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Within- and between-session replicability of cognitive brain processes: An MEG study with an N-back task

L. Ahonen [a,*], M. Huotilainen [a,b], E. Brattico [c,d]

[a] Brain Work Research Centre, Finnish Institute of Occupational Health, Finland
[b] BioMag Laboratory, HUS Medical Imaging Center, Helsinki University Central Hospital, Finland
[c] Center for Music in the Brain (MIB), Department of Clinical Medicine, Aarhus University, Denmark
[d] Cognitive Brain Research Unit, Institute of Behavioural Sciences, University of Helsinki, Finland

HIGHLIGHTS

- Repeated recordings showed over time stability in cognition associated features ERF
- Latency showed less fluctuation compared to amplitude in within-subject comparisons
- M170 latency and LPP correlated with task performance in a cognitively demanding task

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ABSTRACT

In the vast majority of electrophysiological studies on cognition, participants are only measured once during a single experimental session. The dearth of studies on test-retest reliability in magnetoencephalography (MEG) within and across experimental sessions is a preventing factor for longitudinal designs, imaging genetics studies, and clinical applications. From the recorded signals, it is not straightforward to draw robust and steady indices of brain activity that could directly be used in exploring behavioral effects or genetic associations. To study the variations in markers associated with cognitive functions, we extracted three event-related field (ERF) features from time-locked global field power (GFP) epochs using MEG while participants were performing a numerical N-back task in four consecutive measurements conducted during two different days separated by two weeks.

We demonstrate that the latency of the M170, a neural correlate associated with cognitive functions such as working memory, was a stable parameter and did not show significant variations over time. In addition, the M170 peak amplitude and the mean amplitude of late positive component (LPP) also expressed moderate-to-strong reliability across multiple measures over time over many sensor spaces and between participants. The M170 amplitude varied more significantly between the measurements in some conditions but showed consistency over the participants over time. In addition we demonstrated significant correlation with the M170 and LPP parameters and cognitive load. The results are in line with the literature showing less within-subject fluctuation for the latency parameters and more consistency in between-subject comparisons for amplitude based features. The within-subject consistency was apparent also with longer delays between the measurements. We suggest that with a few limitations the ERF features show sufficient reliability and stability for longitudinal research designs and clinical applications for cognitive functions in single as well as cross-subject designs.

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1. Introduction

Electromagnetic correlates of cognitive functions in the human brain form an intriguing topic, which has been studied abundantly for decades [1]. In electrophysiology, cognitive processes are traditionally studied with long-latency neural responses of the event-related potential (ERP), or field (ERF) that are extracted from the continuous electroencephalograph (EEG) or magnetoencephalograph (MEG), respectively, by signal averaging. Typically, the ERPs or ERFs, with associations to cognition, peak several hundreds of milliseconds after the onset of an event and originate in associative cortical areas. The use of MEG as a method can be preferable in some situations since it reveals activity with high spatial and temporal precision to provide information on the overall stability in neural activation during comprehensive

* Corresponding author.
E-mail address: lauri.ahonen@ttl.fi (L. Ahonen).

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cognitive tasks [2, 3]. Unraveling the neural basis of human information processing is intriguing and potentially beneficial task since the longer-latency ERP components have shown some promise as tools in clinical applications [4, 5]. The importance of electromagnetic measures relies on their extreme accuracy in time, which enables a deep understanding of the temporal succession of neural events. In contrast, the temporal approximation of metabolic measures, such as those provided by functional magnetic resonance imaging (fMRI), typically average over several seconds, skipping over the fast, local neural events and evidencing only the dominant, systemic ones [6].

Variations in recorded brain responses result partially from noise and partially from true and persistent inter-individual differences, e.g., endophenotypes. Endophenotypes are specific traits that are meaningfully associated with a disorder of interest, a type of behaviour or exposure to a specific environment, and are an interesting source of information for brain research to tackle [7]. Since the N-back has shown promise in linking genetic traits to cognitive performance [8], we chose to use the task in our test-retest study on ERF reliability since it is cognitively a much more demanding task than the ones used previously in studies of ERP/ERF replicability [9]. Some properties in evoked brain activations are successfully linked to genome and gene expression [10, 11]. However, due to the interaction and variations in environmental factors, internal conditions in participants' physiological state, as well as task dependent variables, the results of electrophysiological measurements on higher cognitive activations are difficult to interpret [12, 13]. The lack of studies concentrating on test-retest reliability and replicability of electrophysiological correlates of working memory is a serious concern and partly preventing eletrophysiological research on the topic.

Using PubMed searches with keywords ‘replicability’ and ‘test-retest’, and restricting the results to studies with MEG, we found 16 studies of which none considered cognitive task-related activation. In addition, one reliability study by [14] on graph metrics stability was found outside the PubMed search. The study reports greater stability in connections between cortical areas in cognitively demanding situations compared to the resting state. Within EEG research, test-retest studies on different features of evoked potentials has a long history reaching back three decades. A large number of studies on the test-retest reliability in EEG inspect the mismatch negativity (MMN) [15, 16, 17] reporting fair stability in early ERP components, both at individual and at interindividual level. And many of the studies focus also on latter components and error-related negativity in EEG [18, 19, 20, 21]. These studies have found stability in P3 component latency over weeks, however reporting earlier components as more stable over longer period of time. The studies regarding error-related features report fair stability in interindividual tests but suggest high number of trials. MEG studies with reliability as their main research question concentrate mainly on early sensory responses, e.g., on the auditory N1 response [22], and on somatosensory evoked fields (SEF) [23]. These studies suggest equal stability for both EEG and MEG signals. We found only three studies focusing on the replicability of evoked responses during a demanding cognitive task [14, 24, 25]. Huffmeijer et al. [24] recommend more trials to be used for latter components in ERPs while the early sensory components can be studied with fewer trials. While [25] reports stronger replicability to test-retest amplitudes compared to split-half amplitudes of various ERP components.

Here, we adopted a basic visually presented N-back paradigm as a cognitive task. N-back is a classic working memory test and has been used in electrophysiological studies as a cognitive task for several reasons [1]. Performing an N-back task requires monitoring, updating, and manipulating the information flow on-line and is assumed to occupy numerous key processes within working memory and other executive functions [26]. N-back is abundantly used and reviewed in the field of neuroimaging and imaging genetics, mainly in fMRI [27, 28], and has also been used in a replicability study of fMRI responses [29]. Thus, it is well suited for studying stability of neural activations. Recently, the task has also received publicity within the field of cognitive training, advocating its use as a cognitive performance measure [30].

We aimed to explore the source of variability between participants and to study the stability of repeated measures within participants. In this repeated-measures cognitive MEG paradigm, we investigated the effect of daily variations within healthy participants performing cognitively demanding tasks against the instrument derived and random noise sources. To explore the traces of individual ERFs we computed the global field power (GFP) for the MEG data. In MEG, GFP reduces the dimensions of the multisensory electrophysiological data and yet serves as an excellent quantifier for neural activity. GFP is a global and well-established quantifier of the overall neuronal field strength. It is based on spatial standard deviation, and quantifies the amount of activity of all neuronal sources at a given time instant to its largest possible extent. Hence, it serves as an excellent summation to study traces of event related fields (ERF) [31, 32]. It is also a measure with very few presumptions. Unlike many techniques such as source modelling, GFP does not require a priori assumptions on the studied brain responses, allowing a more direct and easily replicable estimate of total brain activity. Thus, GFP is a good quantifier of MEG activity also when large amounts of recordings need to be analyzed in automated paradigms such as in, e.g., imaging genetics.

In particular, we focused on the ERF component termed M170, peaking at around 150–200 ms from event onset, and reflecting attention [33] and cognitive processes such as face recognition [34], and complex lexical decisions [35, 36]. The loci of M170 neural generators converge to left or right fusiform gyrus, depending on the task [37]. We also examined the long-latency ERF component labeled late positive potential (LPP). This somewhat controversial ERF feature is elicited during evaluative classification of various stimuli [38, 39]. For extracting the LPP, we measured the difference between the target and non-target stimuli in a post-response time window. This modulation of ERF strength begins approximately 300–400 ms after stimulus onset and lasts several hundreds of milliseconds [40]. Its neural generators have been identified in lateral to frontal regions for cognitive tasks [41]. Despite its controversial status, LPP seems to, e.g., consistently reflect the awareness of an error [42, 43].

2. Methods

2.1. Protocol, participants, and questionnaires

Seven healthy right-handed participants (2 males, mean(sd) age 26(5.8) years) were recorded in four replicated measurements. Subjects were recruited via mailing lists and compensated for the time used (equivalent to ca. 24€). The study consisted of four separate sessions for each participant. The measurements were conducted during two days separated by a period of approximately two weeks so that each measurement day included two repeated measurements. Each measurement consisted of an N-back task and two other cognitive tasks that lasted altogether for approximately an hour. Thus each session consisted of 2 h for the tasks, and an additional hour for preparations and questionnaires about vigilance, performance, and mood (KSS (Karolinska Sleepiness Scale), NASA-TLX (NASA Task Load Index), and POMS (Profile of Mood States) [44, 45, 46] respectively). Here we analyze the test-retest reliability in all of the concluding 28 N-back blocks (7 subjects, 4 blocks each), resulting in over 500 min of recorded MEG data.

We aimed at inducing some natural variation in the mental state of the participants during the N-back measurements. For this reason, the two session days differed in the type of pause the participants had between the two measurement blocks (see Fig. 1): one break was made pleasant and the other one unpleasant. Other parameters such as caffeine consumption and the time of the day were controlled. A common workload score was evaluated from NASA-TLX questionnaires. Mood

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