency. Our result is comparable to the one described by Mathewson et al. (2009), who reported an effect of pre-stimulus phase at 10 Hz. The analysis in source space confirmed a significant effect of pre-stimulus phase in the alpha band, and revealed that the effect mainly involved frontal areas. This result is consistent with EEG studies describing a more frontal topography for the effects of alpha phase compared to alpha power, suggesting that the power and phase in the alpha frequency range may impact visual perception through distinct mechanisms (Busch, Dubois and VanRullen, 2009; Busch and VanRullen, 2010; Zoefel and VanRullen, 2017).

2.6.1 Limitations

The study we described here shares a few limitations with the original work (Busch, Dubois, and VanRullen, 2009). First, the use of near-threshold stimuli prevented a deeper investigation on the mechanisms involved in alpha-driven modulation of visual perception (Chaumon and Busch, 2014; **Section 1.5**). Moreover, the number of target-absent trials presented did not enable the calculation of a bias-free measure of performance (e.g., *d* prime), thus preventing to distinguish whether the effects of ongoing oscillations were due to fluctuations of sensitivity or of response criterion (the latter recently associated with spontaneous fluctuations of pre-stimulus alpha power; Iemi and Busch, 2018; Iemi, Chaumon, Crouzet, and Busch, 2017; Limbach and Corballis, 2016; Samaha, Iemi, and Postle, 2017; **Section 1.4.2**).

2.6.2 Conclusions and future directions

To conclude, in the present study we successfully replicated several findings described in Busch and colleagues (2009) and provided novel advances in the field by describing the effects of ongoing oscillations in source space.

First, our findings showed that both pre-stimulus power and phase in the alpha band have an effect on visual detection of near-threshold stimuli. Moreover, the effects of ongoing oscillations as well as the neurophysiological response appear to involve feed-forward and/or feed-back mechanisms, rather than being mainly considered local phenomena restricted to sensory regions. Finally, the different source localization for pre-stimulus alpha power and phase is consistent with recent hypotheses suggesting that they subtend independent mechanisms (**Section 1.4.1**; Zoefel and VanRullen, 2017**)** and in general

with the hypothesis that alpha activity may not be considered a unitary phenomenon (Sadaghiani and Kleinschmidt, 2016).

Given the high computational demands especially for phase statistical testing, together with the variability in the measures that can be used to evaluate phase opposition between experimental conditions, future research is needed in order to establish whether the variability in reporting the effect of pre-stimulus alpha phase is due to technical limitations, to experimental factors or to physiological reasons.

3. Study 2: MODULATION OF PRE-STIMULUS OSCILLATIONS

Effects of a dark adaptation paradigm on phosphene perception and TMS-evoked potentials

3.1 Background and aim

Ongoing magneto/encephalographic (M/EEG) alpha power represents a measure of cortical excitability, with a decrease reflecting a state of enhanced excitability, and a stronger activity indicating higher inhibition (Jensen and Mazaheri, 2010; Klimesch, Sauseng, and Hanslmayr, 2007). Perceptual outcome and neurophysiological evoked response appear to be influenced not only by rapid pre-stimulus fluctuations in alpha activity (Busch, Dubois, and VanRullen, 2009; Busch and VanRullen, 2010; Hanslmayr et al., 2007; Iemi and Busch, 2018; Lange et al., 2014; Mathewson et al., 2009; van Dijk, Schoeffelen, Oostenveld, and Jensen, 2008), but also by the excitability state of the cortex during longer periods of time, for example as revealed by alpha power measured during resting state recordings (Romei, Rihs, Brodbeck, and Thut, 2008).

Cortical excitability can be non-invasively and transiently modulated through several procedures, such as adaptation paradigms (Silvanto, Muggleton, and Walsh, 2008), repetitive transcranial magnetic stimulation (TMS; Boroojerdi, Prager, Muellbacher, and Cohen, 2000b; Rossini et al., 2015), transcranial electrical stimulation (Huang et al., 2017) and learning protocols (Bortoletto, Pellicciari, Rodella, and Miniussi, 2015; Muellbacher et al., 2001).

Current literature suggests that changes in cortical excitability may be obtained also by light deprivation paradigms (Boroojerdi et al., 2000a; Boroojerdi, Battaglia, Muellbacher, and Cohen, 2001; Fierro et al., 2005). In healthy volunteers, the duration of sensory deprivation appears to be crucial in determining the direction of the modulatory effects: while relatively short-lasting (min/hours) dark adaptation (DA) protocols suggest an increase in visual cortex excitability (Boroojerdi et al., 2000a; Boroojerdi, Battaglia, Muellbacher, and Cohen, 2001; Fierro et al., 2005), longer periods of DA have been associated to excitability decrease (Pitskel et al., 2007), consistently with what observed in blind patients compared to controls (Gothe et al., 2002).

Here we exploited a short-lasting DA paradigm to study how different cortical excitability states affect perceptual and neurophysiological response, by means of an experimental protocol combining TMS and EEG (TMS-EEG). According to the literature, we expected higher cortical excitability after DA, reflected by lower pre-stimulus alpha power. In order to establish the causal role of visual cortex in determining the effects of DA, we directly stimulated the area with TMS. When delivered over the visual cortex, TMS may elicit phosphenes, illusory flashes of light which have been related to visual cortex excitability (Merabet, Theoret, and Pascual-Leone, 2003). In the present study, the concurrent EEG recording allowed not only to assess the effects of cortical modulation on perceptual outcome, i.e., TMS-induced phosphenes, but also to simultaneously investigate the neurophysiological response by means of TMS-evoked potentials (TEPs). The wide range of TMS intensities we used enabled us to assess phosphene perception beyond sensory threshold and to describe the relationship between stimulation intensity and evoked response, up to now unknown within the visual cortex.

3.2 Materials and methods

3.2.1 Participants

Fifteen young healthy participants took part in the study after giving written informed consent. Consistently with previous literature (Romei et al., 2008; Taylor, Walsh, and Eimer, 2010, 2010), phosphene perception could be induced in ten participants (66%) without extensive training. Two further participants did not show a reliable phosphene report at baseline (see procedure below), leaving 8 participants (5 females, 6 right-handed, mean age ± SD: 23 ± 3 years) taking part in the main experiment. All participants had no contraindication for TMS application (Rossi et al., 2009), they all had normal or corrected-to-normal vision and no history of neurological disorders. The study was run in accordance of the declaration of Helsinki, the TMS safety guidelines (Rossi et al., 2009) and was approved by the local ethics committee of the IRCCS Centro San Giovanni di Dio Fatebenefratelli, in Brescia.

3.2.2 Experimental procedure

Participants were comfortably seated in a sound-attenuated room. At the beginning of the experiment, the optimal stimulation hotspot was defined as the posterior scalp location over the left hemisphere where TMS could reliably induce stable phosphene perception in the right visual field. A training block was run to familiarize participants with the task and to further assess their reliability in phosphene perception.

After the training block, participants underwent 30 minutes of dark and light adaptation, in counterbalanced order (**Figure 3.1-A**). In DA condition participants were blindfolded. To ensure similar conditions during both adaptation periods and across participants (e.g., to avoid drowsiness or mind-wandering in the absence of a task), participants were asked

to verbally answer the *Temperament and Character Inventory* (Cloninger, 1994; Fossati et al., 2007), whose items were read aloud by the experimenter. Data from the inventory were not stored or analysed. Phosphene perception was assessed at the end of each adaptation periods (see following section for details).

3.2.3 Phosphene perception assessment

During the assessment of phosphene perception, participants were blindfolded and were asked to fixate an imaginary point in front of them. Each trial started with an acoustic stimulus, followed by a TMS pulse after a variable interval between 1 and 2 seconds. One second following the TMS pulse, a second acoustic stimulus indicated participants to report whether they perceived a phosphene or not, by pressing one of two buttons on a conventional computer keyboard (**Figure 3.1-B**).

Phosphene perception was assessed with the Method of Constant Stimuli (MOCS; Kammer, Beck, Erb, and Grodd, 2001; Mazzi, Savazzi, Abrahamyan, and Ruzzoli, 2017), by applying single TMS pulses over the left visual cortex at 11 different intensities (from 46% to 76% of the maximal stimulator output - MSO, in steps of 3%). Each intensity was applied 20 times in a randomized order, for a total of 220 trials and 30 minutes of duration for each adaptation period (**Figure 3.1-A**). The stimulation was delivered by means of a figure-of-eight coil connected to a bi-phasic Magstim Rapid Stimulator (Magstim Company, Whitland, Dyfed, UK). The coil position was monitored throughout the experiment by means of a stereotaxic neuronavigation system (SofTaxic, Electro Medical Systems, Bologna, Italy).

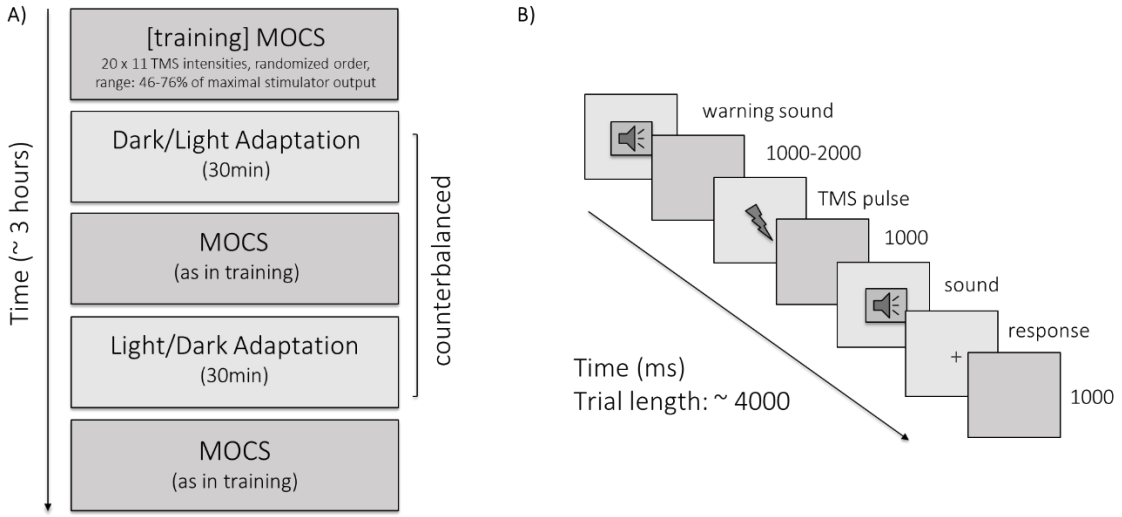


Figure 3.1 Experimental procedure of Study 2. **A)** Experimental session. **B)** Trial structure.

3.3 Analyses

3.3.1 TMS-EEG preprocessing

TMS-EEG data processing was performed using BrainVision Analyzer 2 (Brain Products GmbH, Munich, Germany). The EEG signal was re-referenced offline to the average of the two mastoids and high-pass filtered at 2 Hz (Butterworth zero phase filter; 12 db/oct). TMS-induced artifact was removed by interpolating the signal from 2 ms before to 10 ms after the pulse. Independent component analysis (ICA) was applied to identify and remove components reflecting eye movements and residual TMS-related artifacts (ICA algorithm: infomax). After visual inspection, signal from corrupted electrodes (no more than 3 in any subject) was interpolated. Line noise was removed (50 Hz notch filter) and the signal low-pass filtered at 40 Hz (Butterworth zero phase filter; 12 db/oct). TMS-EEG data was segmented into epochs ranging from 1 s before to 1 s after the TMS pulse and baseline corrected for the 100 ms preceding the TMS pulse. Epochs were visually inspected and rejected if the signal amplitude was higher than ±70 μV in any channel, and

if eye movements and/or muscle artifacts were detected (less than 28% of the epochs were rejected).

3.3.2 Pre-stimulus activity: alpha power

With the aim of assessing the modulation of cortical excitability induced by the DA paradigm, we performed time-frequency analysis on single trial data. We applied a Hanning taper for frequencies from 2 to 45 Hz, with a time window of a frequency-dependent length (3 cycle per time window), sliding in steps of 25 ms. Given our specific hypotheses, we lowered the number of comparisons by averaging power-spectral densities over a time window, frequency range and group of channels of interest. Based on the literature on the effects of pre-stimulus alpha power (Busch, Dubois, and VanRullen, 2009; Busch and VanRullen, 2010; Hanslmayr et al., 2007), we selected a time period of 400 ms, ranging from -0.6 s to -0.2 s preceding the TMS pulse. In particular, we avoided the time window just before the TMS pulse, which may be contaminated by the post-stimulus data, especially in low frequencies (Iemi and Busch, 2018). Moreover, based on power spectrum and topographical maps obtained from grand average collapsing both adaptation conditions, we averaged over alpha range between 10 and 12 Hz (**Figure 3.2-A**), and on a subset of parieto-occipital electrodes, according with to the literature (Hanslmayr et al., 2007).

Since pre-stimulus alpha power is known to be lateralized, reflecting top-down mechanisms of spatial attention (i.e., higher power level in the hemisphere ipsilateral to the attended visual hemifield), we expected not only a modulation of pre-stimulus power by means of DA, but also a difference in alpha power between the left and right hemisphere. Therefore, we averaged over two sets of electrodes, one on the left (PO3, P3, PO7, O1) and one on the right (PO4, P4, PO8, O2) hemisphere (**Figure 3.2-B**).

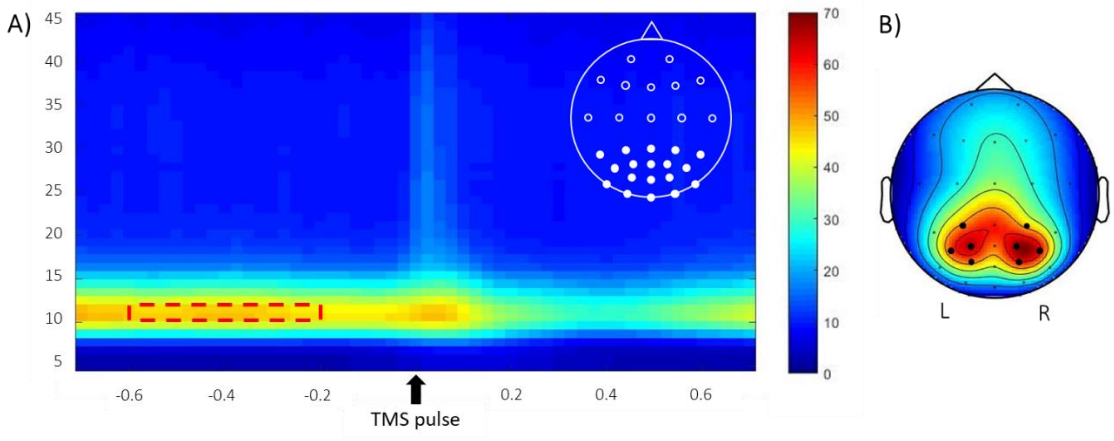


Figure 3.2. Spectral power collapsing DA and LA. **A)** Time-frequency plot on parieto-occipital electrodes, as shown in upper-right inset by filled black dots in electrode layout. The red rectangle indicates the time-frequency interval averaged in subsequent analyses. **B)** Topography of the averaged activation in the time-frequency of interest (10-12 Hz; from -0.6 to -0.2 s); filled black dots were subsequently averaged for left (L) and right (R) hemisphere. Amplitude range for both A) and B) is shown in colorbar (μV^2).

3.3.3 Behavioral outcome: phosphene report

For each condition (DA and LA) and participant, phosphene perception was analysed by fitting a Weibull function (lapse rate at 4%) to phosphene report as a function of TMS intensity, by using the maximum likelihood procedure implemented in Palamedes toolbox (Prins and Kingdom, 2009) in MATLAB (The MathWorks). Then, from the individual psychometric function we extracted the threshold (i.e., the TMS intensity at which participants reported phosphenes in 50% of the trials) and the slope (i.e., a parameter indicating the steepness of the function).

3.3.4 Neurophysiological outcome: TEPs

The grand-average of all trials, regardless of TMS intensities and condition, was used to identify TEP main components (**Figure 3.3**). Only components below 100 ms were considered, since TEPs at later latencies may be contaminated by auditory and

somatosensory processing (Herring, Thut, Jensen, and Bergmann, 2015; Nikouline, Ruohonen, and Ilmoniemi, 1999). From the grand-average across TMS intensities, we identified five main components within the first 60 ms peaking over the parieto-occipital electrodes (group-averaged peak latency indicated in brackets): P25 (23 ms), N35 (34 ms), P40 (43 ms), N50 (52 ms), and P60 (66 ms).

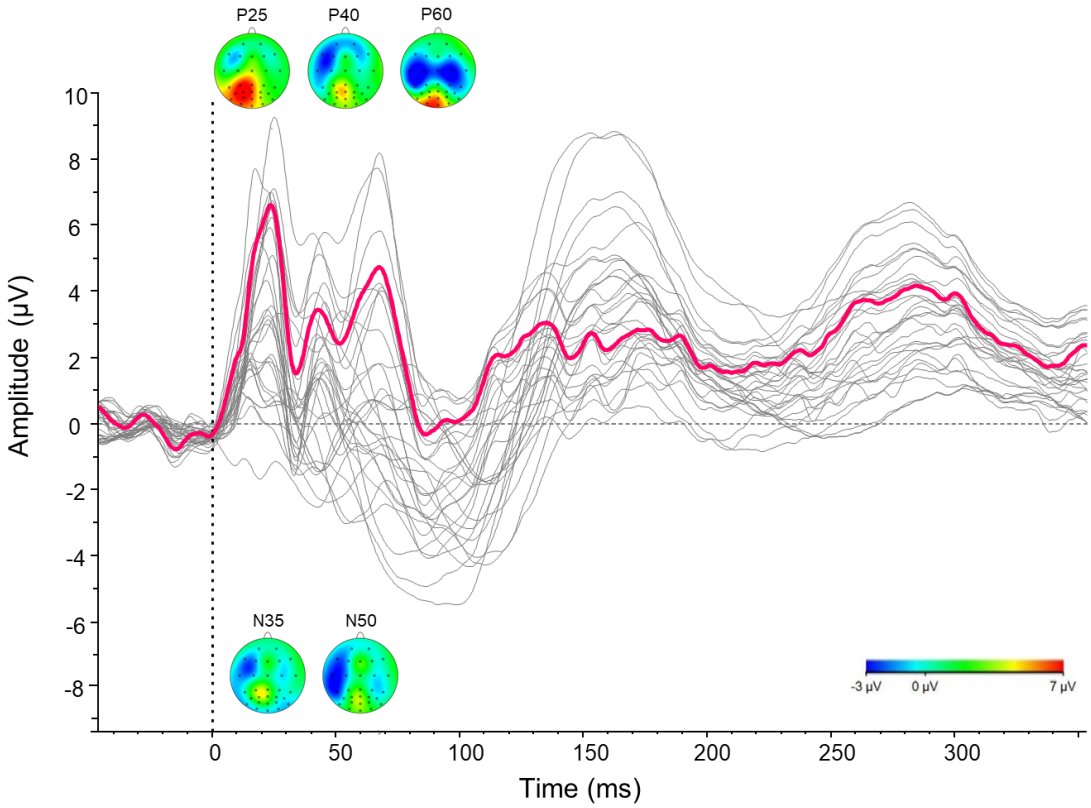


Figure 3.3 Grand-average after DA across all TMS intensities (data after LA are comparable). Signal from parieto-occipital electrodes pooling in thick-colored line. Topographical maps of main components (amplitude range as shown in colorbar).

Additionally, epochs were averaged separately for each TMS intensity, in order to characterize the relationship between TMS intensity and TEP amplitude and to explore possible interactions between experimental conditions (DA and LA). TEP amplitude was measured by pooling the signal recorded from 8 electrodes (POz, PO3, PO7, PO9, Oz,

O1, Iz, I1) covering the area of stimulation, over a fixed time-window of 5 ms around the peak of each component.

Dark adaptation *versus* light adaptation

First, we aimed at testing the effects of adaptation conditions on TEP amplitude and its interaction with TMS intensity. Specifically, we were interested in evaluating whether the effects of adaptation could be seen below threshold, at threshold and above threshold. Therefore, we averaged TEPs based on three groups of intensities: low (46-52%), medium (58-64%) and high (70-76%). Low and high intensities were below and above group level phosphene threshold, respectively (low: 46-52% MSO; high: 70-76% MSO; averaged threshold ± SE: 62.98 ± 1.54% MSO).

TEP amplitude as a function of TMS intensity

To investigate whether our results could be affected by adaptation-related changes in the relationship between TEP amplitude and TMS intensity, we ran a trend analysis for each adaptation condition and component, including all TMS intensities.

Beside expecting TEP amplitude to increase as a function of TMS intensity (Komssi, Kähkönen, and Ilmoniemi, 2004; Kähkönen, Komssi, Wilenius, and Ilmoniemi, 2005), we did not have any *a-priori* hypotheses about the parametric function which would best describe this positive relationship (e.g., linear, quadratic, etc.). For this reason, we performed a two-steps trend analysis. In the first step, the amplitude of TEP components from all participants was submitted to a non-parametric smoothing spline analysis, a data-driven procedure that facilitates the detection of the type of relationship between variables without any *a-priori* assumption (Ramsay and Silverman, 2005; Pellicciari et al., 2016; R, version 3.3.1 - R Core Team, 2016; **Figure 3.4-A**). The degree of smoothing in the

spline analysis is defined by the *span* parameter (*span* range: 0-1, the higher the value, the smoother the fitted curve). The *span* value was selected using the Akaike Information Criterion (AIC) method, which allows models comparison on the basis of their maximum-likelihood fit to the data, taking into account model complexity (Burnham and Anderson, 2002; Burnham and Anderson, 2004). In the second step of the trend analysis, aimed at identifying the best parametric function from step one, we fitted a set of parametric functions of increasing complexity (i.e., increasing number of parameters: linear, logarithmic, exponential, quadratic, cubic) to the spline results (**Figure 3.4-B**). For components in which TEP amplitude was negative, data was linearly transformed to positive values in order to apply the exponential fitting. The coefficient of determination R^2 was used to evaluate the goodness of fit of each function to the spline results. In this step, we always selected the function with a lower number of parameters that fitted the spline results. A function with a higher number of parameters was selected only if R^2 increased by 10%. This second step allows making predictions about TEP amplitude beyond the range of tested TMS intensities (i.e., 46-76% of MSO).

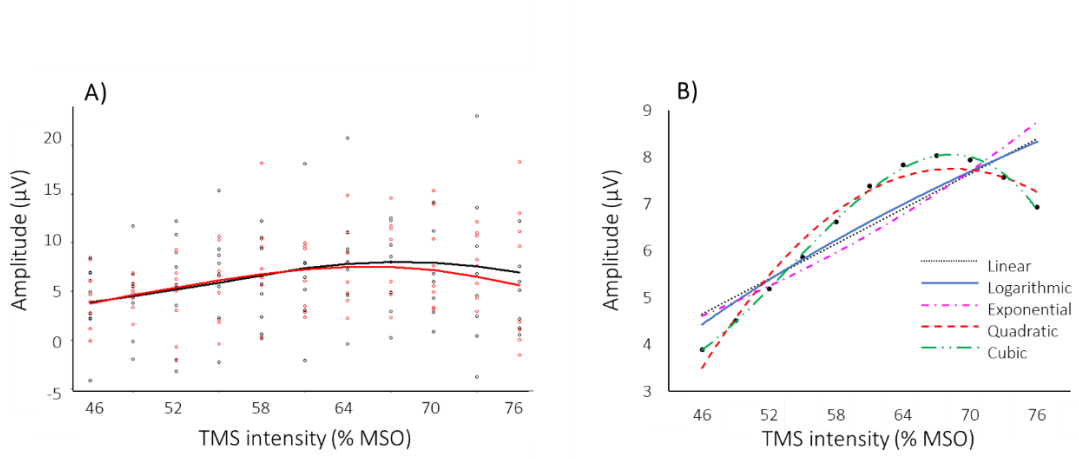


Figure 3.4 Two-steps trend analysis: example on P25. **A)** Step1: non-parametric smoothing spline analysis on single-subject data, after LA (red) and DA (black). **B)** Step2: parametric fitting on spline values; comparison among a set of functions for DA.

3.3.5 Statistical analysis

The level of statistical significance was set at $p < 0.05$. For parametric comparisons, the Kolmogorov-Smirnov test confirmed the normality of the distributions, and Tukey honest significant difference was applied in order to correct for multiple comparisons whenever appropriate. Statistical testing was performed using Statistica for Windows (version 10, StatSoft).

Pre-stimulus activity: alpha power

Pre-stimulus alpha power after DA and LA was compared by means of a repeated-measures analysis of variance (rm-ANOVA), with Condition (DA, LA) and Hemisphere (left, right) as factors.

Behavioral outcome: phosphene report

In order to investigate the effect of adaptation conditions on phosphene perception, we ran a two-tailed Student's paired *t* test on the phosphene threshold and slope separately.

Neurophysiological outcome: TEPs

To compare the effects of the adaptation conditions and TMS intensity on TEP amplitude a separate rm-ANOVA was performed for each component with Condition (DA, LA) and Intensity (low, medium, high) as factors.

3.4 Results

Unless otherwise specified, mean ± SE is reported.

3.4.1 Pre-stimulus activity: alpha power

Pre-stimulus alpha power was modulated by Condition and Hemisphere, as shown by a significant interaction in the 2 by 2 rm-ANOVA ($F_{(1, 7)} = 6.296$, $p = 0.040$). Post-hoc comparisons revealed a significant difference between DA and LA, with pre-stimulus alpha power after DA being significantly lower than after LA, both on the left (DA: 51.51 $\mu V^2 \pm 17.04$; LA: 56.05 $\mu V^2 \pm 20.33$; $t = 0.88$; $p = 0.029$) and on the right pooling (DA: 50.74 $\mu V^2 \pm 15.83$; LA: 59.6 $\mu V^2 \pm 19.98$; $t = 1.50$; $p < 0.001$). Furthermore, we observed a trend for significance in the difference between left and right pooling after LA ($t = 1.29$; $p = 0.084$; **Figure 3.5**).

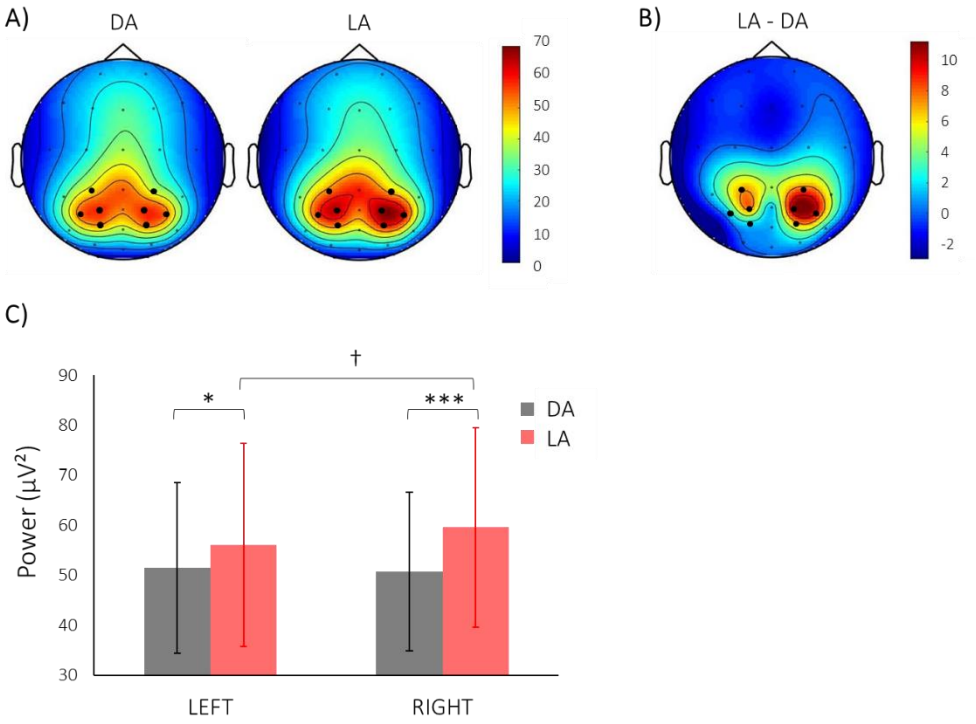


Figure 3.5 Spectral power in pre-stimulus time-frequency range of interest. **A)** Topographic map of power activation after DA and LA, showing a bilateral parieto-occipital activation. **B)** The topographic map of power difference between LA and DA shows a lateralized effect, greater in the right electrode pooling. Amplitude range shown in colorbars. **C)** Bar plot showing the interaction between Condition and Hemisphere; statistical significance as revealed by post-hoc comparisons (†: $p = 0.084$; **: $p < 0.05$; ***: $p < 0.001$; SE in error bars).

3.4.2 Behavioral outcome: phosphene report

DA affected the slope of the psychometric function, which was significantly higher after DA compared to LA (DA: 11.56 ± 1.74; LA: 9.35 ± 1.64; t = 2.61; p = 0.035; **Figure 3.6-A-B**). This result indicates a greater visual sensory reliability (i.e., the steeper the function, the lower the variability around threshold; Parker and Newsome 1998). The estimated threshold for phosphene perception did not change between conditions (DA: 62.77 ± 2.24% MSO; LA: 63.20 ± 2.25% MSO; t = 0.44; p = 0.675), suggesting that DA did not modulate visual cortex sensitivity (**Figure 3.6**).

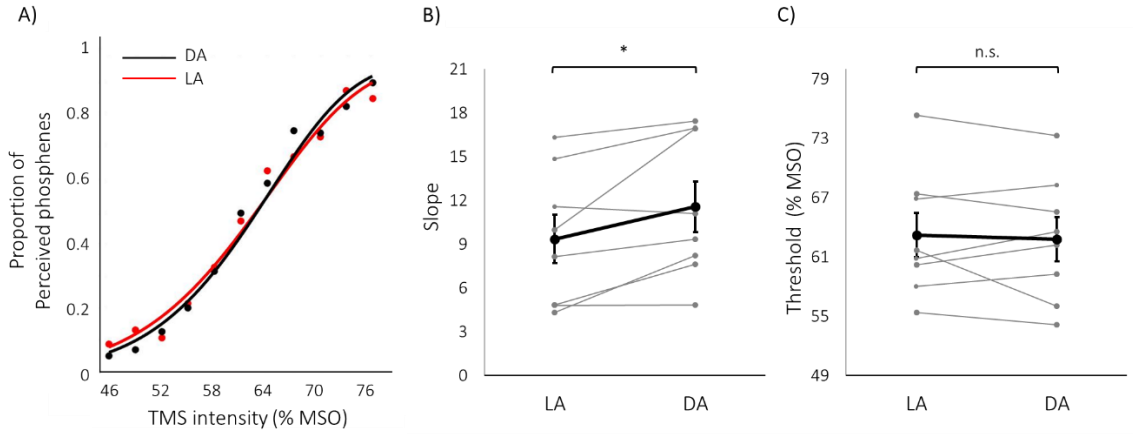


Figure 3.6 Phosphene perception. **A)** Weibull function fitted to subjective report of perceived phosphenes averaged across subjects as a function of TMS intensity, after LA (red) and DA (black). **B)** The slope of the psychometric function after DA is significantly higher than after LA (p=0.035). **C)** No significant difference in phosphene threshold between DA and LA.

3.4.3 Neurophysiological outcome: TEPs

Dark adaptation *vs.* light adaptation

We observed a main effect of Intensity for N35 and P40 (N35: $F_{(2, 14)} = 13.77$, $p < 0.001$, $\eta_p^2 = 0.66$; P40: $F_{(2, 14)} = 7.48$, $p = 0.006$, $\eta_p^2 = 0.52$), showing an increase in peak amplitude as a function of TMS intensity. A trend towards significance in the same

direction was present also for the other components (P25: $F_{(2, 14)} = 3.57$, $p = 0.056$, $\eta_p^2 = 0.34$; N50: $F_{(2, 14)} = 3.51$, $p = 0.058$; P60: $F_{(2, 14)} = 3.52$, $p = 0.058$, $\eta_p^2 = 0.33$). Furthermore, the rm-ANOVA revealed a significant interaction between Condition and Intensity for P60 only ($F_{(2, 14)} = 6.19$, $p = 0.012$, $\eta_p^2 = 0.47$). Post-hoc comparisons showed a significant difference between DA and LA at high intensities ($t = 2.25$; $p = 0.030$), with the P60 amplitude after DA being significantly lower compared to LA (DA = 5.12 ± 1.08 µV; LA = 8.65 ± 1.67 µV; **Figure 3.7**).

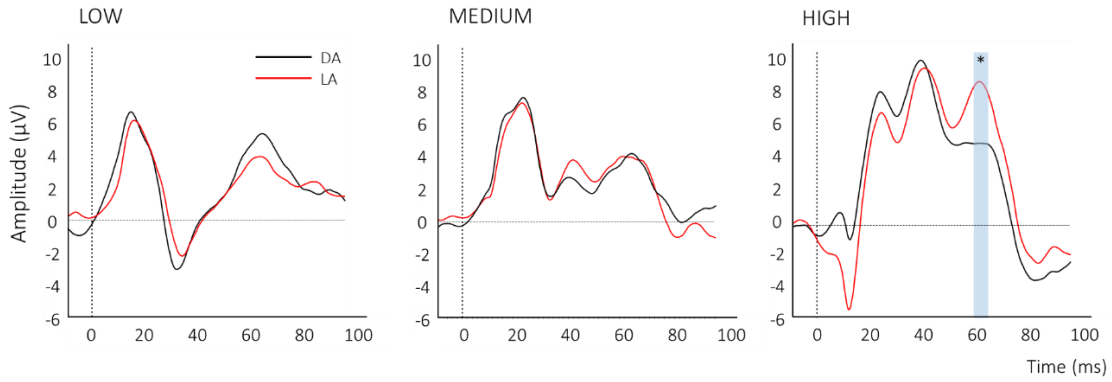


Figure 3.7 Interaction between Intensity (low, medium and high) and Condition (LA – red, DA – black). In high intensities, P60 after DA is significantly lower compared to LA ($p = 0.030$).

TEP amplitude as a function of TMS intensity

As expected, the relationship between TEP amplitude and TMS intensity was positive (**Figure 3.8**). The first step of the trend analysis (non-parametric spline analysis), performed to identify the degree of smoothing (AIC method), showed a consistent span value across TEP components (span: 0.86 ± 0.01). Following the span calculation, we identified the best parametric fitting. The goodness of fit we observed in the selected function was higher than 97% for all the components (R^2 range: 97-100%). **Figure 3.8** shows the best model fitting as a function of TMS intensity after DA and LA. Importantly, for each component, the selected parametric function was consistent between adaptation

conditions. The relationship between TEP amplitude and TMS intensity was linear only for N35 (DA and LA: $R^2 = 0.98$). We observed a quadratic trend with the parabola opening downwards (i.e., negative *a* parameter) for P25 (DA: $R^2 = 0.97$, LA: $R^2 = 0.98$), and an exponential trend for P40 (DA: $R^2 = 0.98$, LA: $R^2 = 1$). Finally, both N50 (DA and LA: $R^2 = 0.98$) and P60 (DA and LA: $R^2 = 0.99$) best fitted to a quadratic function with the parabola opening upwards (i.e., positive *a* parameter). Corroborating findings from the rm-ANOVA (i.e., a significant interaction between Intensity and Condition for P60), confidence intervals calculated for spline values showed that the only case in which DA and LA do not overlap was represented by the amplitude of P60 at highest TMS intensities (**Figure 3.8**).

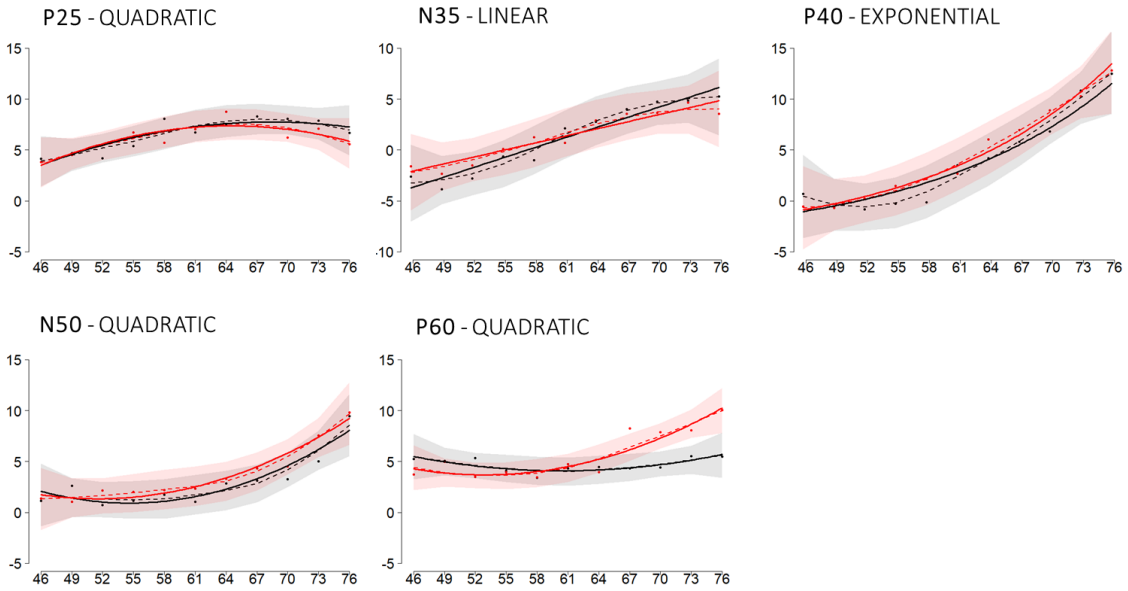


Figure 3.8 Best model fitting (continuous line) to spline results (dashed line), for each component separately (dots: original TEPs amplitude averaged across subjects), after LA (red) and DA (black). Abscissa: TMS intensity (% MSO); ordinate: TEP amplitude (μV).

3.5 Discussion

In the present study we aimed at experimentally modulating cortical excitability by means of short-term DA, in a TMS-EEG paradigm. Consistently with what expected, we observed lower pre-stimulus alpha power after DA compared to LA. Moreover, we found a modulation of the behavioral response to TMS, i.e., a steeper slope of the psychometric function describing phosphene report as a function of TMS intensity, associated with a lower TEP amplitude of a component peaking at 60 ms after the TMS pulse, for high TMS intensities only. The interaction between adaptation condition and TMS intensity could not be explained by an effect of DA on the positive relationship between TEP amplitude and TMS intensity, which was linear for N35, quadratic for P25, N50, P60 and exponential for P40, consistently in the two adaptation conditions.

The time-frequency analysis on pre-stimulus alpha oscillations showed higher power levels after DA compared to LA not only in the left sensors, corresponding to the hemisphere we stimulated with TMS, but also in the contralateral one. This result suggests that DA has a general effect on cortical excitability in parieto-occipital activation of alpha power, although the effect of adaptation condition was stronger in the right electrode pooling compared to the left one. The trend towards significance in the difference between the left and the right pooling, with the power recorded by left sensor being lower than the right ones, is consistent with findings on spatial attention (Worden, Foxe, Wang, and Simpson, 2000; Sauseng et al., 2005). Indeed, in the present paradigm, TMS pulses were always delivered on the left hemisphere; therefore, participants were likely to attend the contralateral visual hemifield, where phosphenes could appear. This finding is also consistent with the Gating by Inhibition framework, which underlines the need of

inhibiting task-irrelevant areas (in this case, the right hemisphere) to ensure task execution (Jensen and Mazaheri, 2010).

Phosphene perception assessment revealed that DA significantly affected perceptual outcome, as shown by a steeper slope of the psychometric function describing phosphene report as a function of TMS intensity. In phosphene report, the slope of the psychometric function provides information about the increment rate of perceived phosphenes as a function of TMS intensity. A steeper slope, as found here after DA, suggests an improvement in visual sensory reliability: the variability around the threshold is reduced, and participants are more likely to report the presence of a phosphene for TMS intensities above the threshold, and, conversely, less likely to report phosphenes below threshold (Parker and Newsome, 1998). Our result is consistent with a previous finding about the effects of DA on phosphene perception, in which the positive relation between perceived phosphenes and TMS intensity appeared to be steeper after 180 min of DA compared to before light deprivation (Boroojerdi et al., 2000a). However, the authors could not statistically test this effect, because the slope parameter can be obtained only by applying a function fitting to phosphene report as a function of TMS intensity, which has not been performed in the work by Boroojerdi and colleagues (2000a).

Previous works on DA also described a significant reduction of phosphene threshold after DA (Boroojerdi et al., 2000a; Fierro et al., 2005), which we did not observe here. Nonetheless, the above-mentioned studies (Boroojerdi et al., 2000a; Fierro et al., 2005) tested longer periods of DA (i.e., a minimum of 45 min), suggesting that 30 min of DA, as used in the present work, may be insufficient to induce a reduction of phosphene threshold. Moreover, it should be noted that the present study differs from the previous ones (Boroojerdi et al., 2000a; Fierro et al., 2005) in the way of estimating phosphene

threshold. While in those studies (Boroojerdi et al., 2000a; Fierro et al., 2005) it was defined as the minimum intensity able to elicit a phosphene in 3 out of 5 trials, here phosphene threshold was calculated more systematically, by using the MOCS, a reliable procedure commonly used in psychophysics (Kammer, Beck, Erb, and Grodd, 2001; Mazzi, Savazzi, Abrahamyan, and Ruzzoli, 2017).

Finally, we looked at the neurophysiological response. TEP components we observed are comparable to previous findings within the visual cortex in terms of polarity and latency (Herring, Thut, Jensen, and Bergmann, 2015; Taylor, Walsh, and Eimer, 2010; Bagattini, Mazzi, and Savazzi, 2015). To the best of our knowledge, only one study so far has described visual TEPs within the first 50 ms (Herring, Thut, Jensen, and Bergmann, 2015), whereas in other two studies (Bagattini, Mazzi, and Savazzi, 2015; Taylor, Walsh, and Eimer, 2010) the signal in the first tens of milliseconds has been interpolated in order to remove the TMS artifact. Early components reported by Herring and colleagues are consistent with our findings (P20-P25, N40-N35, respectively); however, the authors did not observe P40 and N50. We argue that this apparent contrast between the present study and the one by Herring and colleagues (2015) can be accounted by a difference in TMS intensity. Indeed, Herring and colleagues (2015) applied TMS intensity below phosphene threshold (i.e., 80%). Consistently, also in our data the P40-N50 complex is absent for low intensities (which on average are below phosphene threshold): emerging at medium TMS intensities, it becomes clear at high intensities.

After DA, TEPs showed a lower amplitude of P60. This component has been associated with inhibitory processes: a recent study within the motor cortex reported an increase of P60 amplitude in a condition of low cortical excitability (Casula et al., 2014), induced by means of low-frequency rTMS. The finding by Casula et al., 2014 suggests the

involvement of inhibitory mechanisms underlying P60, likely modulated by slow $GABA_B$-(gamma-aminobutyric acid)-mediated inhibitory post-synaptic potentials (Rogasch, Daskalakis, and Fitzgerald, 2013). Therefore, the opposite pattern we observed (i.e., lower P60 after DA compared to LA), is consistent with what expected in a condition of higher cortical excitability.

It is worth noting that P60 was lower after DA for high TMS intensities only. Similarly, a recent TMS-EEG study on the motor cortex has shown that the effects of two different antiepileptic drugs known to alter cortical excitability as assessed by TEP amplitude (i.e., lamotrigine and levetiracetam), cannot be disentangled by applying TMS at motor threshold, but only at higher intensities (Premoli et al., 2017). Taken together, the present result as well as existing literature on TEPs highlight that supra-threshold TMS intensities might be needed in order to detect modulations in cortical excitability, although TEPs are clearly present also at subthreshold intensities (Kähkönen, Komssi, Wilenius, and Ilmoniemi, 2005; Komssi, Kähkönen, and Ilmoniemi, 2004). Importantly, the present findings are consistent with the hypothesis that neural excitability at baseline interacts with TMS intensity in producing not only behavioral (Silvanto, Bona, and Cattaneo, 2017; Silvanto, Bona, Marelli, and Cattaneo, 2018) but also neurophysiological effects of TMS (i.e., TEPs). Nonetheless, future studies are needed to understand the origin of P60 (Rogasch, Daskalakis, and Fitzgerald, 2013) and its relationship with TMS intensity, especially in the visual cortex.

Evoked response to TMS vary across TMS intensities, and can therefore be considered as an indicator of the brain activation state (Casarotto et al., 2010; Kähkönen, Komssi, Wilenius, and Ilmoniemi, 2005; Komssi, Kähkönen, and Ilmoniemi, 2004; Rosanova et al., 2009). Previous studies on the prefrontal and motor cortices (Kähkönen, Komssi,

Wilenius, and Ilmoniemi, 2005; Komssi, Kähkönen, and Ilmoniemi, 2004) revealed that clear TEPs can be elicited also by TMS intensities below motor threshold (i.e., 60%), suggesting that TMS-EEG may be sensitive also to sub-threshold perturbations. However, the relationship between TMS intensity and TEP amplitude appears to differ among brain areas: while a non-linear dependence emerged for the motor cortex (Komssi, Kähkönen, and Ilmoniemi, 2004), within the prefrontal cortex a linear regression was observed (Kähkönen, Komssi, Wilenius, and Ilmoniemi, 2005). However, the limited number of TMS intensities applied in the above mentioned studies (Kähkönen, Komssi, Wilenius, and Ilmoniemi, 2005; Komssi, Kähkönen, and Ilmoniemi, 2004) prevented to systematically investigate the relationship between TEPs and TMS intensity. Here we extended previous findings not only by exploring TEP amplitude as a function of TMS intensity within the visual cortex, but also by describing this relationship by means of a parametric function fitting, by means of a wide range of TMS intensities. Among TEP components, P25 appeared to be the only one in which the parametric fitting (i.e., quadratic function with the parabola opening downwards) did not predict a further increment in peak amplitude at higher intensities beyond the range we tested.

3.5.1 Limitations

The present study provides novel advance in the field of cortical excitability modulation by means of short-lasting light deprivation, although it presents a few limitations. First, from the 15 participants involved in the study, we could analyze data from 8 only, thus confining the generalization we can draw from the data. Second, the limited number of trials for each TMS intensity prevent us to perform more detailed analyses on single-intensity TEPs (e.g., analysis on latency). Finally, as described in detail in the introduction as well as in the previous study (**Study 1**), spontaneous power fluctuations are likely to

occur in the pre-stimulus window, thus adding variability to the study of "tonic" effects such as the one we were interested in here. An alternative measure that could be used to investigate more stable changes in cortical excitability may be resting state measurements before and after the adaptation conditions.

3.5.2 Conclusions and future directions

The present findings showed that DA was effective in modulating cortical excitability, as shown by pre-stimulus oscillatory pattern in the alpha band, TMS-induced phosphene perception and TEPs. Importantly, this study highlighted that a wide range of stimulus intensities is informative both at behavioral and neurophysiological level (**Section 1.5**). Indeed, this approach allowed the psychometric function parametrization, which unveiled a modulation in phosphene perception as a consequence of DA (i.e., higher slope), even in the absence of a change in phosphene threshold. At the neurophysiological level, the application of several stimulation intensities allowed to identify an interaction between DA and TMS intensity, with DA inducing a lower P60 at high intensities TEPs only. Moreover, this method revealed that one TEP complex (P40-N50) was absent at low TMS intensities, allowing to reconcile our findings with an apparent inconsistency in the literature (Herring, Thut, Jensen, and Bergmann, 2015). Finally, using multiple TMS intensities enabled the identification of a specific trend of each TEP component as a function of TMS intensity, extending previous reports (Kähkönen, Komssi, Wilenius, and Ilmoniemi, 2005; Komssi, Kähkönen, and Ilmoniemi, 2004).

4. Study 3: NEURAL MECHANISMS

A formal model for the effects of ongoing M/EEG oscillations on visual perception

4.1 Background and aim

Neurons' response does not depend entirely on external input: the repeated presentation of the same stimulus gives rise to a highly variable response (Arieli, Sterkin, Grinvald and Aertsen, 1996; Vogels, Spileers, and Orban, 1989), a phenomenon that interestingly has been observed also in anesthetized animals (Tomko and Crapper, 1974). Crucially, such variability can be accounted by ongoing brain activity, as revealed with several methodological approaches (Arieli et al., 1996; Hesselmann, Kell, and Kleinschmidt, 2008; Hesselmann, Kell, Eger, and Kleinschmidt, 2008; Kayser, McNair, and Kayser, 2016; Martin, Barnes, and Stevens, 2012; Sadaghiani and Kleinschmidt, 2013; Schölvinck, Friston, and Rees, 2012; Weisz et al., 2014). In this context, time-frequency patterns of oscillatory activity play a crucial role in affecting both behavioral and neural response (Ai and Ro, 2014; Baumgarten, Schnitzler, and Lange, 2016; Haegens et al., 2011; Leske et al., 2015; Linkenkaer-Hansen, 2004; Mazaheri, Nieuwenhuis, vanDijk, and Jensen, 2009; Schubert et al., 2008; Van Dijk, Schoeffelen, Oostenveld, and Jensen, 2008). Ongoing oscillations within the alpha band (frequency range: 8-13 Hz) are especially relevant in accounting for response variability in the domain of visual perception (Busch, Dubois, and VanRullen, 2009; Iemi and Busch, 2018; Iemi, Chaumon, Crouzet, and Busch, 2017; Lange et al., 2014; Mathewson et al., 2009; Van Dijk, Schoeffelen, Oostenveld, and Jensen, 2008).

In the last decades neuroscientists have developed fundamental theories on the role of neural oscillations in brain dynamics (e.g., Communication Through Coherence, Fries 2005; Inhibition Timing Hypothesis, Klimesch, Sauseng, and Hanslmayr, 2007; Gating By Inhibition, Jensen and Mazaheri 2010). Nonetheless, current advancements in the study of neural oscillation still leave crucial issues underexplored. Indeed, the neural mechanisms involved in ongoing oscillations as measured by magneto/electroencephalographic (M/EEG) recordings are far from being established (Cohen, 2017; Musall et al., 2014); likewise, the effects of micro-level mechanisms on behavior are largely unknown.

In the present work, we propose a model based on a psychophysical approach, namely the Oscillation Response Probability (ORP) hypothesis, that presents possible mechanisms subtending the effects of pre-stimulus M/EEG oscillations in the alpha band on visual perception (Lange et al., 2014; Ruhnau, Hauswald, and Weisz, 2014; Sadaghiani and Kleinschmidt, 2016; Zoefel and VanRullen, 2017). The aim of the ORP model is twofold: first, it suggests hypotheses on possible neural mechanisms involved in ongoing oscillations; second, it allows to disentangle distinct functional mechanisms associated with the same M/EEG feature, i.e., alpha activity.

The ORP hypothesis is based on the following key-points: 1) alpha oscillations affect visual perception; 2) alpha activity plays an inhibitory role; 3) alpha inhibition occurs through alpha-gamma cross-frequency interactions; 4) alpha-modulated gamma power fluctuations affects the probability of sensory neurons to respond to an incoming stimulus; 5) response probability is selectively modulated by distinct neural mechanisms.

A central concept of the ORP model is the estimation of the response probability of visual sensory neurons, that we linked with the psychometric function observed at the behavioral

level when facing a wide range of stimulus intensities. In this framework, the psychometric function estimation could represent an extremely powerful tool, because it provides suggestions on the selective involvement of different neural mechanisms, which cannot be discerned non-invasively. We therefore suggest that the ORP model may be helpful in making hypotheses on the neural mechanisms involved in alpha-driven modulation of sensory processing, starting from selective modification of the psychometric function.

4.2 The Oscillation Response Probability (ORP) hypothesis

4.2.1 Alpha oscillations affect visual perception

Oscillatory activity within alpha band is the strongest electrophysiological signal that can be measured by non-invasive recordings, and it raised interest since the earliest EEG studies (Berger, 1929; Klimesch, 2012). In the pre-stimulus window, both M/EEG power and phase have been shown to have an effect on perceptual performance in the visual domain. A number of studies reported the effect of pre-stimulus power, with lower levels leading to a higher probability to perceive a near-threshold stimulus or a TMS-induced phosphene (Busch and VanRullen, 2010; Hanslmayr et al., 2007; van Dijk, Schoeffelen, Oostenveld, and Jensen, 2008). Moreover, detected and undetected trials are preceded by opposite phases of oscillations within the alpha range (Busch, Dubois, and VanRullen, 2009; Busch and VanRullen, 2010; Mathewson et al., 2009). Importantly, findings from recent works which aimed at modulating alpha activity were consistent with correlative studies, proving evidence for a causal role of pre-stimulus alpha rhythm on visual perception (Landau and Fries, 2012; Romei, Gross, and Thut, 2010; Spaak, de Lange, and Jensen, 2014).

4.2.2 Alpha activity plays an inhibitory role

The direction of the effects of alpha activity described above has led the most widespread interpretation to consider alpha activity as playing an inhibitory role: the larger the EEG alpha power, the stronger the inhibition (i.e., the lower the cortical excitability; Klimesch, Sauseng, and Hanslmayr, 2007; but see Palva and Palva 2007; Jensen and Mazaheri 2010). Moreover, inhibition appears to be cyclic, depending on the phase of alpha oscillations (referred to as "pulsed inhibition"; Mathewson et al., 2009).

A possible way to account for the inhibitory function played by both power and phase in the alpha band is to think of alpha oscillations in terms of biased/asymmetric oscillations (Hyafil, Giraud, Fontolan, and Gutkin, 2015; Jensen and Mazaheri, 2010; Schalk, 2015). According to this view, alpha oscillations are not zero-mean, but the mean amplitude within an alpha cycle varies with the amplitude of oscillatory power, as shown in **Figure 4.1-A**. Therefore, the instantaneous voltage level may represent a more direct measure of cortical excitability, compared to power and phase, as suggested by the Function Through Biased Oscillations framework (Schalk, 2015; Schalk, Marple, Knight, and Coon, 2017). Moreover, given their inhibitory function, alpha asymmetric oscillations may be described as negative: higher amplitudes of alpha activity (in absolute value) correspond to a more negative instantaneous voltage level, which leads to higher inhibition (Hyafil, Giraud, Fontolan, and Gutkin, 2015; **Figure 4.1-B**). Hence, high cortical excitability is reflected by both the through of a high-amplitude alpha oscillations, as well as by low-amplitude alpha fluctuations.

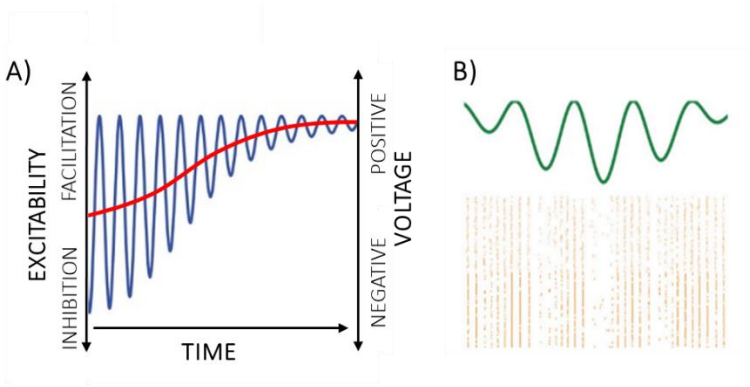


Figure 4.1 Negative and asymmetric alpha oscillations. **A)** An increase in alpha amplitude is accompanied by a general decrease in the mean voltage level (blue trace: time-varying instantaneous voltage; red trace: mean voltage level); adapted from Schalk, 2015. **B)** Alpha band oscillations (green trace) modulate spiking activity (bottom); pulsed inhibition of neural spiking is stronger when the amplitude of alpha oscillations is higher; adapted from Hyafil, Giraud, Fontolan, and Gutkin, 2015.

A major framework in the context of alpha inhibition is represented by Gating By Inhibition (GBI; Jensen and Mazaheri 2010), which originally focused more on alpha functional inhibition of cortical areas not involved in task execution, than on the mechanisms that engage task-relevant areas. Nonetheless, alpha activity appears to play a relevant role also at the local level, as highlighted in a recent version of GBI framework (Bonnefond, Kastner, and Jensen, 2017). Consistently with an asymmetry in alpha oscillations, the GBI account introduced the concept of "duty cycle": when alpha power is high, the time window for sensory processing for a given input is shorter compared to lower level of alpha. This hypothesis is consistent with evidence showing the effects alpha phase only when alpha power is high (Cohen and Van Gaal, 2013; Mathewson et al., 2009).

4.2.3 Functional inhibition through alpha-gamma cross-frequency interactions

Existing evidence (Spaak et al., 2012) and current theories on alpha inhibition (Bonnefond, Kastner, and Jensen, 2017; Jensen and Mazaheri, 2010) suggest that alpha activity modulates gamma oscillations of sensory neurons by means of cross-frequency interactions. Intriguingly, alpha-gamma interactions have been observed during rest and in the pre-stimulus window beside during stimulus processing (Bahramisharif et al., 2013; Osipova, Hermes, and Jensen, 2008; but see Ray and Maunsell 2015; Spaak et al., 2012), at the local level as well as in communication among brain areas (Bonnefond, Kastner, and Jensen, 2017).

The relationship between alpha and gamma oscillations is regulated not only by amplitude-amplitude coupling (AAC), i.e., alpha power increase associated with gamma decrease, but also by phase-amplitude coupling (PAC) interactions, i.e., gamma power nested within the phase of alpha (Spaak et al., 2012). Specifically, PAC and AAC appear to be linked, with stronger alpha power increasing PAC (Osipova, Hermes, and Jensen, 2008). This mechanism could be explained by the asymmetry in alpha oscillations, such that an increase in alpha amplitude is accompanied by a general decrease in alpha level (Hyafil, Giraud, Fontolan, and Gutkin, 2015; **Figure 4.1-A)**.

The ORP framework fits in this perspective and describes fluctuations in gamma power nested within a sinusoidal alpha cycle, as defined in (4.1) and shown in **Figure 4.2**.

(4.1)

$$0 \leq t < 2\pi, \qquad G_F = G\sin(t)$$

$G_F =$ gamma power fluctuation

$G =$ gamma power

$t =$ time interval

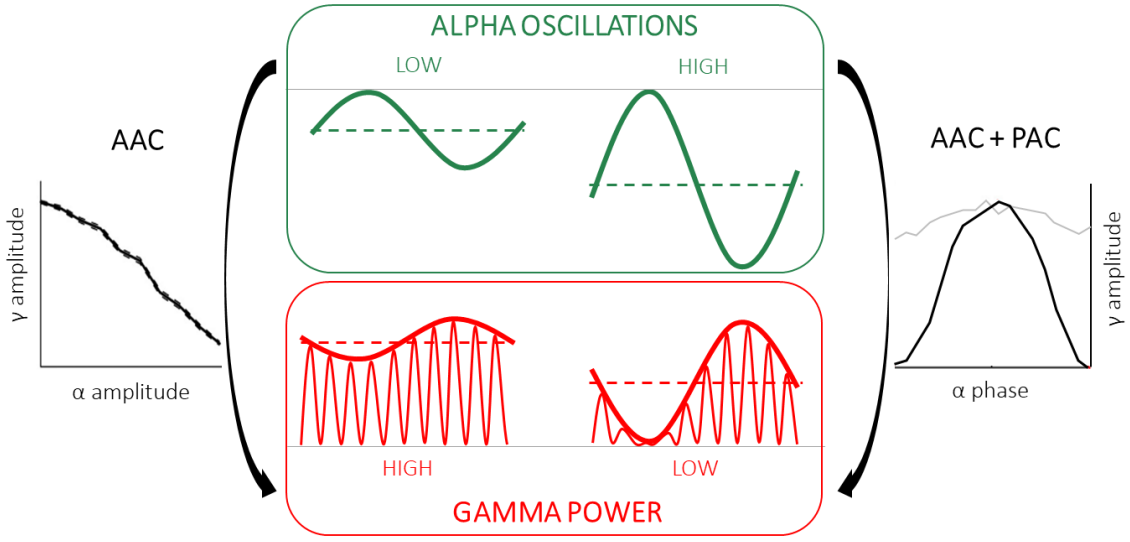


Figure 4.2 Alpha-gamma cross-frequency interactions. Schematic representation of amplitude-amplitude coupling (AAC) and phase-amplitude coupling (PAC) within an alpha cycle, during low (left) and high (right) alpha functional inhibition. During low alpha power (left), alpha-gamma interaction is regulated by negative AAC, i.e., gamma power decreases as a function of alpha amplitude; during high alpha power (right), gamma power is determined by both AAC and PAC (gray line in right inset indicates the alpha-gamma relationship in high alpha power). Left and right insets adapted from Hyafil, Giraud, Fontolan, and Gutkin, 2015.

4.2.4 Alpha-modulated gamma power affects response probability of sensory neurons

Based on alpha-gamma AAC and PAC mechanisms (i.e., gamma power inversely related with alpha power and nested within alpha phase), the ORP model estimates the response probability of sensory neurons, oscillating in gamma, when facing a range of stimulus intensities presented at a random phase within an alpha cycle.

The ORP model takes into account the concept of duty cycle described by Jensen and Mazaheri (2010), which is consistent with the idea of a threshold for gamma power to enable sensory processing. We expressed the response probability as the portion of the alpha cycle in which a given input may elicit a response (**Figure 4.3-A**). For example, a

low-intensity input may determine a response only when presented around the through of alpha cycle (i.e., peak of gamma power), both in a situation of low or high alpha power. Nonetheless, the probability (or, in other words, the proportion of the cycle) of inducing a response is shorter for the condition of high alpha power compared to low alpha power. On the other hand, while a high-intensity input presented during low alpha power may always induce a response, it might not be the case during high alpha power (**Figure 4.3-A**). Therefore, when considering a single alpha cycle, response probability depends on input intensity, the phase and the amplitude of gamma power fluctuation, as defined in (4.2).

(4.2)

$$0 < G < T$$

$$T - G < I < T + G, \qquad P_{\mathrm{RP}} = \frac{\pi + 2\arcsin\frac{(I-T)}{G}}{2\pi}$$

$$I \leq T - G, \qquad P_{\mathrm{RP}} = 0$$

$$I \geq T + G, \qquad P_{\mathrm{RP}} = 1$$

$$T = \text{threshold for gamma power}$$

$$I = \text{input}$$

$$P_{\mathrm{RP}} = \text{population response probability}$$

Figure 4.3-B shows the response probability as a function of input intensity. Below a critical intensity (a), which is the same independently of alpha inhibition, an incoming input may not induce a response (response probability = 0), while for higher intensities, neural response depends on the phase of gamma power fluctuation, giving rise to a response probability between 0 and 1. Finally, input intensities beyond a given value (i.e., (b) for low alpha inhibition; (c) for high alpha inhibition), may induce a response independently of alpha phase (response probability = 1).

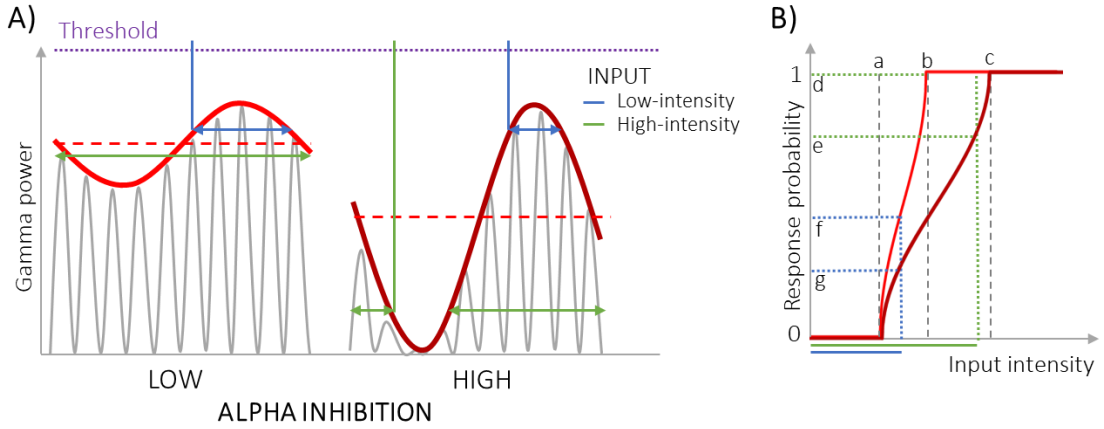


Figure 4.3 Response probability as a function of input intensity in low (light color) and high (dark color) alpha inhibition. **A)** Response probability (double-headed arrows) to a low- (blue) and a high- (green) intensity input in two conditions, i.e., of low alpha inhibition (high gamma power, low PAC; left) and high alpha inhibition (low gamma power, high PAC; right). During low alpha inhibition, the high-intensity input determines a response independently of when it is presented along the sine wave, while the low-intensity stimulus only when occurring within a limited portion of the alpha cycle (i.e., around the peak of gamma power). During high alpha inhibition, the portion alpha cycle in which the low-intensity input gives rise to neural response is shorter compared to low alpha inhibition (concept of duty cycle); moreover, even the high intensity input does not always give rise to neural response. Dashed lines: averaged gamma power within an alpha cycle. **B)** Response probability as a function of input intensity for low and high alpha inhibition, as defined in (4.2). The minimum input intensity able to elicit neural response (a) is the same for both low and high alpha power, due to the asymmetry in alpha oscillations, while the minimum input intensity which determines a response independently of the phase is smaller for the low (b) compared to the high (c) alpha power. Input range between (a) and (b) or between (a) and (c) indicate intensities which induce a response depending on phase (probability between 0 and 1). Response probability for the low-intensity input shown in A) is higher during low alpha inhibition (f) than during low alpha inhibition (g); response probability for the high-intensity input is equal to 1 for low alpha inhibition (d), while is lower for high alpha inhibition (e).

When considering populations of neurons, we can assume a degree of variability in the strength of cross-frequency interactions within a neural assembly, e.g., PAC may be stronger for some neurons compared to others (**Figure 4.4-A)**. Considering PAC strength to be normally distributed among neurons, the global response probability can be

expressed as the weighted average of single response probabilities (4.3). As shown in **Figure 4.4-B**, the global response probability reveals a sigmoid trend, resembling the psychometric function observed at the behavioral level.

(4.3)

$$G_{\mathrm{RP}} = \frac{\sum_{i=1}^{n} P_{\mathrm{RP}\ i}\ w_i}{\sum_{i=1}^{n} w_i}$$

G_{RP}= response probability of the neural population

w = weight, number of neurons of a given PAC strength

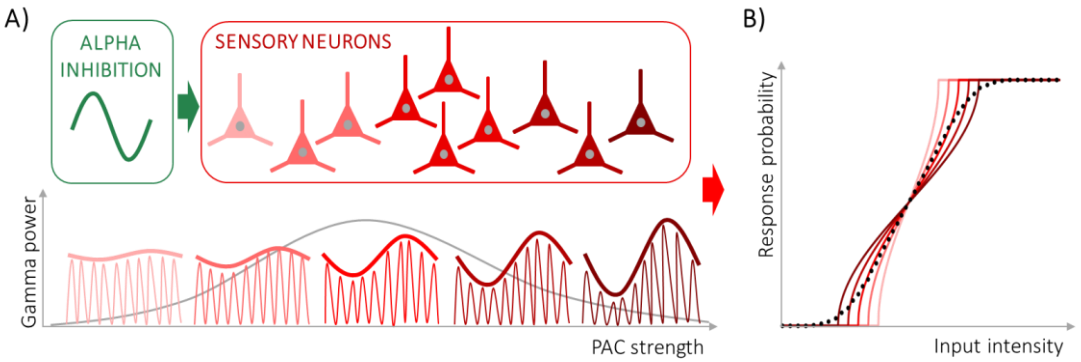


Figure 4.4 Response probability of sensory neurons involved in cross-frequency interactions. Color gradient indicates PAC strength. **A)** Normally distributed PAC strength among neural assemblies. **B)** Continuous traces: single response probability; dashed line: global response probability.

If we approximate the behavioral response probability so that it is proportional to one at the neural level, and the intensity of the stimulus presented to the input to neurons, quantified in terms of depolarizing current, we can consider the response probability function obtained from (4) as the psychometric function observed behaviorally in visual perception. The psychometric function fitting may be defined as a data modelling technique in which an observer's performance in a detection or discrimination perceptual task is related to the physical quantity of a stimulus, e.g., its intensity (Wichmann and

Hill, 2001). To this respect, near-threshold stimuli used in most of the studies published in the field of pre-stimulus activity represent a special case obtained from the psychometric curve. One of the benefits of fitting the psychometric function to psychophysical data relies in making hypotheses on functional mechanisms underlying cognitive or perceptual processes, which are associated with specific changes in the psychometric curve.

4.2.5 Response probability is selectively modulated by distinct mechanisms

Although compelling evidence about the inhibitory role of alpha activity on visual perception and cross-frequency interactions with the gamma band, still little is known about the neural mechanisms associated with ongoing alpha activity, and whether it represents a unitary phenomenon is still a matter of debate (Cohen, 2017; Hyafil, Giraud, Fontolan, and Gutkin, 2015; Sadaghiani and Kleinschmidt, 2016; Spaak et al., 2012). Indeed, the general relation between M/EEG features and micro-level mechanisms is likely to be few to some rather than one to one: the same M/EEG oscillatory feature (e.g., alpha activity) may be generated by distinct mechanisms as well as may subtend several functions (Cohen, 2017). However, non-invasive M/EEG recordings do not allow to disentangle between them.

According to the ORP hypothesis, gamma power fluctuations associated with alpha activity, as observed by M/EEG, may be generated both by changes in amplitude and in synchronization. This hypothesis is supported by evidence from simultaneous invasive local field potentials and non-invasive EEG recordings, showing that synchronization is linearly combined to amplitude changes in local field potentials to give rise to EEG gamma power (Musall et al., 2014). Here, we modelled the effect of changes in local amplitude and in synchronization on the response probability of the visual system, when

a wide range of stimulus intensities is presented. According to the ORP model, changes in local amplitude and synchronization have distinct effect on the psychometric function, i.e., a modification of sensory threshold and of the upper asymptote, respectively. Such modifications are commonly referred to as contrast- and response-gain mechanisms, and both of them have been described in the literature on the effects of attention and adaptation on visual perception and neural response (Cameron, Tai, and Carrasco, 2002; Carrasco, Ling, and Read, 2004; Ling and Carrasco, 2006; McAdams and Maunsell, 1999; Pestilli, Viera, and Carrasco, 2007; Reynolds, Pasternak, and Desimone, 2000).

(1) *Amplitude*. A change in the amplitude of gamma power fluctuation affects the response probability of single group of neurons within a neural assembly (4.2), and, consequently, the global response probability, by altering the threshold of the sigmoid function (**Figure 4.5**). Such effect is mainly represented by a shift of the function. A change in sensory threshold (i.e., sensory sensitivity), commonly described in terms of contrast gain mechanism, is believed to act at the input level of the system and it is considered the main functional process underneath sustained covert attention and adaptation (Cameron et al., 2002; Carrasco et al., 2004; Ling and Carrasco, 2006; Pestilli, Viera, and Carrasco, 2007; Reynolds, Pasternak, and Desimone, 2000).

(2) *Synchronization.* According to the ORP model, gamma synchronization is expressed as a scalar coefficient in a range between 0 and 1. Modulations in synchronization lead to a distinct influence on the global response probability function: acting at the output level of the system, synchronization leaves response probability of single group of neurons unaffected, thus altering the upper asymptote of the global response probability (4.4; **Figure 4.5**). A modification in the upper bound of the psychometric function, or response gain mechanism, mainly affects performance in response to high intensity stimuli,

possibly due to an altered lapse rate (Wichmann and Hill, 2001), and it has been related to transient attention (Ling and Carrasco, 2006).

(4.4)

$$0 < S < 1, \qquad G_{\mathrm{RP}} = \frac{\sum_{i=1}^{n} G_{RP\,i}\ w_i\, S}{n \sum_{i=1}^{n} w_i}$$

$S =$ scalar, degree of synchronization

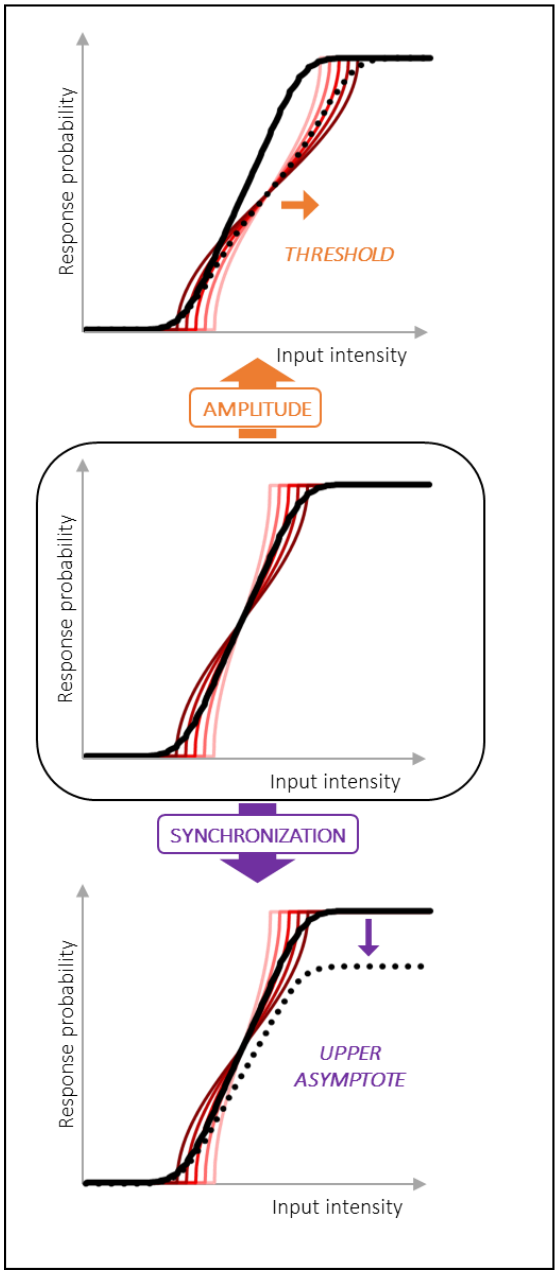


Figure 4.5 ORP predictions on the response probability function. Central panel: response probability of single neural assemblies (colored thin lines) and global response probability (black thick line) in a condition of low alpha inhibition. The effect of an increase in alpha power on the response probability depends on the mechanism involved: if associated modifications in gamma power are due to amplitude changes, the ORP model predicts a change in the sensory threshold mainly explained by a shift of the function (upper panel); while if gamma power changes are associated with a modulation of gamma synchronization, the response probability function is expected to show a decrease of the upper asymptote (lower panel). Dashed line: global response probability function during high alpha inhibition.

To sum up, according to the ORP framework, the approach of the psychometric function estimation may be extremely valuable in non-invasive M/EEG studies on the effects of pre-stimulus activity on visual perception, because it may reveal the existence of different mechanisms associated with the same M/EEG feature (e.g., alpha activity). To our knowledge, so far only two studies have applied this method to the study of the effects of pre-stimulus alpha activity on perception, and in both cases changes in the psychometric function have been related with ongoing alpha power. In a first study by Chaumon and Busch (2014), spontaneous fluctuations in pre-stimulus alpha power has been interpreted as reflecting a response gain mechanism: higher pre-stimulus alpha power was associated with a decrease in the upper asymptote. In the second work investigating the effects ongoing alpha activity on the psychometric function (Benwell et al., 2017a), it has been shown that pre-stimulus alpha power predicts visuospatial bias, but not discrimination sensitivity. It is worth noting that in this study (Benwell et al., 2017a) the proportion of correct responses is not represented as a function of stimulus intensity, but of visuospatial bias instead; therefore, the two studies (Benwell et al., 2017a; Chaumon and Busch, 2014) are not comparable on the psychometric curve's parameters, and the ORP model cannot be applied the work by Benwell and colleagues (2017).

Furthermore, the ORP model allows to make suggestions on possible neural mechanisms that may be associated with selective modifications of the psychometric function. For example, according to the ORP model, findings from Chaumon and Busch 2014 could be interpreted as subtending a modulation in synchronization of gamma sensory neurons.

4.3 Sensitivity or criterion?

Recent works have shown that the effect of fluctuations in pre-stimulus alpha power do not affect sensory sensitivity (**Section 1.4.2**; Benwell et al., 2017b; Iemi, Chaumon, Crouzet, and Busch, 2017; Lange, Oostenveld, & Fries, 2013; Limbach and Corballis, 2016; Samaha, Iemi, and Postle, 2017). Rather, lower levels of alpha power preceding stimulus presentation appear to affect response criterion toward a more liberal one, i.e., a general tendency of reporting to have seen a stimulus, resulting in an increase not only in hit rate but also in false alarms (Iemi, Chaumon, Crouzet, and Busch, 2017; Limbach and Corballis, 2016). Furthermore, a recent finding suggest that the nature of this biased response is perceptual and not decisional in nature (Iemi and Busch 2018). Similar conclusions were drawn by Chaumon and Busch (2015), who showed that variations in ongoing alpha power could better explained as reflecting a response gain mechanism rather than contrast gain. Finally, on the same line, recent studies reported that pre-stimulus alpha power impacts discrimination confidence (Samaha, Iemi, and Postle, 2017) and conscious awareness (Benwell et al., 2017b), but not perceptual acuity.

At the present stage, the ORP model does not consider false alarms, and therefore it has to be applied to performance measures not affected by criterion bias. Nonetheless, the ORP model provides information about the level at which alpha exerts its modulatory effects, i.e., at the input (i.e., amplitude) or at the output (i.e., synchronization) of the sensory system. In this framework, a response gain-like mechanism, as the one described by Chaumon and Busch (2014) is interpreted as depending on synchronization of sensory neurons and not on the presence of noise or subsequent decisional processes.

4.4 Conclusions and future directions

By means of a psychophysical approach based on the psychometric function estimation, the ORP proposal may allow to test for distinct mechanisms associated with the same M/EEG feature, i.e., ongoing alpha activity, and to make hypotheses on the selective involvement of different mechanisms involved in cross-frequency interactions.

The ORP hypothesis is to be intended as a great simplification of the relationship between neural mechanisms and behavior, and future research combining simultaneous invasive and non-invasive recordings, as well as the development of computational models, are needed in order to test the ORP model. Moreover, future developments of this model may take into account other factors that can mediate the relationship between neural and behavioral response, such as: coding mechanisms for response strength, a variable preference for the stimulus for different neural assemblies, global mechanisms related to signal propagation, the presence of neural and, finally, decisional processes.

Nonetheless, in M/EEG studies the application of the ORP model in the present form may shed light on the open question of whether ongoing alpha rhythm represents a unitary phenomenon, for example to explore whether the same mechanisms are involved in spontaneous fluctuations of alpha activity and when it is modulated (e.g., by means of spatial attention). Indeed, while spontaneous variations in alpha power have been associated to a change in the upper asymptote of the psychometric function, interpreted as reflecting a response gain mechanism, spatial attention has been associated to a change in threshold, suggesting an enhanced sensitivity of the visual system (Reynolds, Pasternak, and Desimone, 2000; Cameron et al., 2002). Considering that visuo-spatial attention is related to a decrease in alpha power contralateral to the attended hemifield, it may be hypothesized that when alpha power is modulated by attention, it could reflect a

contrast gain mechanism. However, to our knowledge, the relationship among attention, ongoing alpha oscillations and changes in the psychometric function has not been directly addressed so far. To establish the relationship between ongoing oscillations and visual perception in different experimental conditions is a critical matter for future research, and we argue that valuable insights may arise from combining the psychophysical approach of studies on visual attention and research on the effects of pre-stimulus oscillatory pattern.

While arising from the existing literature in the field of alpha oscillations on visual perception, the ORP model not only could be extended to other perceptual domains, but also it may encourage a fruitful discussion about the relationship between neural activity and behavior, bringing together efforts from several methodological and theoretical perspectives.

5. GENERAL DISCUSSION

A growing number of studies have shown that ongoing brain activity influences both behavioral and neurophysiological response to an incoming stimulus (Arieli, Sterkin, Grinvald, and Aertsen, 1996; Hesselmann, Kell, Eger, and Kleinschmidt, 2008; Kayser, McNair, and Kayser, 2016; Martin, Barnes, and Stevens, 2012; Schölvinck, Friston, and Rees, 2012; Weisz et al., 2014). In this field of research, a crucial role is played by the neural oscillatory activity, and the high temporal resolution of magneto/electrophysiological (M/EEG) recordings proved to be extremely valuable in the study of time-frequency patterns in the pre-stimulus time-window (Hanslmayr et al., 2007; Lange et al., 2013; Mathewson et al., 2009; Romei et al., 2008).

In our studies presented in detail in previous sections, we aimed at non-invasively investigating distinct mechanisms regarding the role of pre-stimulus alpha activity on visual perception and neurophysiological outcome. From a methodological point of view, we have shown how different approaches may be valuable to address distinct questions in the study of the effects of ongoing alpha oscillations. While MEG enabled the investigation of brain sources of ongoing oscillatory activity, the concurrent use of transcranial magnetic stimulation and EEG (TMS-EEG) approach allowed to investigate the causal involvement cortical excitability. Moreover, a modelling approach proved to be helpful in making hypotheses that may drive experimental research. Importantly, the present work highlights that a psychophysical method may be transversally applied together with several techniques to shed light on the mechanisms involved in the impact of ongoing brain activity on perception.

In **Study 1** we used MEG to investigate the effects of spontaneous fluctuations in ongoing alpha activity on visual detection and to explore the brain sources of such effects. Our results showed that both pre-stimulus alpha power and phase affected perceptual performance and neurophysiological response to near-threshold stimuli. Consistently with current literature, detected targets gave rise to a larger neurophysiological response compared to undetected ones (Busch, Dubois, and VanRullen, 2009). Moreover, we observed stronger alpha power preceding misses compared to hits, although the effect did not reach statistical significance at sensor level when correcting for multiple comparisons, possibly due to characteristics of the detection task. Finally, analyses in source space revealed the involvement not only of visual cortex but also of temporal and frontal areas, both in the evoked response and in the pre-stimulus activity, suggesting that even a simple task such as visual detection cannot be considered a local phenomenon restricted to sensory areas. Specifically, while the effect of pre-stimulus alpha power appeared to be located in the left visual cortex, the effect of phase involved frontal areas. Such difference in source localization of the two parameters of ongoing alpha activity is consistent with topographical activations described in EEG studies and with the hypothesis that ongoing alpha power and phase may rely on distinct mechanisms (Busch & Van Rullen, 2010; Zoefel & VanRullen, 2017).

In **Study 2**, we focused on the modulation ongoing alpha activity, by means of a sensory deprivation paradigm. Our findings showed that ongoing alpha activity can be effectively modulated by short-lasting dark adaptation (DA): as expected, we observed lower levels of pre-stimulus alpha power after DA compared to light adaptation. Moreover, we described how modulated-alpha power was associated to changes in phosphene perception as well as TMS-evoked potentials (TEPs). Importantly, Study 2 highlighted the importance of applying a psychophysical approach by using a wide range of

stimulation intensities beyond sensory threshold. Indeed, assessment of phosphene perception through the psychometric function revealed a modulation which did not involve phosphene threshold, i.e., a steeper slope after DA, suggesting an improved sensory reliability. Furthermore, this approach allowed to unveil an interaction between stimulation intensity and the effects of experimental manipulation on TEPs, as well as the relationship between TMS intensity and TEP amplitude.

Finally, in **Study 3** we exploited the psychophysical approach of the psychometric function estimation to explore distinct neural mechanisms associated with of ongoing alpha activity by describing a formal model, namely the Oscillations Response Probability (ORP) hypothesis. Based on cross-frequency alpha-gamma interactions (Spaak, de Lange, and Jensen, 2014), the ORP model suggests that fluctuations in ongoing alpha rhythm may subtend different neural mechanisms which cannot be disentangled from non-invasive recordings, specifically amplitude and synchronization in the gamma power (Musall et al., 2014). Crucially, according to the ORP model, these mechanisms lead to distinct modification of the psychometric function, i.e., a change in sensory threshold due to a shift of the function and a modification of the upper asymptote. Therefore, we suggest that selective modifications of the psychometric function may provide insights on distinct neural mechanisms, making the ORP model helpful in non-invasive studies.

Taken together, the present findings suggest that the effects of alpha activity on visual perception are subtended by a neural network involving also associative cortical regions, rather than being a local phenomenon restricted to sensory areas. This aspect clearly emerged from Study 1, which showed the involvement of different brain sources both in the prestimulus activity and in the evoked response. Moreover, also the modulation TEPs

in Study 2 is consistent with this interpretation. Indeed, alpha power modulation by DA was associated with a change in a relatively later component (i.e., P60), which is more likely to emerge from information exchange with other regions, rather than reflecting the excitability of visual cortex. Finally, also Study 3 is consistent with this view: while gamma power was clearly modelled within the sensory areas, we did not make specific predictions on the origin of alpha activity.

Findings from Study 1, especially the different brain sources for alpha power and phase, may suggest distinct mechanisms for alpha power and phase, whereas in Study 3 the two parameters are integrated. We argue that the two interpretations are not mutually exclusive. Indeed, in Study 1 the experimental paradigm we used was not optimal to investigate a possible local effect of alpha phase in the visual cortex. The presentation of visual stimuli in the right hemifield only was likely to induce lower alpha power in sensory regions involved in stimulus processing. During low alpha power, not only an effect of phase may technically be hard to detect, but also it may not be physiologically relevant (Schalk, 2015). Therefore, from Study 1 we could not exclude that the phase of alpha oscillations may also be relevant in posterior sensory regions, as defined in Study 3 and consistently with recent frameworks (Schalk, 2015).

Crucially, the use of near-threshold stimuli in Study 1 prevented to investigate whether alpha power and phase have a distinct effect on performance and therefore whether the mechanisms they subtend are independent. Indeed, although alpha power and phase appear to be generated in different brain regions, they could be integrated in a single functional mechanism. To this respect, we argue that a psychophysical approach could be extremely powerful in providing further information on the effects of ongoing oscillations and in disentangling the contribution of distinct mechanisms, as shown by Study 2 and 3.

Indeed, the psychophysical approach in Study 2 not only enabled the assessment of a modulation of perceptual performance also in the absence of a change in phosphene threshold, but importantly it allowed to detect the modulation of DA on TEPs, which was detected in response to high TMS intensities only. Finally, Study 3 highlighted that selective modulations of the psychometric function may suggest the involvement of distinct neural mechanisms associated with ongoing alpha activity.

To conclude, our findings have shown that ongoing alpha activity plays a crucial role in determining perceptual and neurophysiological response to an external stimulus, both when ongoing oscillatory activity fluctuates spontaneously and when it is experimentally modulated. Importantly, our results support the idea that alpha rhythm may not be considered a unitary phenomenon, but that distinct processes may explain the effects of pre-stimulus alpha power and phase, as well as the distinct neural mechanisms may be associated with alpha power. In future studies, a psychophysical approach to the study of ongoing oscillations may provide further insights on this issue.

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