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Test–retest reliability of the magnetic mismatch negativity response to sound duration and omission deviants

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ABSTRACT

Mismatch negativity (MMN) is a neurophysiological measure of auditory novelty detection that could serve as a translational biomarker of psychiatric disorders, such as schizophrenia. However, the replicability of its magnetoencephalographic (MEG) counterpart (MMNm) has been insufficiently addressed. In the current study, test–retest reliability of the MMNm response to both duration and omission deviants was evaluated over two MEG sessions in 16 healthy adults. MMNm amplitudes and latencies were obtained at both sensor- and source-level using a cortically-constrained minimum-norm approach. Intraclass correlations (ICC) were derived to assess stability of MEG responses over time. In addition, signal-to-noise ratios (SNR) and within-subject statistics were obtained in order to determine MMNm detectability in individual participants. ICC revealed robust values at both sensor- and source-level for both duration and omission MMNm amplitudes (ICC = 0.81–0.90), in particular in the right hemisphere, while moderate to strong values were obtained for duration MMNm and omission MMNm peak latencies (ICC = 0.74–0.88). Duration MMNm was robustly identified in individual participants with high SNR, whereas omission MMNm responses were only observed in half of the participants. Our data indicate that MMNm to unexpected duration changes and omitted sounds are highly reproducible, providing support for the use of MEG-parameters in basic and clinical research.

Introduction

Mismatch Negativity (MMN) is an auditory event-related potential (ERP) component evoked by irregularities in a constant auditory stream, such as during an oddball paradigm, where responses to repetitive standard sounds are interspersed with infrequent deviants. The auditory MMN is generated in a hierarchical network involving primary and secondary auditory and frontal cortices (Doeller et al., 2003; Garrido et al., 2008; Rinne et al., 2006, 2000) and can be elicited by frequency, duration, intensity changes (Näätänen et al., 2005), and even sound omissions (Nordby et al., 1994; Yabe et al., 1998, 1997). According to the "model-adjustment hypothesis", the MMN, and its magnetoencephalographic equivalent (MMNm), result from a comparison process between sensory input and a "memory-based" perceptual model (Näätänen et al., 2005; Näätänen and Winkler, 1999). Alternatively, the "adaptation hypothesis" suggests that the MMN results from differential neural adaptation to repetitive and deviant sounds (May and Tiitinen, 2010). The predictive coding framework postulates a synthesis of these two accounts. While the MMN reflects a bottom-up prediction-error resulting from the failure to suppress top-down predictions (Garrido et al., 2009), neural adaptation could play a modulatory role by weighting the precision of prediction-errors (Auksztulewicz and Friston, 2016; Feldman and Friston, 2010).

In addition to basic research, one of the most promising roles of MMN is its use in the detection and assessment of neuropsychiatric, neurological and neurodevelopmental disorders (Näätänen et al., 2015), as well as in healthy ageing (Näätänen et al., 2012). Specifically, MMN impairments are particularly robust in schizophrenia (ScZ) (Light and Braff, 2005; Näätänen and Kähkönen, 2009; Umbricht and Krljes, 2005) and could constitute a biomarker for early detection and diagnosis of the disorder (Light and Näätänen, 2013). MMN amplitude reduction in ScZ can be linked to aberrant predictive processing that could explain cognitive deficits as well as certain symptoms of the disorder, such as hallucinations and delusions (Adams et al., 2013; Fletcher and Frith, 2009). MMN deficits in early and prodromal stages of ScZ are particularly robust to deviations in sound duration (Bodatsch et al., 2011; Nagai et al., 2013; Todd et al., 2008). However, only few studies have shown reduced sound omission responses in ScZ (Kreitschmann-Andermahr et al., 1999; Salisbury and McCathern, 2016), thought to reflect endogenous predictive mechanisms (Arnal and Giraud, 2012; Schröger et al., 2015; Wacongne et al., 2012).

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Given the potential of ERPs as biomarkers in clinical research, it is essential to investigate their psychometric properties, such as the detectability and test-retest reliability. Previous studies have assessed the reliability of MMN to duration changes in electroencephalography (EEG) (Frodl-Bauch et al., 1997; Hall et al., 2006; Joutsiniemi et al., 1998; Kathmann et al., 1999; Light et al., 2012; Pekkonen et al., 1995; Schröger et al., 2000; Tervaniemi et al., 2005, 1999). Results from these studies indicated correlations ranging between 0.37 and 0.87, indicating moderate to robust reliability for ERPs. In contrast, the robustness of the magnetic MMN is less clear. The only study so far to address this question is by Tervaniemi and colleagues (Tervaniemi et al., 2005) who examined the replicability of MMNm and reported high intra-class correlation coefficients (ICC) to duration (ICC = 0.89) and frequency (ICC = 0.86) deviants in the right hemisphere. Equivalent current dipole (ECD) models of the MMNm did not show significant differences compared to sensor-derived measures. Previous studies indicated a signal increase of source-level estimates for both ERP and oscillatory signals (Tan et al., 2016, 2015), resulting in improved reliability (Lu et al., 2007). Noteworthy, while several studies have assessed the stability of MMN to frequency, duration and intensity deviants, test-retest reliability of the omission MMN is currently unclear.

In the present study, the reliability of both duration and omission MMNm responses was examined across two MEG recordings in healthy volunteers. We employed a short-duration (15 min) oddball design based on a previously tested local-global paradigm (Bekinschtein et al., 2009; Chennu et al., 2016; Wacongne et al., 2011) where MMN responses to duration and omission deviants (durMMNm and omiMMNm hereafter) were examined at both MEG sensor- and source-levels. We employed a minimum-norm estimation (MNE) approach to model distributed sources. In addition, we assessed differences between sensor- and source-estimates and evaluated the stability of MMNm responses. Our findings show a distributed network underlying both duration and omission MMNm generation and provide novel evidence that MMNm responses are highly reproducible.

Methods

Participants

We evaluated the test-retest reliability of MMNm in sixteen participants (7 males, 3 left-handed, mean age (± sd) = 25 (± 3) years) over two MEG sessions (range 20–92 days; mean (± sd) = 47 (± 19) days apart). Participants were recruited from the University of Glasgow School of Psychology participant pool and provided informed consent prior to the experiment. All participants reported no history of psychiatric or neurological disorders and had normal hearing levels. To control for potential influence of hormonal fluctuations, female subjects were scanned during the same phase of their menstrual cycle in both MEG sessions. The experimental protocol was approved by the University of Glasgow College of Science and Engineering Ethics Committee. No subjects were discarded due to excessive head movement (> 0.7 cm).

Stimuli and task

Series of four or five sounds composed of two superimposed sine waves (440 and 880 Hz) were presented at ~70 dB SPL using an Etymotic ER-30 system (Etymotic Research, Inc. United States of America) via 6-m plastic tubes and earpieces. Standard trials comprised series of 5 identical 80-ms tones. Deviant trials comprised four identical 80-ms sounds followed by a shorter 40-ms tone. Omission trials comprised the presentation of only four 80-ms sounds. All sounds were synthesized with 5 ms rise and fall times. The stimulus onset asynchrony (SOA) between sounds was 150 ms, and each series of sounds was separated by a random silent interval of 700–1000 ms.

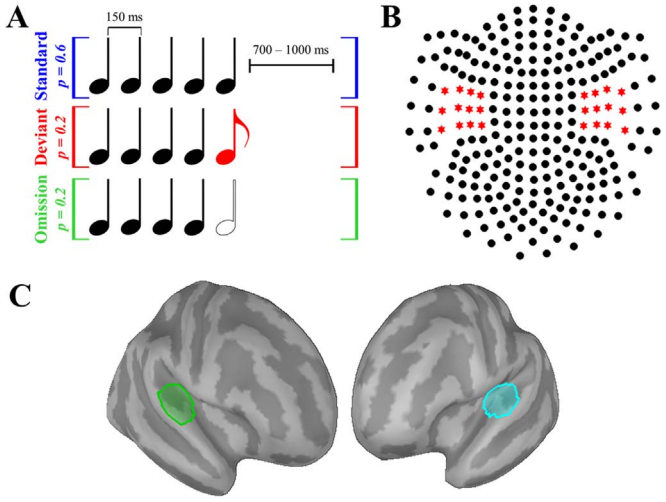

Fig. 1. A) Experimental design. Standard sequences comprised five identical 80 ms tones and were presented with a probability of 0.6. Unexpected deviant sequences comprising four identical 80-ms tones followed by a 40 ms tone (highlighted in red), and omission sequences comprising four identical 80-ms tones only, were interspersed among standard sequences with a probability of 0.4 each. Inter-trial interval randomly varied between 700 and 1000 ms and stimulus-onset asynchrony was set at 150 ms. B) MEG sensor layout depicting sensors of interest highlighted in red used to derive planar-transformed event-related fields (Left hemisphere: 'A158', 'A130', 'A98', 'A157', 'A129', 'A97', 'A156', 'A128', 'A96', 'A67', 'A68', 'A69'. Right hemisphere: 'A144', 'A112', 'A81', 'A145', 'A113', 'A82', 'A146', 'A114', 'A83', 'A171', 'A172', 'A173'). C) Template cortical surface highlighting regions-of-interest used to derive time-courses of activity and individual peak voxels.

Standards trials were randomly presented with a probability of 0.6, while interspersed deviant and omission trials had a probability of 0.2 each. At least one standard sequence was presented after each deviant or omission trial and all blocks started with the presentation of 3 standard trials (Fig. 1A). Overall, 360 standard, 120 deviant, and 120 omission trials were presented across 3 blocks. To promote that attention was not directed to auditory stimulation, participants were instructed to ignore auditory stimuli while performing a simple visual detection task (with 98–100% accuracy). In each trial, a letter was presented on the screen for 150 ms and participants were requested to press a button in response to the detection of target letter "X". Visual stimuli onset was randomized between 0 and 90 ms from the onset of the first sound to avoid time-locked interactions with auditory stimuli. Twenty visual target trials were presented in each block during standard trials only. Trials containing button responses were removed from the analysis. The experiment was performed using Presentation® software (Version 18.0, Neurobehavioral Systems, Inc., Berkeley, CA).

Neuroimaging acquisition

MEG data were acquired using a 248-channel magnetometer system (MAGNES® 3600WH, 4D-Neuroimaging, San Diego). Head position was assessed before and after each acquisition run via five coils attached to the participant's head and were co-digitized with participants' head shape (FASTRAK®, Polhemus Inc., VT, USA) for subsequent co-registration with individual magnetic resonance imaging (MRI) (1 mm^3 T1-weighted; 3D MPRAGE). The MEG touch-pad response (LUMItouch™, Photon Control Inc., BC, Canada) was sampled synchronously at 1017.25 Hz, with online 0.1 Hz high-pass filtering.

Preprocessing

Sensor-level processing was performed using Fieldtrip Toolbox (Oostenveld et al., 2011; http://www.fieldtriptoolbox.org, 20150607 and 20160623 releases) functions running under Matlab (version 8.2.,