Temporo-frontal phase synchronization supports hierarchical network for mismatch negativity

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HIGHLIGHTS

- High-density EEG and independent component (IC) analysis reveal brain-regional network associated with auditory change detection.
- Theta, alpha, and gamma band oscillations are associated with the mismatch negativity to deviant stimuli.
- Synchronization between ICs (brain sources) in several frequency bands establishes a dynamic functional network mediating the mismatch negativity.

ABSTRACT

Objective: We performed an experiment designed to reveal the brain-regional network dynamics underlying both automatic and intentional auditory change detection as typically indexed by the mismatch negativity (MMN) event-related potential (ERP).
Methods: High-density EEG was recorded while participants heard a stream of standard pure tones, into which occasional (14%) frequency deviants were inserted. In a first run they listened passively while watching a closed-captioned movie, whereas in a second run they pressed a button each time they detected a deviant while watching the movie with neither sound nor captioning.
Results: Independent component analysis revealed independent components that we localized to temporal and frontal regional brain sources relevant to the generation of the MMN. Relative power in various oscillatory frequency bands, computed from a wavelet analysis on the time series of these independent components, was modulated by task demands and stimulus type, as was dynamic phase-locking between pairs of the independent components in those same frequency bands.
Conclusion: These results support a hierarchical model of MMN generation that emphasizes information processing and transfer between temporal and frontal brain regions.
Significance: In addition to enhancing the use of the MMN to evaluate some aspects of central auditory functioning, these results could be important for the evaluation of alterations in other cognitive functions or in consciousness.

1. Introduction

Automatic change detection is a fundamental capacity of the auditory nervous system. The human brain's involuntary response to rare and unexpected changes to an ongoing acoustic regularity is a negative going potential recorded on the scalp surface shortly after changes occur, roughly 120–250 ms post-stimulus onset (Näätänen et al., 1978). This response, the Mismatch Negativity (MMN), has been studied extensively using EEG/MEG technologies and appears to be sensitive to both the physical and abstract changes occurring within a stream of regular acoustic input (Dehaene-Lambertz, 1997; Näätänen et al., 1997, 2007; van Zuijen et al., 2006; Vuust et al., 2005). Intertwined with the brain's ability

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to detect changes automatically is its capacity to conceptualize aspects of the auditory environment that occur regularly and with high frequency. Therefore the presence of the MMN response to deviant probes provides a measure of the kinds of patterns or stimulus groupings, both learned and innate (Bregman, 1990), a particular auditory system is capable of forming (Garagnani and Pulvermüller, 2011; Ritter et al., 2006). The MMN can be evoked independent of task or attention (Atienza et al., 2002; Daltrozzo et al., 2007; Sussman et al., 2003) to any discernable change in a series of regularly repeating events with a wide variety of stimuli (Näätänen et al., 2007).

Several models have been proposed to explain aspects of the brain's ability to automatically detect environmental changes. The most parsimonious of these is probably the *predictive coding* model (Garrido et al., 2007a,b, 2008, 2009a,b). The proposed mechanism involves changes in the synaptic connections within the auditory cortex in response to the current stimulus, as well as changes in extrinsic connections linking frontal executive areas to the auditory cortices to allow adjustments to the inferences drawn. The model describes efficient sensory processing accomplished by both feed forward and feedback connections, enabling immediate error correction through dynamic matching of anticipatory intrinsic activity with activity generated by the physical input, in a combined top-down/bottom-up fashion (Engel et al., 2001). Simulations of the predictive coding model of the MMN in terms of inhibitory and excitatory interactions of dipole source activity over time (direct causal modeling) found the best fitting brain network to be a 3-level hierarchy consisting of both primary auditory cortices, bilateral superior temporal gyri, and the right inferior frontal gyrus (Garrido et al., 2008). Importantly, although broadband effective connectivity has been thus established between these brain areas, the specific oscillatory frequency bands within which this connectivity occurs, and its precise timing, are unknown (see Boly et al., 2011). One of our goals in the present work is to address this lacuna.

Synchronous neural oscillations have been associated with a number of integrative auditory functions such as the binding of pitch, timbre, and harmony features (Bhattacharya et al., 2001), representing objects (Kaiser et al., 2002), matching acoustic cues to representations in long term memory (Lenz et al., 2007) and also with the operation of selective attention in the auditory cortex (Debener et al., 2003; Tiitinen et al., 1993). Because in many studies modulation of gamma-band (>30 Hz) spectral power in particular has been associated with active processing (e.g., Fries, 2005; Varela et al., 2001; Ward, 2003), there have been some attempts to link such modulations to the MMN. These attempts have been mostly unsuccessful. For example, increased gamma-band (>30 Hz) power is correlated with selective attention but not with changes in stimulus features (Tiitinen et al., 1997). Passive auditory change detection and auditory working memory tasks stimulated gamma-band power increases at MEG sensors over anterior temporal/inferior frontal areas during auditory pattern processing (Kaiser et al., 2002) and over posterior temporo-parietal cortex during auditory spatial processing (Leiberg et al., 2006), but it seems the gamma-band activity (GBA) reflected post-change-detection processing of changed stimulus features and not the change detection process itself. GBA was enhanced relative to standards only for attended targets in a novelty-oddball task, implicating a role for attention but not change detection (Debener et al., 2003). Similarly, GBA has been associated with top-down processing during a counting task of random silences in a rhythmic auditory sequence (Gurtubay et al., 2006).

Other studies have been more positive, however. For example, increased gamma-band coherence was found between EEG sensors over the frontal and temporal regions when what was spoken coincided with what was expected to be heard (no pitch shift), whereas

decreased coherence occurred for pitch shifted voices (Ford et al., 2005). Thus, gamma-band coherence might index interactions between frontal and temporal cortex that are involved in binding expectation with experience. Moreover, the generation of the MMN is thought to depend in part on intracortical inhibition, reflecting GABAergic inhibition of local GABAergic interneurons in the auditory cortex (Javitt, 2000). GABAergic neurotransmission, in particular the excitation/inhibition balance modulated thereby, also has been suggested to be a major determinant of the frequency, power and synchrony of gamma oscillations both within and between brain regions (Muthukumaraswamya et al., 2009; Whittington and Traub, 2003). Thus, there is reason to suspect that the MMN will be associated with changes in gamma-band power or functional connectivity.

There is also evidence that theta oscillations are associated with the auditory MMN. One EEG study found that both theta oscillatory power and intertrial phase coherence at frontal electrodes was greater for deviant tones, whereas at mastoid electrodes only intertrial phase coherence was larger for deviants (Fuentemilla et al., 2008). Similarly, in an MEG study frontal sensors showed increased intertrial phase coherence in the theta band, whereas temporal sensors showed both increases in theta power and intertrial phase coherence, in response to deviants (Hsiao et al., 2009). And in a third study, also EEG, theta power and intertrial phase coherence were larger for deviants at fronto-central electrodes around 250 ms after the stimulus in an oddball task, but not in a control task where the probabilities of the two stimuli were equal (Ko et al., 2012). These studies indicate that theta-band power is closely associated with the auditory MMN. Interestingly theta-band power and phase coherence is also associated with the visual MMN at occipital electrodes (Stothart and Kazanina, 2013).

Unfortunately, there is considerable ambiguity regarding the neural origins of spectral power, coherence or synchronization measured at or between EEG electrodes, because of volume conduction mixing of proximal and distal EEG source signals. Further studies are therefore required to examine the power changes and oscillatory interactions taking place at the level of the neural sources of the MMN. One objective for the present study is to measure neural synchronization between temporal and frontal brain *sources* (not sensors) and thereby more completely describe the functional network underlying the MMN. We used Independent Component Analysis (ICA) to render EEG scalp data into a format where separate electrical activities could be identified and evaluated based on their time locked activity (event-related potentials, ERPs), spectra, scalp maps, and dipole locations, thereby characterizing the unique contributions of the temporal and frontal regions, and their interactions, to the MMN. One advantage of the ICA approach is that it does not limit the neural source analysis to just prespecified parts of the brain so that other anatomically and physiologically distinct regions can also be evaluated (Viola et al., 2009).

In a related study, EEG difference-wave data from an oddball task were decomposed into six independent components (ICs) that accounted for more than 67% of difference-wave variance in the MMN time window of 100–300 ms. The corresponding sources associated with these ICs localized using low-resolution tomography (LORETA) included bilateral superior temporal gyrus (STG) and right inferior frontal gyrus (IFG) but also the anterior and central medial frontal regions, and the right inferior parietal lobule (IPL) (Marco-Pallarés et al., 2005). Unfortunately in that study the unique contributions of the temporal and frontal MMN generators could not be evaluated as these three were folded into a single IC with three dipoles. This might have occurred because only difference waves (single deviant trials subtracted from an average standard trial) in the indicated time range were subjected to ICA.