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Research Report

Theta EEG oscillatory activity and auditory change detection

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ABSTRACT

The mismatch negativity is an electrophysiological marker of auditory change detection in the event-related brain potential and has been proposed to reflect an automatic comparison process between an incoming stimulus and the representation of prior items in a sequence. There is evidence for two main functional subcomponents comprising the MMN, generated by temporal and frontal brain areas, respectively. Using data obtained in an MMN paradigm, we performed time–frequency analysis to reveal the changes in oscillatory neural activity in the theta band. The results suggest that the frontal component of the MMN is brought about by an increase in theta power for the deviant trials and, possibly, by an additional contribution of theta phase alignment. By contrast, the temporal component of the MMN, best seen in recordings from mastoid electrodes, is generated by phase resetting of theta rhythm with no concomitant power modulation. Thus, frontal and temporal MMN components do not only differ with regard to their functional significance but also appear to be generated by distinct neurophysiological mechanisms.

1. Introduction

Delineating the neural basis of cognitive processes for a deeper understanding of the role of the brain's oscillatory activity is important. Indeed, several experimental results have pointed to a key role of neural oscillations. These include intracerebral electroencephalographical (iEEG) studies of the hippocampus in the rat (O'Keefe and Recce, 1993; Huxter et al., 2003) and cortical structures in monkeys (Fries et al., 2001) and humans (Rizzuto et al., 2003; Siapas et al., 2005; Shah et al., 2004). In normal human participants, non-invasive scalp EEG and MEG (magnetoencephalography) (e.g., Makeig et al., 2002; Düzel et al., 2005) have also been examined with regard to oscillatory activity. On the basis of such data, it has been suggested that modulations of oscillatory neural activity may underlie cognitive processes (Ward, 2003; Buzsáki and Draguhn, 2004; Buzsaki and Chrobak, 2005).

Also, a growing body of experimental evidence supports the view that EEG oscillations underlie event-related potential (ERP) generation (Sayers et al., 1974; Basar, 1999; Brandt et al., 1991; Makeig et al., 2002; Fuentemilla et al., 2006). Stimulus- or task-related brain responses interact trial-by-trial with EEG background activity in a non-stochastic manner, which leads to an ERP when individual trials are averaged (Penny et al., 2002; Kruglikov and Schiff, 2003; Makeig et al., 2004a). It has been demonstrated that these time-locked interactions manifest themselves in modulations of spectral power and/or phase-resetting of EEG rhythms (Makeig et al., 2002; David et al., 2005; Fuentemilla et al., 2006; Hanslmayr et al., 2007).

For example, test stimuli that need to be compared with other recently presented items lead to phase-resetting of theta (4–8 Hz) oscillations both, in animals (Adey and Walter, 1963; Givens, 1996) and humans (Klimesch, 1999; Rizzuto et al., 2003). Thus, these findings suggest that processing of mem-

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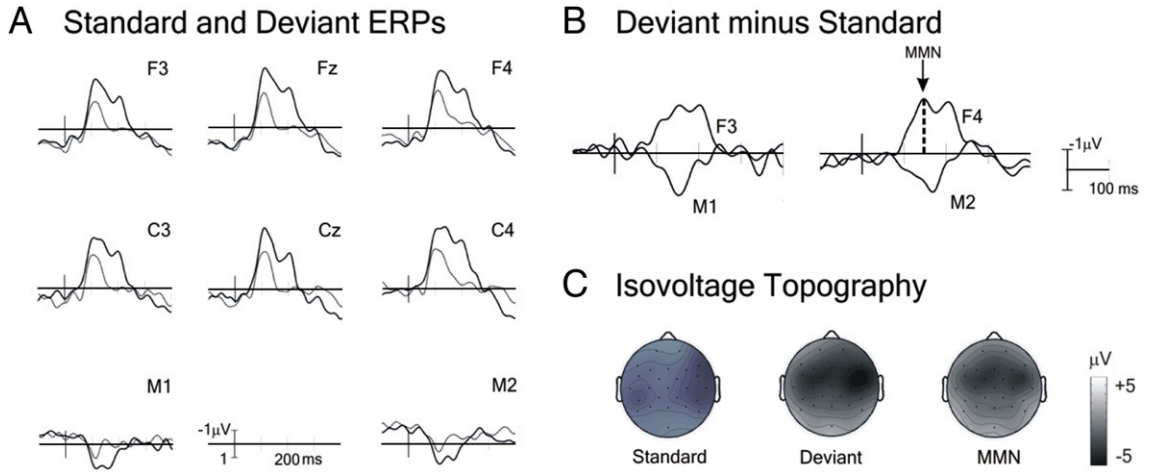

Fig. 1 – (A) Grand mean Standard (thin line) and Deviant (thick line) ERPs at fronto-central and mastoid electrodes. Note that the baseline was defined by computing the mean prestimulus activity of stimulus 1 in each series. (B) Difference wave between responses to deviant and standard stimuli at frontal and mastoid electrodes, the polarity inversion for the mastoid process clearly indicates that this difference wave represents the MMN. (C) Isovoltage topographic maps for standard and deviant stimuli and the deviant-minus-standard difference wave at 152 ms (peak latency of the MMN at F4, marked by a dotted line in (B)).

ory-related stimulus events involves a phase reset or shift of ongoing oscillations (Rizzuto et al., 2003).

In the auditory domain, one of the most basic operations is the detection of sudden changes against a background of uniform stimuli. This operation, which may occur outside the focus of attention, requires a comparison of the deviant stimulus with a template derived from the previous stimulus series, i.e. a very basic memory process. The detection of a mismatch between the incoming deviant stimulus and the template is reflected in the averaged event-related potential (ERP) by the so-called mismatch negativity (MMN; Näätänen et al., 2001). MMN has been shown to be elicited by simple (e.g. duration, pitch) mismatches but also occurs for deviations in complex repetitive sound patterns (Näätänen and Winkler, 1999; Picton et al., 2000).

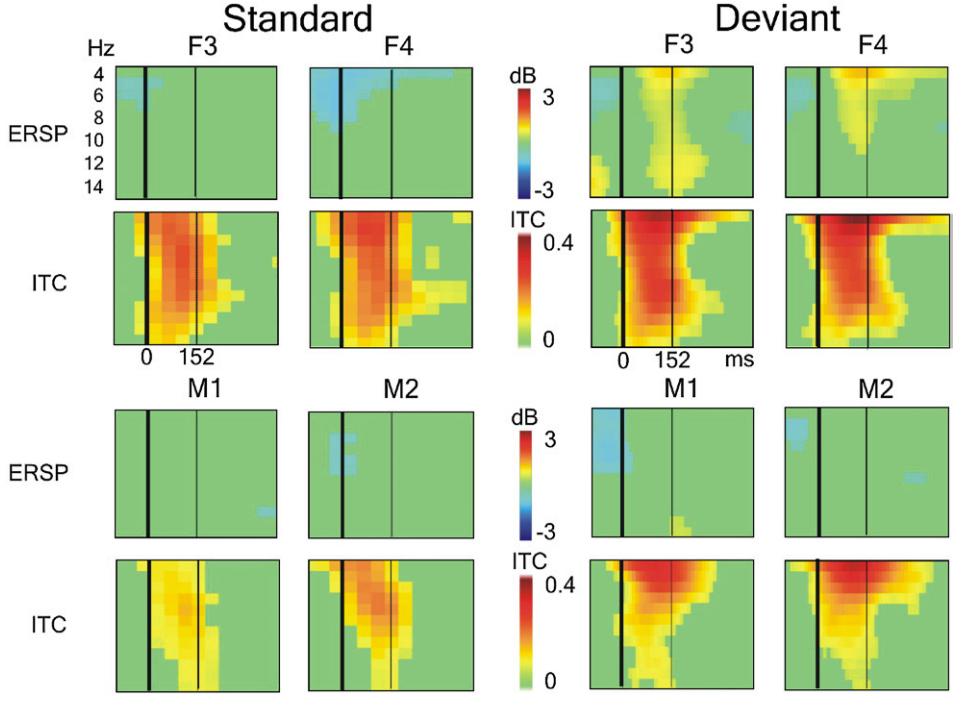

Fig. 2 – Overall time–frequency analysis at F3, F4, M1 and M2 electrodes (pooled over participants). Coloured areas correspond to significant ($P<0.01$) Inter-Trial Coherence (ITC) and Event-Related Spectral Perturbation (ERSP) modulations after bootstrap analysis using the baseline period for comparison. The thick line shows the onset of the stimuli (0 ms). The thin line indicates the peak latency (152 ms) at which standard and deviant responses are compared. This latency corresponds to the MMN amplitude maximum at the F4 electrode.

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While there is strong evidence that brain oscillations underlie the generation of ERP components (Makeig et al., 2002; Gruber et al., 2005; Fuentemilla et al., 2006), their contributions to the MMN have not been properly studied. In the present work, we therefore analyzed the oscillatory basis of the MMN by using trial-by-trial time–frequency techniques. Given the reported involvement of theta phase-resetting in memory processes, we hypothesized that the MMN is similarly brought about – at least in part – by phase-resetting of the EEG theta rhythm.

In the present work, spectral phase-resetting and power modulation were measured through the Inter-Trial Coherence (ITC) and the Event-Related Spectral Perturbation (ERSP) modulation indices, respectively (Makeig et al., 2002). ITC and ERSP measures associated to MMN were studied through the differences between responses to deviant sounds and responses to repetitive standard sounds in an auditory paradigm comprising two different stimulus classes: trains of three consecutive identical tones preceded by long silent intervals (30 s) served as standard stimuli and trains of three sounds with a duration deviant in the third position served as deviant stimuli ($P=0.5$). The long silent intertrain interval excludes the influence of the neighbouring stimuli trains. An MMN was expected for the third sound of deviant trains compared to the third sound of standard trains.

2. Results

2.1. Analysis of MMN event-related potential

An enhanced negativity to the deviant tone relative to standard tone is clearly seen in Figs. 1A and C. Thus, when subtracting averaged standard from deviant responses, a clear MMN peak appeared for all but the two excluded participants and electrodes as compared with baseline ($F(1,13)=71.13$; $P<0.001$) (Figs. 1B and C).

2.2. Overall ERSP and ITC of standard and deviant responses in single trials

Overall time–frequency analysis (analysis of all participants' pooled single trials) of responses to standards revealed an

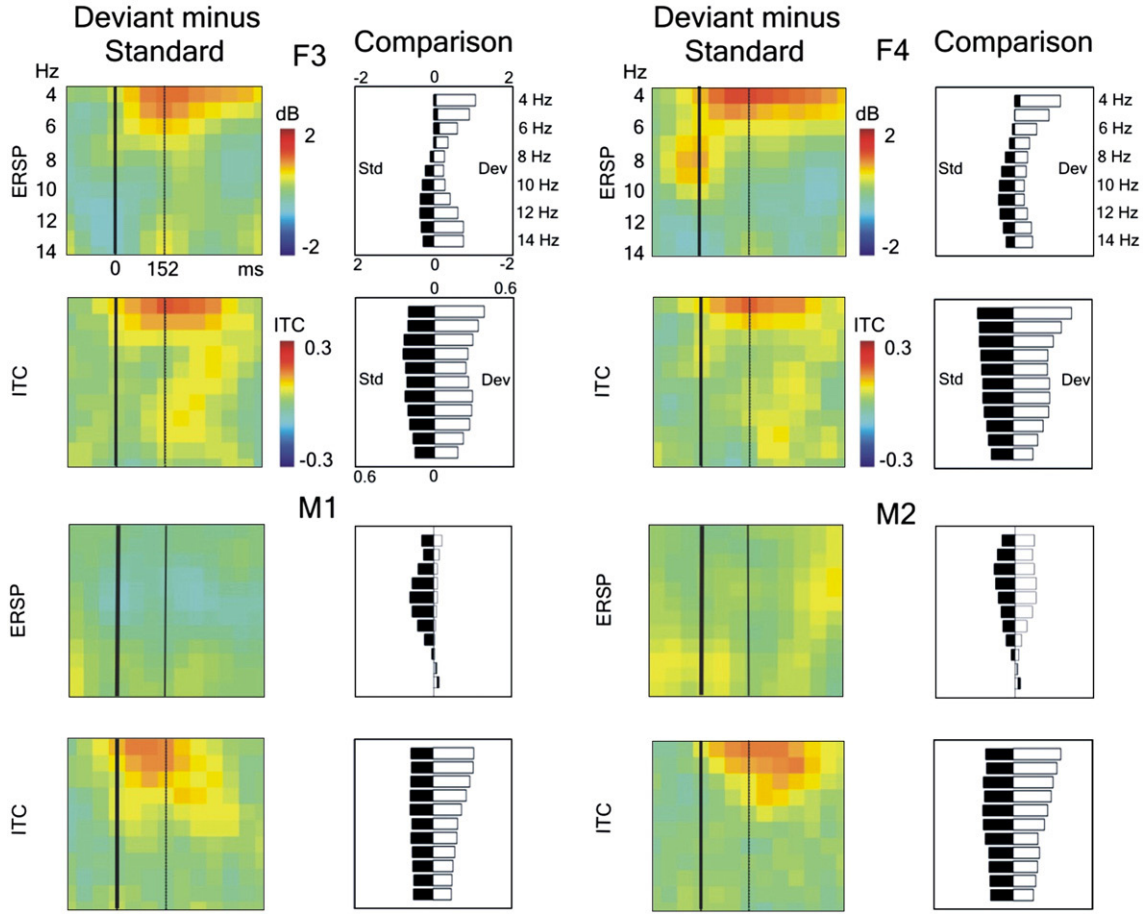

Fig. 3 – Subject-to-subject comparisons were made of those electrodes that reached significant ERSP and/or ITC values to standard or deviant responses in the overall analysis (see results and Fig. 2). *Deviant minus Standard panels* show ITC and ERSP difference between standard and deviant trials. *Comparison panels show* frequency-to-frequency comparisons between standard and deviant ERSP and ITC values at MMN latency peak (152 ms; thin line in *Deviant minus Standard panels*). Each bar corresponds to the mean single-frequency value across participants. Deviant ERSP and ITC are plotted in white bars (right side) and their corresponding index values (ERSP: −2 to 2 dB; ITC: 0 to 1) are displayed on top of the box. Standard ERSP and ITC correspond to the black bars (left side) and their indexes are displayed at the bottom of the box.

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increase of ITC of theta and alpha rhythms (3.9 to 14.6 Hz from ~50 to 220 ms, $P<0.01$) with no concomitant significant ERSP at those frequencies (Fig. 2). All the other frequencies studied showed no relevant modification in both ERSP and ITC analysis (both $P>0.05$) (see Supplementary material).

However, deviant responses gave rise to significant ERSP and ITC values. Theta and alpha ERSP changes were found in the MMN latency range in frontal ($P<0.01$) but not mastoid electrodes ($P>0.05$) (Fig. 2). A change of ITC was seen for theta and alpha frequency bands (3.9 to 14.6 Hz; $P<0.01$) for both, frontal and mastoid electrodes and thus contributed to both standard and deviant ERPs (Fig. 2).

2.3. *Subject-to-subject ERSP and ITC of MMN*

Channels exhibiting significant ITC and ERSP values were then re-analyzed to evaluate the contribution of individual participants. Fig. 3 shows mean ERSP and ITC differences across participants between responses to standard and deviant stimuli.

Fig. 3 also shows standard and deviant mean ERSP and ITC values for specific theta and alpha frequencies at 152 ms from stimuli onset (MMN peak). At F3, deviant responses showed significantly greater ERSP and ITC than to standard ones at theta band (ERSP: $t(13)=2.57$, $P<0.05$; ITC: $t(13)=3.58$, $P<0.05$). Similar results were found at theta band at F4 for ITC values ($t(13)=4.62$, $P<0.05$) while ERSP did not reach significant differences ($t(13)=1.80$, $P>0.05$). There was no significant theta band spectral power modulation in the responses to deviants compared to responses to standards at both M1 ($t(13)=1.60$, $P>0.05$) and M2 ($t(13)=0.10$, $P>0.05$). All theta band comparisons were Bonferroni corrected. Although in the previous overall time–frequency analysis a weak alpha band ERSP increase in the deviant response had been found (Fig. 2), this was not confirmed when S3 and deviant responses were compared in the between-subject analysis (all $P>0.05$) (Fig. 3B).

The additional analysis employing complex Morlet wavelets confirmed these results: a significantly greater theta (mean 4.5, 5.9 Hz) spectral power was found for deviant compared to standard responses at the F4 electrode ($P<0.05$). A similar, albeit non-significant, effect was seen at F3 ($P<0.075$). Also, an increased theta phase alignment was observed at F4 and F3 electrodes (both $P<0.05$). Comparisons at the M1 and M2 electrodes showed greater theta phase alignment for deviant than standard responses (both $P<0.05$), without concurrent spectral power modulation ($P>0.05$, both electrodes). No differences in spectral power or phase alignment were seen for the alpha-frequency band (7.5–11.9 Hz) in any of the electrodes analyzed.

To illustrate the scalp topography of ERSP and ITC at theta frequency range (3.9, 4.9 and 5.8 Hz) and the number of participants with significant ($P<0.01$) effects at the MMN peak latency is illustrated in Fig. 4. Again, ERSP theta frequency enhancement to deviant responses was observable for fronto-central electrodes but not in the rest of scalp locations, whereas significant ITC appeared at both fronto-central and mastoid locations. Moreover, ERSP and ITC scalp topographies were highly similar to the isovoltage maps of the MMN (see Figs. 1C and 4).

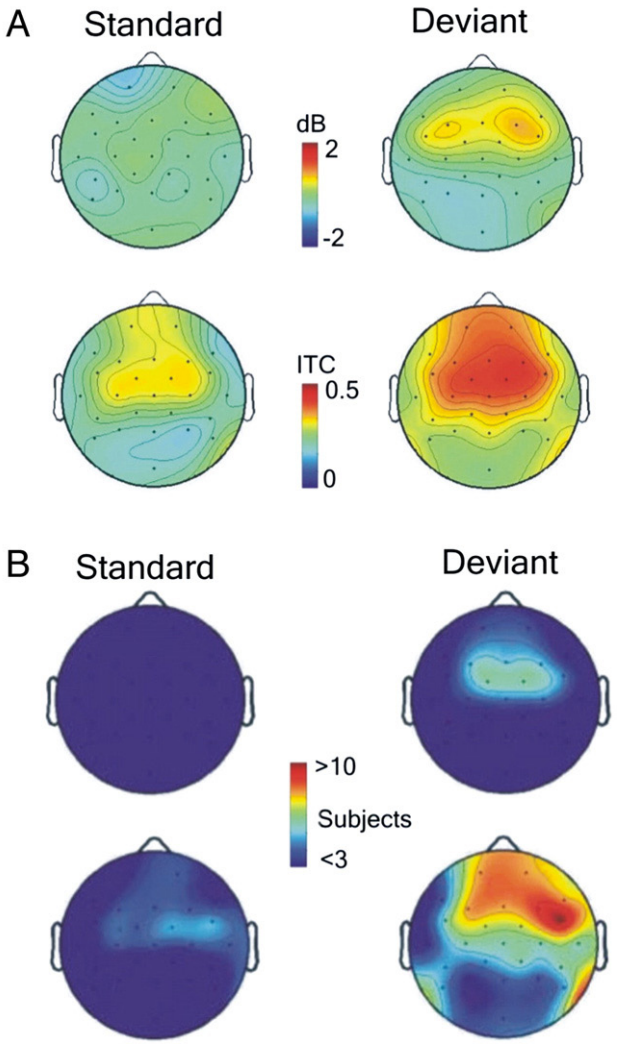

Fig. 4 – (A) Mean spectral power (ERSP) (top) and Inter-Trial Coherence (ITC) (bottom) across subjects to all electrodes at MMN latency peak for the standard and deviant stimuli responses. (B) Scalp plots corresponding to mean percentage of participants with significant ($P<0.01$) ERSP (top) and ITC (bottom), when compared with baseline, at theta frequency range at MMN latency peak after standard and deviant sound.

2.4. *Theta EEG oscillatory activity and MMN magnitude*

To study the relationship between theta oscillations and the MMN response in the ERP, linear regression analysis (R^2) between theta frequency band (mean 3.9, 4.9 and 5.8 Hz) ERSP and ITC at the peak latency of the MMN and MMN amplitude (μV) was performed for F4 and M2. Specifically, individual participants' MMN amplitude was plotted against the difference between deviant and standard ERSP and ITC.

MMN amplitude at F4 showed a linear relationship (see Fig. 5 ERSP ($F(1,13)=7.42$, $R^2=0.37$, $P<0.05$) and ITC ($F(1,13)=5.11$, $R^2=0.29$, $P<0.05$). For the M2 electrode a significant correlation was found only for ITC ($F(1,13)=16.61$, $R^2=0.51$ $P<0.05$) but not ERSP ($F(1,13)=0.26$, $R^2=0.01$, $P>0.5$). Similar analyses for the alpha frequency range (mean 7.8, 8.8, 9.7, 10.7 and 11.7 Hz, not shown in Fig. 5) revealed no effects for F4 (ERSP: $F(1,13)=3.35$, $R^2=0.21$,

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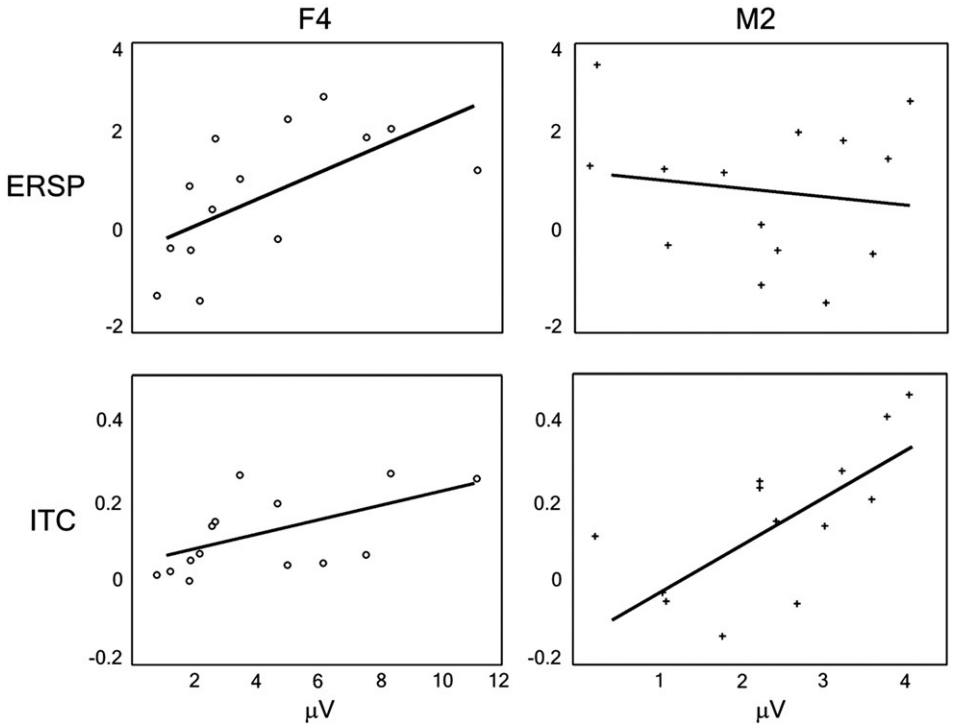

Fig. 5 – Regression (R^2) linear fit between MMN amplitude and theta band increases in ERSP and ITC associated to MMN. Each ERSP (in dB) and ITC theta band modulation resulted from computing ERSP and ITC differences between standard and deviant condition at 152 ms from the stimuli onset (MMN peak). Both ERSP and ITC contributions in the deviant condition show a linear increase in relation with MMN amplitude response at F4. However, M2 results show that, while MMN amplitude increases as ITC does, ERSP values remain unaffected. Note that MMN amplitude values in F4 were inverted in this analysis in order to bring out more clearly the ERSP and ITC effect on MMN parameters.

$P>0.05$; ITC: $F(1,13)=0.11$, $R^2=0.01$, $P>0.05$) and M2 (ERSP: $F(1,13)=0.13$, $R^2=0.01$, $P>0.05$; ITC: $F(1,13)=0.11$, $R^2=0.01$, $P>0.05$).

3. Discussion

The present investigation suggests that the MMN component of the ERP is driven by changes in phase alignment of theta oscillations and, in addition, by changes in the power of the signal. Moreover, our data demonstrate that these two mechanisms, phase alignment (as reflected by ITC) and power modulation (as reflected by ERSP), affect the different components (i.e. temporal and frontal) of the MMN to a different extent. In the following, we will explore the relationship between the oscillatory changes demonstrated in the present investigation and the different portions of the MMN component of the ERP. The MMN is measured on the scalp in the range of 120 to 300 ms post-stimulus with its onset latency depending on stimulus parameters. It is frontally negative with declining amplitudes towards posterior sites and sometimes accompanied by a positive deflection at the mastoid electrodes. EEG and MEG studies have localized the main MMN sources in the supratemporal cortex about 1 cm anterior of the generator of the N1 component (Alho, 1995; Hari et al., 1984). Combined EEG/fMRI studies have shown in addition that activity from the inferior frontal cortex can also contribute to the MMN (Doeller et al., 2003; Rinne et al., 2005). This is in line with intracranial recordings (in presurgical patients) which have found MMN generators in secondary auditory areas (Halgren et al., 1995), in the auditory association cortex (Kropotov et al., 2000), and in the inferior frontal cortex (Rosburg et al., 2005; Marco-Pallarés et al., 2005). Thus, while one has to bear in mind that the exact location of the MMN generator may vary depending on stimulus features and on stimulus complexity (Alho, 1995; Molholm et al., 2005), the involvement of supratemporal (STG) and inferior frontal generators has been shown by a number of approaches. With regard to the temporal generators, it is important to note, that a generator in this location will result in a polarity inversion between electrodes located above and below the Sylvian fissure. It has been argued that the inverted-polarity MMN recorded at mastoid scalp electrodes reflects activity from the STG, while the MMN obtained at fronto-central electrodes picks up activity from frontal sources in addition (Giard et al., 1990; Alho, 1995; Jääskeläinen et al., 1996). The notion of a "temporal" and "frontal" MMN component (Näätänen and Michie, 1979; Näätänen, 1992; Muller et al., 2002; Doeller et al., 2003) is also important for the current investigation.

An enhanced theta ITC but no ERSP changes found at the mastoid electrodes (see Figs. 1 and 3) suggest that the temporal component of the MMN is driven by theta phase realignment (ITC increase) without concurrent spectral power modulation (no ERSP change) in the supratemporal area. The relevance of phase concentration in the generation of the temporal component of the MMN was corroborated further by the significant linear relation between MMN amplitude and ITC (but not ERSP) at the mastoid electrodes (see Fig. 5).

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Interestingly, recent modeling work (David et al., 2005) has shown that oscillatory phase resetting might appear without a concurrent change in power. Specifically, David et al. (2005) showed that for high activity levels, ongoing and stimulus-dependent portions of the signal interact in such a way as to produce phase resetting and result in a typical ERP waveform in the average. Conversely, no interaction between stimulus-related and ongoing activity is seen at low activity levels. In such a case, the ERP can be linearly separated from the ongoing dynamics of the signal and thus a power change can be observed. Thus, the activity levels in the neural networks generating the evoked response appear to be critical. In our study critical stimuli (deviant or standard) were preceded by two standard stimuli (see Stimuli and procedure), which could generate transient responses resulting in a change in the activity level of the temporal generator. This could modify the response of the temporal generator to repeated and deviant stimuli, resulting in a phase resetting in the latter.

In contrast to the mastoid electrodes, fronto-central electrodes showed changes of theta ERSP and ITC in the MMN interval. The increase of spectral power during the MMN interval for deviant stimuli proves that evoked activity underlies the appearance of the frontal component of the MMN. The increased ITC in fronto-central sites might have been due to enhanced transient EEG synchrony and/or the enhanced ERSP (Yeung et al., 2004; Fuentemilla et al., 2006).

It has been suggested (Näätänen, 1992) that the frontal MMN component is related to an involuntary switch of attention to a stimulus change occurring outside the focus of attention. The frontal transient evoked oscillatory theta component could represent a top–down mechanism acting upon sound feature analysis taking place in the frontal and/or temporal cortex. Interestingly, theta evoked oscillatory components related to attentional mechanisms have been observed in visual (Makeig et al., 2004b) and auditory (Yardonova and Kolev, 1998) experiments.

3.1. *Disentangling "temporal" and "frontal" components of the MMN*

Automatic sound change detection as evidenced by the MMN requires the encoding of the physical and abstract features of sound stream regularity, the comparison of newly encoded information with these representations and, possibly, attentional reorientation (Näätänen et al., 2001). Of these processes, encoding and comparison of sensory features have been proposed to be reflected by the temporal component of the MMN, whereas attentional aspects of sound change detection are thought to be supported by the frontal component (Näätänen, 1992; Rinne et al., 2000; Doeller et al., 2003).

Such a view is supported by several functional and clinical results: the temporal component has an earlier onset than the frontal one (Rinne et al., 2000; Marco-Pallarés et al., 2005), they are modulated differentially as a function of the number of repetitions of standard stimuli (Sato et al., 2000; Haenschel et al., 2005) and show differences in their modulation by attention (Alho et al., 1992; Kathman et al., 1999; Escera et al., 1998; Yucel et al., 2005). The two components also react differently to contextual (Sussman and Winkler, 2001) and dichotic (Deouell et al., 1998) changes in auditory stimulation. Alcohol attenuates mainly the frontal but not the temporal subcomponent (Jääskeläinen et al., 1996). It has also been proposed that the frontal component is attenuated in schizophrenia, whereas the temporal component is of normal magnitude (Baldeweg et al., 2002), but this finding has not been unequivocal (Kreitschmann-Andermahr et al., 1999; Pekkonen et al., 2002). In addition to these multiple findings suggesting a functional differentiation of the two components, the present data suggest that the neurophysiological mechanisms underlying the two components of the MMN are different as well.

To strengthen the link between the neurophysiological and functional levels, future studies should assess the sensitivity of temporal and frontal ITC and ERSP changes to the different experimental manipulations that are known to affect MMN amplitude such as attention, magnitude of change, deviant feature (loudness, duration, pitch, deviants in complex and hyper-complex sequences), inter-stimulus interval, and psychopathology (Picton et al., 2000). Performing such studies is important to show the generality of our findings.

Such studies may also shed light on the general role of phase-resetting in information processing by the brain, which is still not clear (Buzsáki and Draguhn, 2004) in spite of several proposals.

One proposal argues that theta phase-resetting defines excitability windows of phase-locked neurons, which could be used for directing information flow and maintaining activity within neuronal networks (Siapas et al., 2005). In a similar manner, Klimesch et al. (2006) suggested (a) that phase resetting might control the timing of the activation of task-relevant brain areas and (b) that theta oscillations might reflect the excitatory state of task-related brain areas at the time of processing. Extending this reasoning to the present findings, theta phase resetting at mastoid electrodes could reflect the temporal window in which sensory representations and incoming deviant sounds are compared.

Another important role of oscillatory phase synchrony has been seen in the communication between functionally connected neural structures (e.g., Varela et al., 2001). For example, Siapas et al. (2005) recently showed that theta rhythms in the prefrontal lobe synchronize with theta activity in the hippocampus during a memory task. It might well be that the temporal and frontal generators of the subcomponents of the MMN are functionally connected by phase locking of the theta rhythm as well.

Finally, time–frequency analyses along the lines of the present study may help to clarify the involvement of theta oscillatory activity in mental disorders such as schizophrenia, in which MMN has been proposed as a biological marker of duration and severity (Umbricht and Krljes, 2005) and in which impaired neural oscillatory synchrony has been described (Spencer et al., 2004).

4. Experimental procedures

4.1. *Participants*

After receiving a complete description of the study, 16 right-handed healthy participants (7 women, mean age 25.4 years, range 20–28) gave their written consent to take part in the study. None of the participants had a history of head injury, neurological disease, hearing problems, severe medical illness or drug abuse. The experiment was approved by the Ethics Committee of the University of Barcelona.

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4.2. Stimuli and procedure

Pure sinusoidal tones were delivered binaurally through headphones by the Stim Interface System (Neuroscan Inc.). Stimuli (90 dB SPL) consisted of trains of three pure sine-wave tones (1000 Hz, 10 ms rise/fall times). The first two tones (S1 and S2) were of 75 ms in duration (standard tones) while the third tone (S3) was either a standard ($N=100$) or a deviant (25 ms in duration) ($N=100$) (Fuentemilla et al., 2006; Grau et al., 2007). The order of standard and deviant trains was random, intra-train interval (SOA) was 584 ms, and inter-train interval was 30 s.

Participants sat in a comfortable chair in a dimly lit and electrically and acoustically shielded booth. During the EEG recording, each subject was instructed to perform an irrelevant visual task (reading), to ignore the auditory stimuli and to avoid extra eye movements and blinking.

4.3. EEG recording

EEG activity (0.01–70 Hz bandpass; 50 Hz notch filtered) was recorded by a 32-channel amplifier (Synamps, Neuroscan, Inc.) at a sampling rate of 500 Hz. EEG electrodes were placed following the enhanced 10–20 position system (Fp1/2, F3/4, C3/4, P3/4, F7/8, T3/4, T5/6, Fz, Cz, Pz, Oz, FC1/2, FT3/4, M1/2, IM1/2, TP3/4, CP/2) and were all referenced to the tip of the nose. Impedances were maintained below 5 kΩ. Ocular movements (EOG) were recorded from two electrodes at the outer canthus of each eye. A single ground electrode was attached at AFz.

4.4. Analysis of ERPs (Standard, Deviant and MMN responses)

ERPs were obtained off-line by averaging 3000 ms EEG epochs starting 1000 ms prior to S1 separately for standard and deviant sound conditions. EEG epochs were excluded automatically if amplitudes exceeded ±100 μV in EEG and/or EOG. A total of 942 trials was selected in the standard condition (67.2±13.2 per subject (mean±SD)) and 905 in the deviant condition (64.6±14.8). For MMN wave analysis epochs of 500 ms, a 100-ms prestimulus baseline containing responses to standard (S3) or deviant sounds was selected. A low cut-off of 25 Hz digital off-line band-pass filter was applied to the ERPs.

The amplitude and latency of MMN were measured on the difference wave obtained by subtracting the ERPs to the standard tones from those to the deviant tones (Näätänen, 1992). As MMN shows a maximum amplitude at frontal electrodes and inverted polarity at mastoids (Alho et al., 1998), F3, F4, M1 and M2 were analysed. Two participants were excluded from further analysis because they did not show a clear MMN component at frontal and mastoid electrodes.

A repeated-measures ANOVA was used to test significant differences in MMN amplitude and latency across electrodes. The degrees of freedom were corrected with the Greenhouse–Geisser factor when needed.

4.5. Event-Related Spectral Perturbations (ERSP) and Inter-Trial Coherence (ITC)

Event-Related Spectral Perturbations (ERSPs) and Inter-Trial Coherence (ITC) were computed by using EEGLAB v4.5 (Delorme and Makeig, 2004) under Matlab 7 (The Mathworks, Inc.).

Trial-by-trial time–frequency analysis was computed by a sinusoidal moving Hanning-windowed wavelet with linearly increased cycles (Delorme and Makeig, 2004), from 2 cycles for the lowest frequency (3.9 Hz) to 13 cycles for the highest frequency (48.8 Hz) analysed.

Changes in event-related spectral power response (in dB) were computed by the Event-Related Spectral Perturbation (ERSP) index (Makeig, 1993) (1),

$$\mathrm{ERSP}(f,t) = \frac{1}{n}\sum_{k=1}^{n}\left(F_k(f,t)\right)^2 \quad (1)$$

where, for n trials, $F_k(f,t)$ is the spectral estimate of trial k at frequency f and time t. Significant changes in ERSP are reflected by mean time–frequency power values that exceed the significant cut-off threshold extracted from the −1000 ms baseline period prior to the first tone of a triplet (S1). To determine the threshold significance of both ERSP and ITC, bootstrap distributions ($P<0.01$), extracted randomly from baseline data (−1000 ms previous S1) and applied 200 times, were used (Makeig et al., 2002).

Event-locked EEG phase coherence was computed by the Inter-Trial Coherence index (ITC) (2), analogous to the "phase-resetting index" (Tallon-Baudry et al., 1996),

$$\mathrm{ITC}(f,t) = \frac{1}{n}\left|\sum_{k=1}^{n}\frac{F_k(f,t)}{|F_k(f,t)|}\right| \quad (2)$$

where $\|$ represents the complex norm. ITC values range from 0 to 1, with values near 1 implying almost perfect phase coincidence across trials. To determine the threshold significance of both ERSP and ITC, bootstrap distributions ($P<0.01$), extracted randomly from baseline data (−1000 ms previous S1) and applied 200 times, were used (Makeig et al., 2002).

4.6. Overall ERSP and ITC analysis to standard and deviant sound responses

Time–frequency analysis including all participants' pooled trials under standard and deviant stimuli conditions was performed at F3, F4, M1 and M2 electrodes. Each condition was computed separately and included 1000 ms before S1 as a baseline period, from which random ERSP and ITC distributions were extracted for bootstrap analysis.

4.7. Subject level ERSP and ITC analysis of MMN

To account for the possibility that the above-mentioned ERSP and ITC analyses have been influenced by the averaging process across participants, time–frequency analysis was also computed separately for each subject in the standard and deviant sound condition and all 30 electrodes. Time–frequency analysis was performed similar to the one described previously.

To study the neural changes associated with the tone–deviance detection system reflected by MMN (Näätänen, 1992), frequency bands ERSP and ITC comparison between standard (S3) and deviant responses was performed at MMN latency peak for those electrodes showing a significant ERSP or ITC at MMN latency in the previous analysis (all participants' pooled trials). MMN peak latency was defined by the maximum MMN wave

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amplitude of the difference value at the F4 electrode (152 ms). A paired *t*-test between standard and deviant stimuli responses was computed in the centre of the wavelet window at each frequency band, that is for theta (mean 3.9 and 5.9 Hz) and alpha (mean 7.8, 9.7, 11.7, 13.6 Hz) bands. *T*-values with $P<0.05$ (two-tailed) were accepted as showing differences between conditions.

In addition, and to exclude possible frequency resolution-dependent effects due to the sinusoidal moving Hanning-windowed wavelet used, a complex Morlet wavelet (minimum of 5 cycles to all frequencies studied) was applied in each subject to single-trial standard and deviant responses to those electrodes that yielded significant results in the overall ERSP and ITC analysis. The complex Morlet wavelet was defined as (3):

$$w(f,t) = \left(2\pi\sigma_t^2\right)^{-1/2} e^{\frac{-t^2}{2\sigma_t^2}} e^{2i\pi f_0 t} \quad (3)$$

where the relation f_0/σ_f (where $\sigma_f = 1/(2\pi\sigma_t)$) was set at 7 (Tallon-Baudry et al., 1997). The time–frequency representation of the signal $s(t)$, at trial k, frequency f and time t is computed as (4):

$$F_k(f,t) = w(t,f) \times s_k(t) \quad (4)$$

where × indicates complex convolution. The corresponding Event-Related Spectral Perturbation and Inter-Trial Coherence are computed using (1) and (2), respectively (Tallon-Baudry et al., 1997). A *t*-test was computed between standard and deviant responses at MMN latency with $P<0.05$ (two-tailed) set as the limit for accepting differences as significant.

To study further the influence of increases in ERSP and ITC on MMN amplitude, a linear regression analysis (R^2) between those frequency bands that presented subject-by-subject significant ERSP or ITC differences between standard and deviant conditions and individual MMN amplitude value (μV) was performed. Significant ($P<0.05$) R^2 indicated that the amplitude of MMN was modulated by the studied parameters (ERSP and/or ITC) at certain frequency ranges.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.brainres.2007.07.079.

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