Assessing MMN and P3b reliably within-participant – a comparison between the local-global paradigm and two specialized oddball sequences.

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Abstract

Mismatch negativity (MMN) and P3b are well known for their clinical utility. There exists no gold standard, however, to acquire these markers. This may explain why the within-individual sensitivity of MMN/P3b is often quite poor and why seemingly identical markers can behave differently across studies. Here we compare two traditional paradigms for MMN or P3b assessment with the recently more popular local-global paradigm which promises to assess MMN and P3b orthogonally within one oddball sequence. All three paradigms were administered to healthy participants (N=15) with concurrent EEG. A clear MMN and local effect were found for 15/15 participants. The P3b and global effect were found for 14/15 and 13/15 participants, respectively. There were no systematic differences between the global effect and P3b. Indeed, P3b amplitude was highly correlated across paradigms. The local effect differed clearly from the MMN, however. It occurred earlier compared to MMN and was followed by a much more prominent P3a effect. The two sets of peak latencies and amplitudes were also not correlated across paradigms. We conclude that the local-global paradigm is effective in evoking the traditional P3b component, but it does not capture the MMN. Caution should therefore be exercised when comparing the local effect and MMN across studies. Nevertheless, the within-individual sensitivity of both MMN and the local effect was satisfactory. The within-individual sensitivity of P3b was lower than expected in a healthy control group, which may explain the often-low sensitivity of P3b in patients with disorders of consciousness.

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Data Availability Statement

The code for the auditory paradigms, the code for data analysis, and the cleaned EEG data are available at https://github.com/rrutiku. Raw EEG data is available upon request.

Conflict of interest

MM is a founder of, and holds an executive position, at Intrinsic Powers Inc., a spin-off of the University of Milan. SS is an advisor of Intrinsic Powers.

Author contributions

RR: conceptualization, methodology, software, data collection, formal analysis, visualization, writing - original draft, writing - review & editing. CF: participant recruitment, data collection, formal analysis, writing - review & editing. SS: conceptualization, methodology, software, writing - review & editing, supervision. MM: conceptualization, software, writing - review & editing, supervision, funding acquisition.

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Introduction

Assessing consciousness in unresponsive patients continues to be a challenge. Despite progress in the basic research of consciousness, including the development of no-report paradigms and more advanced analysis techniques (Tsuchiya et al., 2015, Koch et al., 2016), these advancements do not always translate to a clinical application because the procedures still rely on high-quality data (i.e., large amounts of relatively artifact-free data with low signal-to-noise ratio) and a focused, alert participant who is able to understand and follow task instructions. These prerequisites are largely not met in patients with acute or prolonged disorder of consciousness (DoC). In this context, it is thus desirable to adopt approaches that are robust (i.e., quick to apply and relatively insensitive to noisy data) and do not rely on any complicated task-related engagement.

The most obvious candidate for this purpose is resting-state EEG, whose visual inspection is recommended for the standard evaluation of DoC patients (Kondziella et al., 2020). Despite its high specificity, however, resting-state EEG might lack the desired sensitivity to stratify DoC patients (Hofmeijer et al. 2015; Estraneo et al. 2016; but see also Colombo et al., 2023). TMS-EEG approaches can effectively compensate for this (Casarotto et al., 2016, 2023), but access to this technique is still limited to a few research centers. More importantly, both resting-state EEG and TMS-EEG approaches lack cognitive interpretability. In the healthy brain, consciousness is intimately intertwined with other critical functions such as short-term memory and attention. We still know very little about how the relationship between consciousness and normal cognition might be disturbed in DoC patients. Ideally, an assessment of unresponsive patients would therefore also include EEG components which can tell us more about the cognitive state of the patient and how it relates to their conscious state (Sergent et al., 2017).

Over the years, two cognitive EEG components have been most studied so far - the MMN and the P3b (Daltrozzo et al., 2007). MMN is an index of automatic sensory memory (Näätänen et al., 2007) that is elicited by any perceivable change in sensory stimulation. In the case of auditory perception, MMN occurs when a rare “deviant” sound is perceived among common “standard” sounds. The ERP response to the deviant sounds is more negative on fronto-central electrodes ca. 100-250 ms after stimulus onset. The amplitude difference compared to the standard sounds typically falls between 0.5–5 μV. Importantly, MMN occurs well after the N1 component (it is normally expected between the N1-P2 complex) and any stimulus-driven modulations of the N1 component should not be mistaken for MMN (Duncan et al., 2009; Näätänen et al. 2011). In the healthy brain, MMN is an automatic response that is evoked regardless of whether or not the individual is paying any attention to the sounds (Näätänen et al., 1990). Due to its automatic nature, MMN is typically not considered a specific marker of consciousness per se. Rather, it should be viewed

as an important precursor process to normal conscious perception (Näätänen et al., 2011).

In theory, the independence from attention makes MMN a very good marker of the integrity of sensory processing in unresponsive patients. Indeed, a number of studies with DoC patients have linked the presence of an MMN response to a higher chance of awakening from coma (e.g., Fisher et al., 2004; Azabou et al., 2018). MMN may also help to delineate between patients in chronic unresponsive wakefulness state and minimally conscious state, and perhaps even identify patients whose sensory processing is better than expected based on their clinical diagnosis (Kotchoubey et al., 2005; Fisher et al., 2010; Boly et al., 2011). It should be clearly pointed out, however, that in practice the sensitivity of MMN in clinical studies is generally quite poor (Comanducci et al., 2020; Kondziella et al., 2020). For example, in the study by Fisher and colleagues (2010), MMN could only be detected in three out of eleven patients in minimally conscious state (27%), and two out of sixteen patients in unresponsive wakefulness state (13%). Thus, if an MMN response was not detected in any given patient, this cannot be taken as strong evidence for a lack of normal mid-level sensory processing in that patient.

The P3b (as opposed to the P3a within the P300 complex) is not an index of sensory processing per se, but it is considered a domain-general marker for access-consciousness (for a review see Mashour et al., 2020; see Block (1995) for a definition of the term access-consciousness). It is also robustly linked to a wide range of higher-order cognitive processes associated with attention and memory operations (Polich, 2007), and stimulus-response mapping (Verleger et al., 2006; Asanowicz et al. 2020). P3b is elicited by rare stimuli that are task-relevant or at least attended to by the participant (Duncan-Johnson & Donchin, 1977). In the case of auditory stimulation, a P3b can be evoked by a very similar paradigm as the MMN. The oddball paradigm should again consist of standard sounds and rare deviant sounds. The critical difference is that all the sounds should be separated by longer interstimulus intervals (ISIs) and participants should be instructed to engage with the deviant sounds (e.g., count them). Under these conditions, the ERP response to the deviant sounds exhibits a prominent late positivity on centro-parietal electrodes starting ca. 200-300 ms after stimulus onset. The amplitude difference compared to the standard sounds depends on various stimulation parameters (Duncan et al., 2009), but it is typically quite large (exceeding several μV) and long-lasting.

The size of the P3b component makes its detection very robust – 20 deviant trials are often already enough to observe a reliable P3b (Cohen & Polich, 1997). Its drawback in clinical application is its reliance on attention and task engagement. One can easily conceive of a conscious patient who may not exhibit a P3b response because she/he is unable to focus or understand the task instructions. It is therefore not surprising that most clinical studies have delivered mixed results regarding the presence or absence of a P3b response in DoC patients (e.g., Kotchoubey et al.,

2005; Fisher et al., 2008, 2010; Steppacher et al., 2013; Rohaut et al., 2015; Estraneo et al., 2020). Given these conflicting results, the P3b (as well as MMN) should currently be considered only as a positive predictor in comatose patients rather than a marker of the presence/absence of consciousness.

In summary, MMN and P3b are promising candidate ERP markers that can inform us of an unresponsive patient's cognitive capabilities and should therefore be included in a multimodal assessment of DoC patients (Kondziella et al., 2020). However, their sensitivity in DoC patients is often not satisfactory, and therefore they can only deliver additional information which is not critical for a patient's evaluation. In order for these cognitive components to become more informative on a single-patient level, efforts should be made to improve their acquisition (Duncan et al., 2009). First, a major but often overlooked shortcoming in all of the above-listed clinical studies is the wide range of different paradigms and stimulation parameters used. This lack of a gold standard has been hypothesized as one important source for the inconsistent results described above and the low sensitivity/specificity of the MMN and P3b results (Kondziella et al., 2016). Second, the specific methodologies and paradigms used in clinical studies are rarely validated in healthy control participants first. Therefore the baseline sensitivity of the specific implementations of MMN/P3b assessment is often unknown.

In an effort to overcome these discrepancies and limitations, more recently, another paradigm was proposed promising to measure MMN and P3b orthogonally within one oddball sequence. The local-global paradigm has two levels of deviance. Locally deviant sounds are not task-relevant and should only evoke the early MMN response – termed the local effect. Globally deviant sounds on the other hand are task-relevant and should therefore also evoke the late P3b response – termed the global effect (Bekinschtein et al., 2009). This two-way design should ensure that both components of auditory change detection are clearly discriminable in each participant and only the responses to globally deviant sounds should be diagnostic of access-consciousness (Faugeras et al. 2012).

This paradigm might offer clear advantages in the clinical context. First, it could constitute a precise and replicable gold standard for assessing MMN/P3b in patients. Second, its baseline sensitivity in healthy participants has been established (Bekinschtein et al., 2009), which provides a good point of comparison for patient cohorts. And indeed, several studies have already delivered initial results about the potential utility of the local-global paradigm in DoC research (Faugeras et al. 2011, 2012; King et al., 2013a, 2013b; Sitt et al., 2014; but see also Tzovara et al., 2015). In the study by Faugeras and colleagues (2012), for example, 7/8 control participants (i.e., 87.5% baseline sensitivity), 8/13 conscious patients (61.6%), 9/28 minimally conscious patients (32.1%), and 6/24 patients in an unresponsive wakefulness state (25%) exhibited the local effect. In the same study, the global effect was observed in 8/8 control participants (100%), 7/13 conscious patients (53.8%), 4/28 minimally

conscious patients (14.3%), and 2/24 patients in an unresponsive wakefulness state (8%). Despite the fact that these numbers are still very far off from a satisfactory and clinically relevant level of sensitivity, they do suggest an improvement to several earlier landmark studies. Therefore the local-global paradigm might offer an attractive alternative approach for many future assessments of the cognitive capabilities of DoC patients.

Despite the obvious appeal and promising first results of the combined approach of the local-global paradigm, it remains unknown to what extent the local and global effects are indeed comparable to the more traditional MMN and P3b effects from older studies. As described above, the best practice of obtaining MMN or P3b is somewhat different and therefore the traditional paradigms have typically been aimed at a single purpose only. Thus, it does not follow trivially that the neural dynamics evoked by the local-global paradigm are directly comparable to previous MMN/P3b results. Nevertheless, markers of auditory change detection remain a clinical go-to tool, and the local-global paradigm may uncover interesting dynamics in addition to the traditional single-purpose paradigms. It is therefore prudent to investigate and characterize any possible differences between these two approaches.

The aim of this study is to compare the local-global paradigm to two separate paradigms optimized for MMN or P3b assessment, respectively. We do this in a sample of healthy participants in order to establish a firm baseline to which clinical populations can be compared. First, we validate the sensitivity of all three paradigms on a single participant level. We expect to find a discernible MMN/P3b and local/global effect in all participants because there is no reason they should be absent for healthy participants who are able to follow task instructions. Second, we assess whether the local/global effects are comparable to the traditional MMN/P3b effects obtained by dedicated single-purpose paradigms. We expect to find no systematic differences across participants between the local effect and MMN, and the global effect and P3b. The comparative results will help to interpret and relate previously reported findings in the literature. The comparisons will also assist researchers in future decisions about which paradigm or combination of paradigms to use in their studies.

Methods

Participants

Fifteen participants took part in the study (6 male; 3 left-handed; including the first author of this paper). Their age ranged from 20 to 49 years (m = 28, SD = 9). All participants reported normal hearing and no history of audiological or neurological disorders. They were informed about the purpose of the study and gave written consent for participation. The study was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki (World Medical Association, 2013).

Auditory oddball paradigms

Optimum-1 (for MMN)

A slightly adapted version of the Optimum-1 paradigm (Näätänen et al., 2004) was used to assess the traditional MMN according to established guidelines of best practice (Duncan et al., 2009). This paradigm is particularly useful because it assesses MMN in response to several different types of deviant sounds without raising the number of standard sounds in proportion. Optimum-1 is therefore very economical and increases the chance of finding an MMN response for at least one type of deviant sound.

The Optimum-1 paradigm is illustrated in Figure 1A. Stimuli consisted of standard sounds and four different types of deviant sounds. The standard sounds were chords of 523, 1046, and 1569 Hz – with the fundamental frequency corresponding to C5 in the Western musical scale. The second and third partials were of 1/2 and 1/4 intensity with respect to the fundamental frequency. The duration of the standard sounds was 50 ms including a rise and fall time of 5 ms. Each deviant type differed from the standard in only one dimension. The frequency deviants were either higher than the standards (a chord of 609, 1218, and 1827 Hz) or lower than the standards (a chord of 450, 900, and 1350 Hz). The intensity deviants were 15% softer compared to the standards. The duration deviants were 27 ms shorter than the standards. The location deviants consisted of sounds coming either from the left or from the right whereas the standards always came from the front.

All sounds were separated by a fixed ISI of 500 ms. Standard and deviant sounds were presented alternately. Thus, each deviant type constituted 12.5% of all trials (i.e., 180 trials). The order of deviants was semi-randomized: any four consecutive deviants always contained every deviant type once, and two deviants of the same type were never consecutive. The paradigm started with 10 standard sounds to introduce habituation. A movie with Italian subtitles was played without sound on a

separate laptop for the duration of the Optimum-1 paradigm. Participants were asked to concentrate on the movie and give a short summary of what they had seen after the paradigm was finished. The total duration of the Optimum-1 task was 14 minutes.

Learning-oddball (for P3b)

The learning-oddball paradigm (Jongsma et al., 2006, 2013) was chosen for a dedicated P3b assessment. Only slight changes were made to the original parameters in order to better conform to established clinical guidelines (Duncan et al., 2009). Note that this paradigm is designed to also evoke transient pre-stimulus CNV in addition to P3b. Since this additional component only occurs gradually in some trials, its effect on the overall ERP of the deviant condition is negligible. More importantly, no evidence of a systematic effect of the CNV component on P3b dynamics was evident (data not shown). Therefore this additional component which is outside of the present focus will not be treated further and only the P3b component will be assessed.

The learning-oddball paradigm is illustrated in Figure 1B. Stimuli consisted of standard sounds and one type of deviant sound. The standard sounds were the same as in the Optimum-1 paradigm (chords of 523, 1046, and 1569 Hz). The deviant sounds were higher than the standard sounds (chords of 609, 1218, and 1827 Hz) but identical in every other respect. All sounds were separated by a randomly chosen ISI between 800 - 1200 ms.

Although all deviants were interleaved with at least 2 standards the occurrence of deviants was not always unpredictable. The paradigm started out with 8 deviants randomly separated by 2 – 10 (with the exception of 6) standards. The following 8 deviants were always separated by 6 standards. This regularity made them increasingly predictable (a manipulation that should be reflected in the gradual emergence of the pre-stimulus CNV component). The cycle of 8 unpredictable and 8 predictable deviants was repeated 6 times – for a total of 96 deviant trials (14.1% of all trials). The paradigm always started out with at least 10 standard sounds to introduce habituation. Participants were instructed to concentrate on the sounds and count the number of deviants. They were asked to report the number of deviants after the paradigm had finished. The total duration of the learning-oddball task was 12 minutes.

The local-global paradigm (for the local and global effect)

The local-global paradigm (Bekinschtein et al., 2009) was replicated with minimal changes to make it as similar to the other two paradigms as possible. The local-global paradigm is illustrated in Figure 1C.

The stimuli were chords of either 350, 700, and 1400 Hz (hereafter sound A) or 500, 1000, and 2000 Hz (hereafter sound B). For both sounds, the second and third partials were of 1/2 and 1/4 intensity with respect to the fundamental frequency. The duration of the chords was 50 ms (including 5 ms rise and fall times). These stimuli were presented in groups of 5 with 150 ms SOA. The groups or “quintlets” were in turn separated by a variable interval of 800 to 1100 ms (in 50-ms steps).

The first four sounds in each quintlet were always the same (either A or B). The last sound could either be the same as the first four sounds or different. If the last sound was different it was automatically a local deviant. Global deviance depended on the experimental block. In each block (8 in total), one quintlet was designated to be the standard and this quintlet was played 80% of the time. The remaining 20% consisted of quintlets with a different 5th sound. For example, if in a given block quintlet AAAAA was the global standard then in this block AAAAB would be the global deviant. In another block, AAAAB would be the global standard and AAAAA would be the global deviant. Notice that in both cases only quintlet AAAAB contains a local deviant – irrespective of its global status.

Each of the four possible combinations of global standards and global deviants was presented for two blocks. Block order was randomized. The absolute number of deviants varied randomly between 22 and 30 per block. Thus, there were a total of 212 global deviants and 848 global standards on average. All global deviants were separated by at least 2 standards. Each block began with the presentation of at least 10 standard quintlets to establish their regularity. Experimental blocks were separated by 5 seconds of silence to signify block change. There was also an additional break between blocks 4 and 5 (after ca. 15 minutes of recording time) to allow participants to rest. Participants were instructed to concentrate on the sounds and count the rarely occurring quintlets (i.e., task-relevant deviants). They reported how many deviants they had counted after every 4 blocks. The total duration of the local-global task was 33 minutes.

--- Figure 1 ---

Overall procedure

The paradigms were written in Matlab, using the Psychophysics Toolbox extensions (Brainard, 1997; Pelli, 1997; Kleiner et al, 2007), and run from a dedicated laptop (Dell Latitude E6540). Stimuli were presented binaurally via noise-blocking Sennheiser headphones (CX 3.00) at 15% of maximum volume (corresponding to ca. 70 dB).

The order of the 3 oddball paradigms was balanced across participants. Participants were given specific instructions for each paradigm prior to its commencement. They were asked to remain eyes-open during the sound sequences, but could freely rest between paradigms and report their impressions. In all, the 3 oddball paradigms took ca. 70 minutes to complete. Together with an additional paradigm of auditory scene segregation (not related to the purpose of the study at hand) the total recording time added up to ca. 85 minutes.

EEG

Data acquisition

Whole-head EEG recordings were obtained with a BrainAmp system (Brain Products GmbH) using a 62-channel cap (10-20 standard). The ground and reference electrodes were placed on the participant's forehead, slightly to the right. Horizontal eye movements were recorded by two additional electrodes placed at the outer canthi of the eyes. Impedances were kept below 10 kΩ whenever possible. Data were sampled at 2500 Hz and filtered between 0.1 and 250 Hz.

Preprocessing

Data were analyzed in Matlab using custom code and the following toolboxes: the FieldTrip toolbox for EEG/MEG-analysis, developed at the Donders Institute for Brain, Cognition and Behaviour (Oostenveld et al., 2011; http://fieldtriptoolbox.org; version 20221118), EEGLAB (Delorme & Makeig, 2004; https://eeglab.org/ ; version 2022.0), and NoiseTools (de Cheveigné & Arzounian, 2018; http://audition.ens.fr/adc/NoiseTools/). Preprocessing steps were kept as similar as possible for all three paradigms while still conforming to established practices in the field.

As a first step data was cut into trials with respect to stimulus onset: -100 to +400 ms for Optimum-1 and -800 to +700 ms for both the learning-oddball and the local-global paradigm. Note that the last sound in each quintlet was considered as stimulus onset for the local-global paradigm. For the Optimum-1 paradigm data was also high-pass filtered with a 1 Hz zero phase-shift Butterworth filter before epoching. All data were subsequently down-sampled to 1000 Hz and low-pass filtered with a 30 Hz cutoff. For the Optimum-1 paradigm, all trials were additionally detrended.

Noisy electrodes and trials containing high-amplitude artifacts were manually identified. The identified electrodes were interpolated using spherical splines and all trials containing artifacts were discarded from further analysis. ICA was used to clean data of blink artifacts together with other eye movement-related artifacts and

any remaining muscle activity. After ICA, data were re-referenced to average reference and visually inspected one more time. The NoiseTools function nt_find_outlier_trials was used to automatically discard all trials within each paradigm that differed more than two standard deviations in amplitude from the mean. The remaining clean trials – 2941 on average across all paradigms (SD = 108, range = 2717-3055) – were baseline corrected for 100 ms before stimulus onset.

Experimental conditions

We planned to conduct four contrasts between standard and deviant conditions. Below we list all of the eight conditions of interest and how many trials were available for each condition on average. Note, however, that before the within-participant statistical analyses (see next section), trial numbers between the respective standard and deviant conditions were equalized by randomly subsampling from the condition with more available trials.

Two experimental conditions were created for the Optimum-1 paradigm. The standard condition was composed of all trials where the standard sound was played (662 trials on average; SD = 22, range = 633-706). The deviant condition was composed of all trials where a deviant sound – irrespective of deviant type – was played (664 trials on average; SD = 23, range = 625-705). Note that it would be possible to further increase the sensitivity of the Optimum-1 paradigm by assessing MMN for each of the four deviant types separately. This was by and large not necessary for our sample, however, because most participants exhibited a clear MMN to at least two out of four deviant types.

For the learning-oddball paradigm, two conditions were created as well. The deviant condition was composed of all trials where a deviant sound was played (m = 520, SD = 33, range = 457-560). The standard condition was composed of all trials where the standard sound was played (m = 88, SD = 6, range = 74-94).

Four conditions were available from the local-global paradigm: local standard global standard condition (LSGS; m = 400, SD = 33, range = 343-445), local deviant global standard condition (LDGS; m = 409, SD = 36, range = 320-444), local standard global deviant condition (LSGD; m = 94, SD = 10, range = 70-105) and local deviant global deviant condition (LDGD; m = 92, SD = 9, range = 74-103). In order to assess the local effect, the LSGS and LSGD conditions were combined into a local standard condition and the LDGS and LDGD conditions were combined into a local deviant condition. In order to assess the global effect, the LSGS and LDGS conditions were combined into a global standard condition and the LSGD and LDGD conditions were combined into a global deviant condition.

Inferential analysis

Nonparametric cluster-based permutation tests (Maris & Oostenveld, 2007) were carried out for each paradigm and each participant separately. For within-participant assessment, independent t-tests were used and single trials were the units of observation. In case the number of available deviant and standard trials differed for a given comparison, trial numbers were equalized by randomly subsampling from the larger condition. For the local and global comparisons, it was made sure that the standard and deviant conditions included the same number of trials from the other effect, respectively. E.g., the local standard and local deviant conditions both included the same number of global standard trials and the same number of global deviant trials. Additional group-level analyses were carried out with the same cluster-based permutation approach: in this case, paired t-tests were used and individual participants' ERPs were the units of observation. Trial numbers were not equalized before creating the individual ERPs.

The empirical distribution of the permutation tests always consisted of ten thousand random permutations of the data. All alpha levels were set at .05 (two-sided). Significant samples were included in clusters if at least two neighboring electrodes also showed a significant effect at the same time point. In the following, cluster onsets/offset is reported as the first/last time point when at least three electrodes belonging to that cluster showed a significant effect. The MMN and the local effect were assessed within the time window of 0-400 ms after stimulus onset. The P3b and the global effect were assessed within the time window of 0-700 ms after stimulus onset.

Finally, two methodological side-effects of the presently implemented analysis pipeline should be noted. First, auditory ERPs are often reported with linked mastoid reference because this maximizes the components of interest. We chose average reference to make all comparisons between paradigms more straightforward. As a consequence of this choice, all auditory ERPs are approximately half the amplitude of their mastoid-referenced equivalents. Second, due to the nature of average reference many of the conducted cluster-based permutation tests included "mirror clusters". These are significant clusters of opposite polarity surrounding the effect of interest. We do not show these mirror clusters because they are only methodological artifacts and would needlessly crowd the figures.

Results

The purpose of the present study was to compare the local-global paradigm with two separate oddball paradigms optimized for the assessment of either MMN or P3b. In the following, each effect is first described separately giving emphasis to its within-participant sensitivity. Then the paradigms are compared in terms of the neural dynamics they evoke.

Individual effects

MMN

The Optimum-1 paradigm evoked a classical MMN effect, which is well exemplified by the group-level analysis (Fig 2A). The MMN consisted of a systematically more negative response to deviant sounds compared to standard sounds on a cluster of frontal electrodes. It appeared between the N1-P2 complex as expected. Note, however, that the N1-P2 complex was somewhat obscured by an additional component (possibly the P165; Goodin et al., 1978) for both standard and deviant sounds. The peak latency of the group-level MMN at electrode 'Fz' was 136 ms with a peak amplitude of -0.84 μV.

A comparison between all deviant and standard sounds was also conducted for each participant separately. These analyses revealed a clear MMN for each individual participant, although for one participant the effect was only marginally significant (Fig 2C). Additional analyses (not shown) indicated that this participant did have a reliable MMN for the frequency deviants, but not for the other three types of deviants. This explains why the overall comparison between deviants and standards was only marginally significant. In summary, we conclude that the Optimum-1 paradigm exhibited satisfactory within-participant sensitivity for the MMN effect. The average peak latency of the individual participants' MMN at electrode 'Fz' was 132 ms (SD = 27, range = 82-176), and the average peak amplitude was -1.09 μV (SD = 0.31, range = -0.67 to -1.7). Figure 2B illustrates the individual values.

The group-level comparison contained an additional small positive effect following the MMN. This effect is consistent with the P3a component and is frequently reported together with MMN. It appeared on fronto-central electrodes ca. 208-281 ms after stimulus onset. On the single-participant level, this effect was reliably observed for only 6 participants (Fig 2C).

Local effect

A comparison between local deviants and local standards from the local-global paradigm revealed an early negative effect centered around 100 ms after stimulus onset on frontal electrodes. The early negative effect was swiftly followed by a prominent P3a on central electrodes. The group-level comparison exemplifies both effects (Fig 2D). Although no clear N1-P2 complex could be identified from the grand average of local standards it does seem as if the local effect was caused by a shift of N1 latency (and amplitude) for the grand average of local deviants. The peak latency of the grand average local effect at electrode 'Fz' was at 105 ms with a peak amplitude of -1.9 μV.

Within-participant comparisons between local deviants and local standards revealed an early negative effect for all participants, although for one participant the effect was only marginally significant (Fig 2F). The average peak latency of the individual local effects at electrode 'Fz' was 108 ms (SD = 10, range = 95-128) and the average peak amplitude was -2.12 μV (SD = 0.8, range = -1 to -4). Figure 2E illustrates the individual values. We conclude that the local-global paradigm exhibited satisfactory within-participant sensitivity for the local effect. Even though the P3a is not considered a part of the effect of interest, it is worth noting that the local-global paradigm also evoked a reliable P3a response in fourteen out of fifteen participants.

--- Figure 2 ---

P3b

The learning-oddball paradigm evoked a classical P3b component for the deviant sounds compared to the standard sounds. This late effect on parietal electrodes is well exemplified by the group-level results (Fig 3A). The grand average P3b started between 200-300 ms after stimulus onset and continued until the end of the tested time period. Its mean amplitude on electrode 'Pz' was 2.15 μV between 300 and 700 ms.

Within-participant comparisons between deviants and standards revealed a reliable P3b for fourteen out of fifteen participants (Fig 3C). Visual inspection of the outlier participant's ERP confirmed that a P3b was indeed completely absent for this individual. The other participants' P3b components started around 307 ms after stimulus onset (SD = 130, range = 87-524). The average mean amplitude of the individual P3b components at electrode 'Pz' was 2.38 μV between 300-500 ms (SD = 1.72, range = 0-6.86) and 2.34 μV between 500-700 ms (SD = 1.61, range = 0.51-6.51). Figures 3B and 3C illustrate the individual values. We conclude that the

learning-oddball paradigm did not exhibit satisfactory within-participant sensitivity for the P3b effect, because one participant did not have a P3b at all.

The group-level comparison revealed an additional early negative effect on frontal electrodes for the learning-oddball paradigm. The timing and topography of this effect are similar to the MMN. However, on the single-participant level, this frontal negative effect reliably preceded the P3b in only six out of fifteen participants (Fig 3C).

Global effect

A comparison between global deviants and global standards from the local-global paradigm revealed a prominent late positive effect on parietal electrodes. The grand average global effect started between 200-300 ms after stimulus onset and continued until the end of the tested time period (Fig 3D). Its mean amplitude on electrode ‘Pz’ was 2.69 μV between 300 and 700 ms.

Within-participant comparisons between global deviants and standards revealed a reliable global effect for thirteen out of fifteen participants (Fig 3F). Note that one of the participants for whom a global effect could not be determined also did not have a P3b for the learning-oddball paradigm. The other thirteen participants’ global effects started around 265 ms after stimulus onset (SD = 110, range = 89-476). The average mean amplitude of the individual global effects at electrode ‘Pz’ was 3.22 μV between 300-500 ms (SD = 1.83, range = 0.74-6.62) and 2.89 μV between 500-700 ms (SD = 1.87, range = 0-6.85). Figures 3E and 3F illustrate the individual values. We conclude that the local-global paradigm did not exhibit satisfactory within-participant sensitivity for the global effect, because two participants did not have the expected global effect.

Similar to the learning-oddball paradigm, the group-level comparison revealed an additional early negative effect on frontal electrodes for the local-global paradigm. On the single-participant level, this frontal negative effect reliably preceded the global effect in ten out of fifteen participants (Fig 3F).

--- Figure 3 ---

Comparisons between effects

Comparison between MMN and the local effect

It is already clear by visual inspection alone that the MMN obtained by Optimum-1 and the local effect from the local-global paradigm are systematically different across participants. First of all, the local effect peaks earlier for thirteen out of fifteen participants (by an average of 24 ms, SD=30, range=-74 to 30 ms). Second, whereas the MMN occurs between the N1-P2 complex, the local effect is more reminiscent of an N1 modulation. Finally, the local effect seems to be overshadowed by a strong P3a component. The P3a is considerably smaller for the Optimum-1 paradigm.

These observations are confirmed by a group-level comparison of the individual difference waves. The local negative effect is systematically stronger compared to MMN on central electrodes around 35-124 ms after stimulus onset. This is followed by a positive difference on frontal electrodes between 136-303 ms. There is also no correlation between the individual MMN peaks and local effect peaks – neither in terms of latency nor amplitude ($r = -0.04$, $p = 0.88$ and $r = 0.05$, $p = 0.86$, respectively). It can therefore be concluded that the local effect does not seem to capture the classical MMN component.

Comparison between P3b and the global effect

By visual inspection alone no striking differences can be identified between the P3b obtained by the learning-oddball paradigm and the global effect from the local-global paradigm. Indeed, the mean amplitude is strongly correlated between the two paradigms for both time windows ($r=0.78$, $p=0.0006$ for 300-500 ms and $r=0.76$,$p=0.001$ for 500-700 ms). If anything, the global effect seems to be more frequently preceded by frontal negativity on the single-participant level. This is not confirmed by a direct comparison of the two sets of difference waves, however. A cluster-based permutation test did not uncover any systematic differences between the learning-oddball results and the global effect throughout the post-stimulus time period. Thus, it can be concluded that both paradigms evoke a very similar P3b response and earlier effects in this comparison seem not to be systematically different across participants.

Discussion

Both MMN and P3b are well-described ERP components that can be evoked via appropriate oddball sequences. The ideal oddball sequence for MMN assessment comprises short ISIs and an additional task designed to divert attention away from the experimental stimuli (Näätänen et al., 2004). On the other, hand, the ideal oddball sequence for P3b assessment must have sufficiently long ISIs to see the late component of interest. Most importantly, experimental stimuli have to be within the focus of the participant's attention in order to evoke a reliable P3b (Duncan et al., 2009). Thus, optimal MMN assessment and optimal P3b assessment imply somewhat opposing demands on study design. The local-global paradigm promises to circumvent these contradictory requirements by implementing two oddball levels – the local level for evoking MMN and the global level for evoking P3b (Bekinschtein et al. 2009). Despite the appeal of such an orthogonal design, it is not yet clear whether the responses evoked by the local-global indeed reflect the well-defined MMN and P3b components previously described in the literature. Verifying this aspect was the primary aim of the present study.

Of the three tested paradigms, Optimum-1 was the most successful in fulfilling its purpose. This paradigm is designed specifically to obtain reliable within-participant MMN responses and indeed we found a typical MMN response for all of our participants using the Optimum-1 (although the results for one participant were only marginally significant). The assumption of typicality is corroborated by a comparison of previously reported MMN results to the grand average ERP waveforms of the present study (e.g., Norm group in Fig. 2. of Wijnen et al. (2007)). The only noteworthy difference is a slightly smaller than usual MMN amplitude in our data. But even more important than the conformity of the grand average MMN is the fact that individual MMNs were very coherent across participants. This implies that future studies using the Optimum-1 paradigm can adopt strong and precise prior hypotheses with respect to the expected results.

The local effect of the local-global paradigm was less successful in fulfilling its purpose as it failed to elicit a typical MMN response according to standard criteria. More specifically, the local effect occurred too early and not between the N1-P2 complex. Note that the local effect nevertheless resembled previously reported waveforms from the local-global paradigm. E.g., the local effect depicted in Figure 2 by Bekinschtein and colleagues (2009) looks very similar, showing also a modulation of N1 for local deviants. Considering these characteristics, it is possible that the local effect captures a marker of auditory change detection preceding MMN (Grimm et al., 2011; Bendixen et al., 2012).

The fact that the local effect is not equivalent to the classical MMN response, has implications for its clinical significance. MMN has been repeatedly found to predict recovery of consciousness in DOC patients (e.g. Fischer et al., 1999, 2004; Wijnen

et al., 2007). In light of the present results, it is an open question whether the local effect would fare comparably well. Previous studies using the local-global paradigm have found differences in the local effect between groups of vegetative state and minimally conscious patients (Bekinschtein et al., 2009; Faugeras et al., 2011, 2012). However, the sensitivity of the local effect for patients with higher levels of consciousness seems surprisingly low. In Faugeras and colleagues (2012), for example, only 61.6% of the conscious control patients exhibited a reliable local effect.

One possible reason for not observing a typical MMN response in the local comparison is that it is obscured by other, attention-related components. That is to say, the local-global paradigm does evoke the neural generator of MMN, but it is simply not evident in the final ERPs. The very prominent P3a component following the local effect corroborates this possibility. Another – perhaps even more interesting – possibility has to do with the use of quintlets in the local-global paradigm. Unlike P3b, MMN is not sensitive to the predictability of deviant occurrence (Scherg et al., 1989). It does, however, operate on the basis of objects (Ritter et al., 2000) and thus is influenced by perceptual grouping. Sussman and colleagues (1998) employed very similar quintlet stimuli to the ones used in the local-global paradigm and found that when a repeating AAAAB sound sequence was perceptually grouped together into one auditory object no MMN was evident. Perhaps the same phenomenon occurs in the local-global paradigm and the local effect reflects an N1 effect of selective attention or processing negativity (PN; Näätänen, 1990).

Despite the fact that the local effect does not seem to reflect a typical MMN response it is worth noting that the individual local effects are quite coherent across participants and seem to occur in a sufficiently consistent time window. We expected to observe a clear local effect for all of our participants, and indeed we did (although the results for one participant were only marginally significant). Another positive aspect of the local effect is its high amplitude. Thus, if the aim of a study is to evoke strong and complex neural dynamics reliably within every single participant, the local-global paradigm might be just as good as the Optimum-1.

The learning-oddball paradigm was overall able to evoke a strong and reliable P3b response on the single-participant level. However, one participant out of fifteen did not exhibit any discernible P3b in response to the deviant sounds. Considering how robust the P3b results of the other participants were (and how robust P3b is in general in the normal population), the lack of a P3b for this outlier participant is unlikely to stem from too low signal-to-noise ratio in the data. It is more probable that this participant did not follow task instructions for some reason and consequently did not pay enough attention to the deviant sounds. Previous studies have repeatedly shown that a P3b response can be completely abolished if attention is directed away from the critical stimuli (Polich 2004, Duncan et al., 2009, Bekinschtein et al., 2009). It may therefore be concluded that the learning-oddball paradigm is implemented in

such a way that does not guarantee sufficient task engagement in every case. This is a major problem for patient studies where one cannot assume that all patients are able to continuously focus on a task and pay attention to the relevant stimuli.

The global effect from the local-global paradigm was virtually identical to the P3b component obtained by the dedicated learning-oddball paradigm. These two ERPs were also highly correlated on the single-participant level – once again demonstrating the domain-general nature and high test-retest reliability of P3b (Williams et al., 2005; Perez et al., 2017). Its presence relies first and foremost on the task relevance of the critical stimuli and not on the detailed stimulation parameters. P3b is also known for its high signal-to-noise ratio. As few as 20 trials can already provide an acceptable estimate of the P3b component in healthy participants (Cohen & Polich, 1997). It is therefore not surprising that the learning-oddball paradigm, which comprises only about half the number of deviants compared to the local-global paradigm, still performs comparably well in P3b assessment. This is not to say, however, that the local-global paradigm was able to evoke a reliable P3b in all of the tested participants. Two participants out of fifteen did not exhibit the desired effect. In fact, one of these participants also did not have a P3b in the learning-oddball paradigm. This participant either did not pay attention during the local-global paradigm as well or they may for some reason not exhibit a P3b at all. Whatever the reason may be, the absence of a discernible P3b for two out of fifteen participants indicates a design problem in the local-global paradigm. It may not have sufficient safeguards in place to always guarantee enough task engagement from. As mentioned above, this may become particularly problematic for patient studies.

When we set out to conduct this study, we expected to find a clear MMN, P3b, local, and global effect in all of the tested participants, because they were all healthy volunteers who consented to follow the task instructions. Our expectations were confirmed for the MMN and the local effect. The sensitivity of the P3b/global effect was, however, not as satisfactory. This notwithstanding, the sensitivity of all three paradigms in our study was still comparable to or even higher than the paradigms in previous works (e.g., Jongsma et al., 2013; Bekinschtein et al., 2009; Faugeras et al. 2012). Hence, even though there may be practical limits to the highest sensitivity one might expect for MMN/P3b, considerable improvements may still be achieved by carefully choosing the precise stimulation protocol.

Conclusions

Our results indicate that MMN can be most reliably recorded with a single-purpose oddball sequence optimized for the component of interest. The local effect of the local-global paradigm was markedly different from a traditional MMN response. Thus, caution should be exercised when comparing the local effect with MMN literature – especially in the clinical context. The P3b component was very similar in the single-purpose oddball sequence and the global effect of the local-global paradigm. However, not all participants exhibited a reliable P3b/global effect. Therefore, the sensitivity of these paradigms with regard to the P3b component may not be good enough for a clinical application.

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Figures

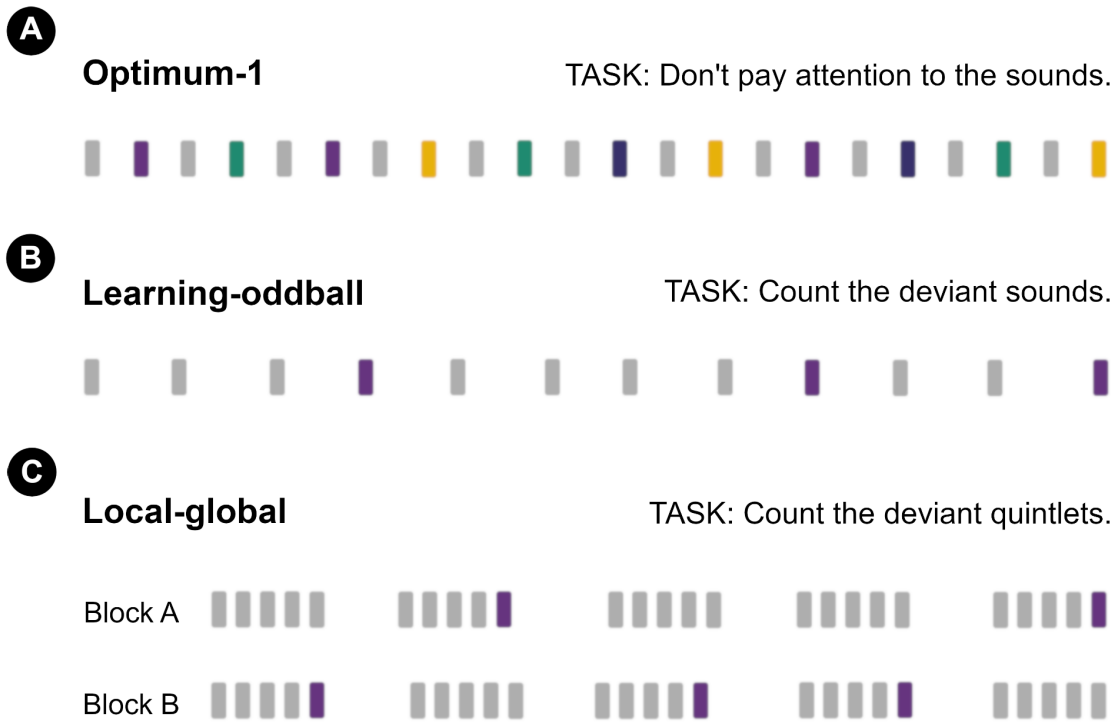

Figure 1. Three oddball paradigms for MMN/P3b assessment.

A. The Optimum-1 paradigm is designed for reliable within-participant MMN assessment. Standard sounds (gray bars) are interleaved with different deviant sounds (colored bars). Four types of deviant sounds are tested – frequency deviants, intensity deviants, duration deviants, and location deviants. The interstimulus interval between all sounds is always 500 ms. The task of the participant is to watch a movie with subtitles and not pay any attention to the sound sequence.

B. The learning-oddball paradigm is designed to evoke the P3b response. Standard sounds (gray bars) are interleaved with rare deviant sounds (purple bars). Only frequency deviants are used in the learning-oddball paradigm. The interstimulus interval between all sounds ranges randomly from 800 to 1200 ms. Participants have to continuously pay attention to the sound sequence and count the rare deviant sounds.

C. The local-global paradigm is a sequence of quintlets, i.e., groups of five sounds presented in quick succession. There are two different quintlets. The AAAAA quintlet

consists of five identical sounds (five gray bars in a row). The AAAAB quintlet consists of four identical sounds followed by a frequency deviant (i.e., a sound that is higher in frequency compared to the first four sounds; depicted as four gray bars followed by a purple bar). The interstimulus interval between quintlets ranges randomly from 800 to 1100 ms. Depending on the block type (Block A or block B), one of the two quintlets occurs often and the other quintlet occurs rarely. This results in two effects. The local effect is simply a contrast between all AAAAB quintlets (i.e., the local deviants) and all AAAAA quintlets (i.e., the local standards). The global effect consists of a contrast between the rare deviant quintlets (i.e., the global deviants) and the common standard quintlets (i.e., the global standards). The task of the participant is to continuously pay attention to the sound sequence and to count the global deviant quintlets.

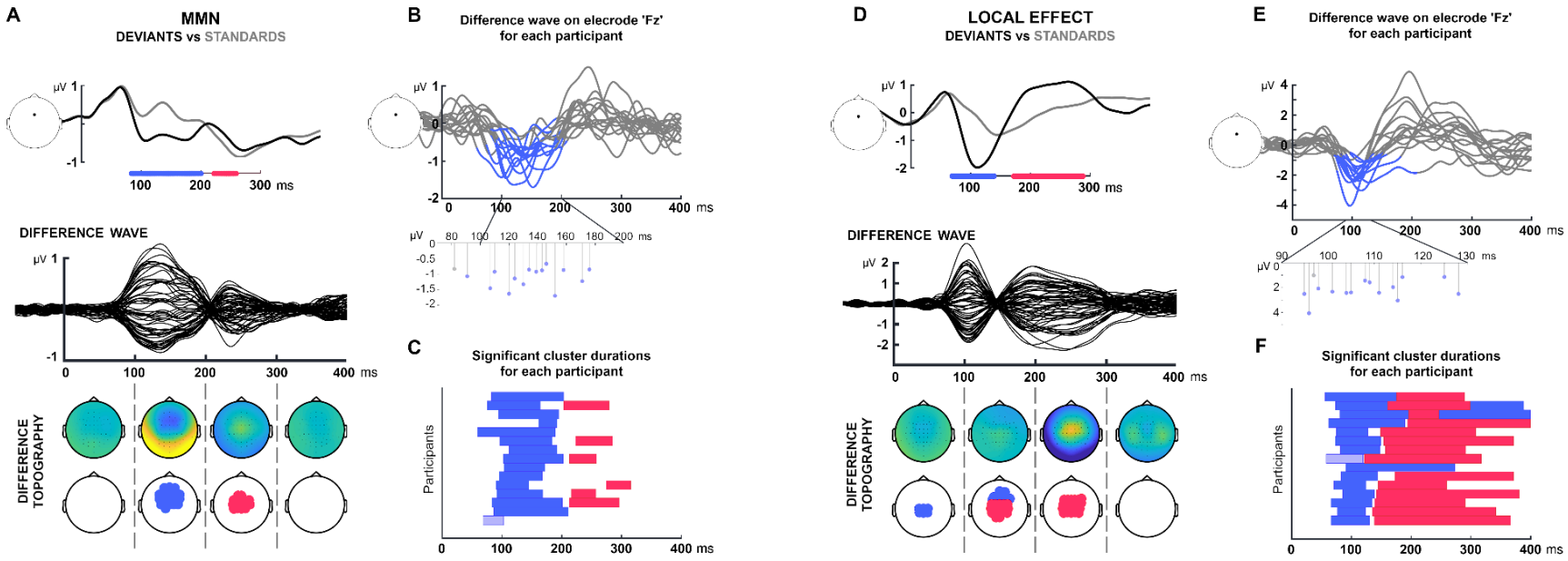
A
MMN
DEVIANTS vs STANDARDS
μV 1
-1
100
200
300 ms
DIFFERENCE WAVE
μV 1
-1
0
100
200
300
400 ms
DIFFERENCE TOPOGRAPHY
B
Difference wave on elecrode 'Fz'
for each participant
μV 1
0
-1
-2
0
100
200
300
400 ms
μV
80
100
120
140
160
180
200 ms
0
-0.5
-1
-1.5
-2
C
Significant cluster durations
for each participant
Participants
0
100
200
300
400 ms
D
LOCAL EFFECT
DEVIANTS vs STANDARDS
μV 1
0
-1
-2
100
200
300 ms
DIFFERENCE WAVE
μV 2
1
-1
-2
0
100
200
300
400 ms
DIFFERENCE TOPOGRAPHY
E
Difference wave on elecrode 'Fz'
for each participant
μV 4
2
0
-2
-4
0
100
200
300
400 ms
90
100
110
120
130 ms
μV 0
2
4
F
Significant cluster durations
for each participant
Participants
0
100
200
300
400 ms

Figure 2. MMN and the local effect.

A. & D. Group-level comparisons between the deviant and standard conditions of the Optimum-1 paradigm (A) and the local deviant and local standard conditions, i.e., the local effect of the local-global paradigm (D). The upper panel shows the grand average deviant condition (black line) and the grand average standard condition (gray line) from electrode 'Fz'. Significant differences from the group-level cluster-based permutation test are highlighted on the x-axis. The middle panel shows the difference wave between deviant and standard conditions across all 62 electrodes. The lower panel depicts the topographies of the difference wave averaged across consecutive 100 ms time windows. Significant differences between the deviant and standard conditions during these time windows are highlighted in the bottom row. The color range of the topographies corresponds to the y-axis of the difference wave depicted in the middle panel.

B. & E. Single participant ERP difference waves from electrode 'Fz' between the deviants and standards of the Optimum-1 paradigm (B) and the local deviants and local standards of the local-global paradigm (E). Significant time points from separate trial-level cluster-based permutation tests for each participant are colored in blue. The lower panel zooms in on the peaks of the individual MMNs/local effects. Each dot marks the MMN/local effect of one participant and describes its peak latency (x-axis) and peak amplitude (y-axis). Note that the two participants whose statistical results were marginally significant are marked with a gray dot as opposed to a blue dot.

C. & F. Summary of the individual cluster-based permutation statistics for each participant (15 in total). The time course of significant negative effects between deviants and standards is depicted as a blue line. The time course of significant positive effects is depicted as a red line. Effect onsets/offset is defined as the first/last time point when at least three electrodes belonging to that cluster showed a reliable difference between deviants and standards. Marginally significant negative effects are colored in a lighter blue.

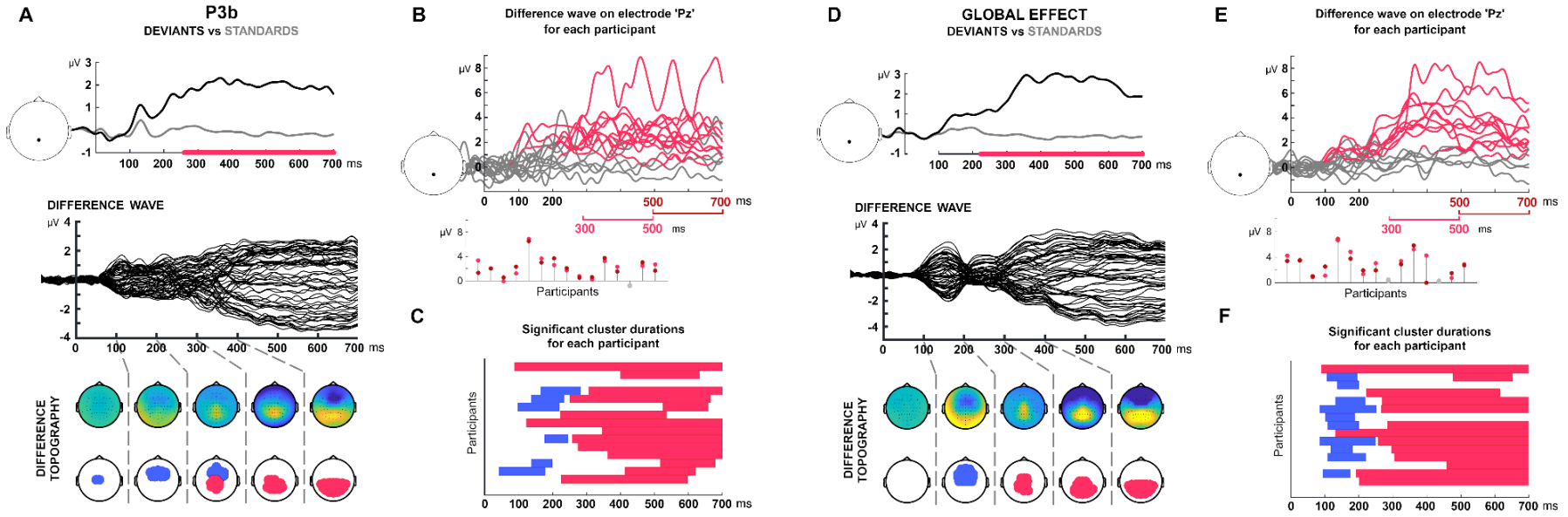
A
P3b
DEVIANTS vs STANDARDS
μV 3
2
1
-1
100 200 300 400 500 600 700 ms
DIFFERENCE WAVE
μV 4
2
-2
-4
0 100 200 300 400 500 600 700 ms
DIFFERENCE TOPOGRAPHY
B
Difference wave on electrode 'Pz'
for each participant
μV 8
6
4
2
0
0 100 200 500 700 ms
300 500 ms
μV 8
4
0
Participants
C
Significant cluster durations
for each participant
Participants
0 100 200 300 400 500 600 700 ms
D
GLOBAL EFFECT
DEVIANTS vs STANDARDS
μV 3
2
1
-1
100 200 300 400 500 600 700 ms
DIFFERENCE WAVE
μV 4
2
-2
-4
0 100 200 300 400 500 600 700 ms
DIFFERENCE TOPOGRAPHY
E
Difference wave on electrode 'Pz'
for each participant
μV 8
6
4
2
0
0 100 200 500 700 ms
300 500 ms
μV 8
4
0
Participants
F
Significant cluster durations
for each participant
Participants
0 100 200 300 400 500 600 700 ms

Figure 3. P3b and the global effect.

A. & D. Group-level comparisons between the deviant and standard conditions of the learning-oddball paradigm (A) and the global deviant and global standard conditions, i.e., the global effect of the local-global paradigm (D). The upper panel shows the grand average deviant condition (black line) and the grand average standard condition (gray line) from electrode 'Pz'. Significant differences from the group-level cluster-based permutation test are highlighted on the x-axis. The middle panel shows the difference wave between deviant and standard conditions across all 62 electrodes. The lower panel depicts the topographies of the difference wave averaged across five consecutive time windows. Significant differences between the deviant and standard conditions during these time windows are highlighted in the bottom row. The color range of the topographies corresponds to the y-axis of the difference wave depicted in the middle panel.

B. & E. Single participant ERP difference waves from electrode 'Pz' between the deviants and standards of the learning-oddball paradigm (B) and the global deviants and global standards of the local-global paradigm (E). Significant time points from separate trial-level cluster-based permutation tests for each participant are colored in red. The lower panel zooms in on the mean amplitudes of the individual P3bs/global effects in two time windows – 300-500 ms depicted in pink and 500-700 ms depicted in maroon. Each dot marks the P3b/global effect of one participant and describes its mean amplitude in the respective time window. Note that the participants who did not exhibit a discernible P3b/global effect are marked with a gray dot as opposed to colored dots.

C. & F. Summary of the individual cluster-based permutation statistics for each participant (15 in total). The time course of significant negative effects between deviants and standards is depicted as a blue line. The time course of significant positive effects is depicted as a red line. Effect onsets/offset is defined as the first/last time point when at least three electrodes belonging to that cluster showed a reliable difference between deviants and standards.