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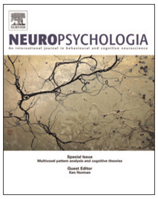

Brain regional networks active during the mismatch negativity vary with paradigm

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ABSTRACT

We used independent component analysis (ICA) of high-density EEG recordings coupled with single dipole fitting to identify the dominant brain regions active during the MMN in two different versions of a passive oddball paradigm: a simple, monotic, frequency-deviant paradigm and a more complex, dichotic, frequency-deviant paradigm with deviants occurring in either ear alone or in both ears at the same time. In both paradigms we found brain regional sources in the temporal and frontal cortices active during the MMN period, consistent with some previous studies. In the simpler paradigm, the scalp-potential variance during the earlier (70–120 ms) MMN was mostly accounted for by a wide array of temporal, frontal, and parietal sources. In the more complex paradigm, however, a generator in the prefrontal cortex accounted for a substantial amount of the variance of the scalp potential during the somewhat later MMN period (120–200 ms). These findings are consistent with a more nuanced view of the MMN and its generators than has been held in the past.

Sudden changes to a recurring sound pattern produce a corresponding brain response now known as the auditory mismatch negativity (MMN; Näätänen et al., 1978; Snyder and Hillyard, 1976). It is evoked automatically, that is, independent of overt attention or behavioral response (Näätänen and Michie, 1979; Paavilainen et al., 1993; Sussman et al., 2003; Muller-Gass et al., 2006), although it is larger when deviant stimuli occur in an attended channel (Woldorff et al., 1991). It is sensitive to both physical and abstract contextual changes (Dehaene-Lambertz, 1997; Näätänen et al., 1997; Näätänen et al., 2005; Pulvermüller and Shtyrov, 2006), and thus is a useful objective tool for probing the discriminatory capabilities of the auditory system.

The collective evidence suggests that the scalp MMN arises from neural sources localized to superior temporal planes bilaterally, and less consistently, regions in or near the inferior frontal gyrus, most often in the right hemisphere (Molholm et al., 2005; Deouell, 2007; Näätänen et al., 2007). Inconsistencies in detecting frontal sources with fMRI or PET suggest that synchronization of neural firing rather than increased firing rate might drive the EEG activation associated with the MMN (Deouell, 2007; Bekinschtein et al., 2009; Burgess, 2012; Klimesch et al., 2007). The localization with fMRI of the frontal generator can include parts of the medial frontal or anterior cingulate cortex (Molholm et al., 2005), and the caudal or rostral inferior and middle frontal cortex on the right, often accompanied by a strong right STG activation (Opitz et al., 2002; Doeller et al., 2003; Molholm et al., 2005; Restuccia et al., 2005, Schönwiesner et al., 2007). It can also include the left inferior frontal cortex (IFC, Molholm et al., 2005), again with a corresponding left STG activation, or both left and right IFC (Doeller et al., 2003; Rinne et al., 2005), and bilateral superior frontal cortex (SFC, Molholm et al., 2005). Additional sources in the inferior parietal regions have also been reported (Tata and Ward, 2005; Kasai et al., 1999). Most of the literature, however, has focused on the temporo-frontal network for which anatomical support (Bignall and Imbert, 1969) forms a biological basis for the involvement of short-term auditory memory (Romanski and Goldman-Rakic, 2002). Findings of numerous different frontal lobe generators have been attributed to the varying nature of the stimuli used to elicit the MMN, suggesting mediation by feature-specific regions in the frontal cortex (Molholm et al., 2005). The idea that both temporal and frontal sources are necessary is supported by the fact that the MMN response is attenuated in patients with either temporal (Aaltonen et al., 1993; Alain et al., 1998) or frontal lobe lesions (Alho et al., 1994; Alain et al., 1998). In spite of a plethora of research, however, and the various inconsistencies and complexities of that research of which some were just

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mentioned, a relatively simplistic view of the neural generators of the MMN still prevails. In this view neural generators in bilateral temporal cortex (Bekinschtein, et al., 2009), or in those regions plus inferior frontal cortex on the right side (e.g., Garrido et al., 2009) are supposed to be sufficient to generate the MMN. An alternative to the temporal only or temporal plus frontal views of MMN generators is that different auditory change detection paradigms engage different brain networks, or at least engage the same brain network differently (e.g., Alain et al., 1998; Alain et al., 1999; Giard et al., 1995). This idea would help to explain the somewhat inconsistent results obtained from the various MMN paradigms by asserting that not only the features of the oddball stimuli, but also the requirements of the particular paradigm implemented, affect how the brain responds to changes in the auditory environment. We designed the present study to investigate whether MMN paradigms with somewhat different requirements but involving detection of the same basic feature difference (frequency deviants) would activate the MMN network differently, or possibly even engage different sets of neural generators. Thus, we implemented a simple MMN paradigm that was expected to engage the most basic MMN network, and also a more complex paradigm that had been shown previously to emphasize the frontal contribution to the MMN (Deouell et al., 1998).

The view of MMN generation as arising from *only* bilateral temporal generators was based on a combined EEG/fMRI study, in which the fMRI data showed only unique activation of bilateral temporal cortices for “local” oddballs (frequency change in a fifth sound after four identical sounds compared to a fifth sound identical to the preceding four; Bekinschtein et al., 2009). fMRI-BOLD and EEG, given their different time courses, however, may not always track the same neural events even if they are responses to the same experimental conditions (Ritter and Villringer, 2006; Whitman et al., 2013). The temporal plus frontal view of Garrido et al. (2009), on the other hand, was based on dynamical causal modeling of EEG MMN data from a roving-frequency paradigm, which chose one model with particular directional interactions from among competing models with different subsets of the same set of three seeded ROI sources (based on Opitz et al., 2002) and their interactions. This approach is useful for discovering the relationship between the neural sources entered into the modeling exercise, but is limited to an advance judgment as to which sources might be sufficient.

An alternative approach that both respects the time course of the EEG-based MMN, and also allows for a wider variety of generators to be involved, is to apply independent component analysis (ICA, a blind source separation method) to EEG data *prior to* any dipole fitting procedure (Makeig et al., 1997, 1999). ICA separates signal mixtures, such as volume-conducted mixtures of neural activity recorded by EEG, into a set of statistically independent signals (Onton et al., 2006; Stone, 2004). ICA decompositions are routinely employed to reject EEG artifacts, thus increasing the signal-to-noise ratio of the data (Viola et al., 2009). Indeed, this approach identifies the MMN more effectively than does the classic difference-wave procedure (Kalyakin et al., 2008).

We reasoned that ICA could be used to identify the unique contributions of the temporal, frontal, and possibly other cortices to the MMN because ICA yields many independent components (ICs) that are almost entirely traceable back to single dipolar sources arising from activity in a small patch of cortical tissue (Delorme et al., 2012). Indeed some promising results with a somewhat different approach using ICA have already been obtained, viz. EEG data from an oddball task yielded six ICs that accounted for more than 67% of signal variance in a MMN time window of 100–300 ms (Marco-Pallares et al., 2005). Unfortunately the unique contributions of temporal and frontal MMN generators could not be evaluated separately in that study as they were not decomposed as separate ICs but folded into a single three-dipole IC.

Previous studies, particularly those combining EEG/MEG and fMRI and utilizing simple frequency-deviant paradigms have found that temporal cortical generators are strongly active during the MMN period (e.g., Bekinschtein et al., 2009; Opitz et al., 2002; Rinne et al., 2005),. Thus, we thought it likely that temporal generators would account for most variance in the scalp MMN in our simple frequency-deviant paradigm (Experiment 1), with perhaps only a small or negligible contribution from a frontal generator. On the other hand, the complex stimulus structure of our Experiment 2 has been shown previously to enhance the frontal contribution to the MMN (Deouell et al., 1998). Thus, we predicted that a frontal neural generator would account for more scalp potential variance, and the temporal generators less, during the MMN period in Experiment 2 than they would in Experiment 1. Such a result would confirm that the type of MMN paradigm employed, independent of which stimulus features it might involve, affects the way in which the auditory change detection network is engaged.

One critical aspect of our approach here is that the temporal ICA approach we employed decomposes the total (continuous) scalp potential time series from the EEG channels into *temporally (time)* independent components. Thus, if the activities of neural generators from, say, the left and right temporal cortices and the frontal cortex, vary from each other over the course of the experiment, they will emerge from the ICA as separate components, and thus their separate contributions to the MMN can be evaluated. The ICA approach thus adds the ability to follow the activity of the identified sources during the entire epoch of interest, and assess their independent contributions to the scalp potential over that epoch or over any sub-epoch we wish to study.

1. Materials and methods

1.1. Participants

Sixteen right-handed volunteers, (7 men) attending UBC, aged 19–30 years (mean age 22.6, SD 3.4 years) participated in Experiment 1. Twelve right-handed volunteers (5 men) attending UBC, aged 18–33 years (mean age 24, SD 4.5 years) participated in Experiment 2. All provided written consent and were paid to participate. The experiments were approved by the Behavioral Research Ethics Board of the University of British Columbia. All participants were assessed by clinical audiometry and found to have hearing within normal range at the time of the EEG acquisition. No history of neurological disorders was reported during a prescreening interview. Data from 2 men and 1 woman in Experiment 1 were excluded from the analysis because of excessive EEG artifact or failure to complete the session. Data from two men in Experiment 2 were excluded, one for possible history of seizure (reported casually during EEG acquisition) and the other for excessive EEG artifact. All remaining participants (13 and 10 respectively) had strong right-hand preferences as measured with the Edinburgh Handedness Inventory (Oldfield, 1971).

1.2. Stimuli and procedure

Experiment 1 was a standard monotic frequency-deviant paradigm (Näätänen et al., 2007). Participants watched a silent video with closed captioning and were asked to ignore the sounds heard through insert (E.A.R. 3A) earphones. The auditory stimuli were presented to the right ear only in a single 20-min block. The stimuli were 65 dB SPL, 100-ms duration, 500-Hz tones (2720 in total) that contained an occasional (14% or 440), deviant, 65 dB, 100-ms duration,1000-Hz tone. ISI was fixed at 500 ms. At least