

Assessing mismatch negativity (MMN) and P3b within-individual sensitivity — 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, for acquiring them as EEG markers of consciousness in clinical settings. This may explain why the within-individual sensitivity of MMN/P3b paradigms is often quite poor and why seemingly identical EEG markers can behave differently across Disorders of consciousness (DoC) studies. Here, we compare two traditional paradigms for MMN or P3b assessment with the recently more popular local–global paradigm that 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 than MMN and was followed by a much more prominent P3a. The peak latencies and amplitudes were also not correlated across paradigms. Caution should therefore be exercised when comparing the local effect and MMN across studies. We conclude that the within-individual MMN sensitivity is adequate for both the local–global and a dedicated MMN paradigm. The within-individual sensitivity of P3b was lower than expected for both the local–global and a dedicated P3b paradigm, which may explain the often-low sensitivity of P3b paradigms in patients with DoC.

KEYWORDS

auditory, intra-individual differences, local–global, mismatch negativity, oddball, P3b

Abbreviations: CNV, contingent negative variation; DoC, disorders of consciousness; EEG, electroencephalography; ERP, event-related potential; ICA, independent component analysis; ISI, interstimulus interval; MMN, mismatch negativity; SI, supplementary information; SOA, stimulus-onset asynchrony; TMS-EEG, EEG combined with transcranial magnetic stimulation.

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1 | 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 an 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 patients with DoC (Kondziella et al., 2020). Despite its high specificity, however, resting-state EEG methodology might lack the desired sensitivity to stratify patients with DoC (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 patients with DoC. 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 mismatch negativity (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 and the polarity of the MMN should be reversed over the mastoids during the same latency range when a nose reference is used (André-Obadia et al., 2018; Duncan et al., 2009). Because MMN reflects sensory processing its peak timing and amplitude are known to vary depending on the exact stimulation

protocol including the type, probability, and strength of the deviant sounds, among other variables (e.g., Dürschmid et al., 2016; Lecaigard et al., 2015; Pakarinen et al., 2007). Even MMN sources may differ to some extent for different types of deviance (Lecaigard et al., 2021). According to the original view, a MMN response to auditory deviance is a distinct neural process that is separate from a modulation of the obligatory N1 component, and therefore the MMN peak should also occur later than the N1 peak (it is normally expected between the N1-P2 complex; Näätänen et al., 2011). This notion has been challenged more recently by the predictive coding model and the adaptation model (Heilbron & Chait, 2018; Fong et al., 2020; May, 2021). In practice, however, a clear separation of the MMN from the N1 is impossible to achieve in most cases and therefore it has become common practice to call any early negative effect between 100 and 250 ms a MMN. 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, 1990). Because of 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 patients with DoC have linked the presence of an MMN response to a higher chance of awakening from coma (e.g., Azabou et al., 2018; Fischer et al., 2004). 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 (Boly et al., 2011; Fischer et al., 2010; Kotchoubey et al., 2005; Wijnen et al., 2007). It should be clearly pointed out, however, that in practice the sensitivity of MMN paradigms in clinical studies is generally quite poor (Comanducci et al., 2020; Kondziella et al., 2020). For example, in the study by Fischer et al. (2010), MMN could only be detected in three out of 11 patients in minimally conscious state (27%), and two out of 16 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 (Asanowicz et al., 2020; Verleger, 2020; Verleger et al., 2005). 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 (Duncan et al., 2009).

The size of the P3b component makes its detection very robust — 20 deviant trials are often already enough to observe a 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 patients with DoC (e.g., Estraneo et al., 2020; Fischer et al., 2008, 2010; Kotchoubey et al., 2005; Rohaut et al., 2015; Steppacher et al., 2013). Given these conflicting results, the P3b (as well as MMN) should currently be considered only as a positive predictor in patients with DoC rather than a marker of the presence/absence of consciousness.

Taken together, 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 patients with DoC (Kondziella et al., 2020). However, the sensitivity of these paradigms in patients with DoC is often not satisfactory, and therefore they can only deliver additional information that 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. Thus 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 advantages in the clinical context. First, it could constitute an “all-in-one” 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., 2013, 2013; Sitt et al., 2014; but see also Tzovara et al., 2015). In the study by Faugeras et al. (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, some of them do suggest an improvement to several earlier landmark studies. Therefore the local–global paradigm might offer an attractive paradigm choice for many future assessments of the cognitive capabilities of patients with DoC.

To make an informed choice about which paradigm or combination of paradigms to use in future DoC studies, however, it is necessary to assess directly how the local–global paradigm performs compared with more traditional single-purpose MMN/P3b paradigms. This is relevant for two reasons:

1.1 | Within-individual MMN/P3b sensitivity

For the work at hand, we define within-individual sensitivity of a paradigm as its power to evoke the effect of interest within each individual provided adequate testing

conditions. As described above, the best conditions for obtaining MMN or P3b are somewhat different. MMN is best observed when attention is diverted away from the experimental stimuli (i.e., passive oddball task). To evoke a P3b, the individual has to directly pay attention to the experimental stimuli (i.e., active oddball task). The local-global paradigm is an active oddball task and there is reason to believe that this may reduce the power of this paradigm to evoke the MMN consistently across individuals (see control participants in Faugeras et al., 2012, for example). Furthermore, the active task in the local-global paradigm is somewhat more complicated compared with traditional oddball tasks (the different block types are described in the [Methods](#) section). It has not been assessed directly whether this affects within-individual P3b sensitivity compared with a simpler task. There are of course also many other reasons why the effect of interest may not be observed with a given paradigm. For example, EEG data quality may be too poor. The participant may not be able to detect the deviants, misunderstand the task, or ignore the test entirely. These concerns are particularly relevant in DoC research where testing conditions are often suboptimal and patients cannot directly confirm that they understood task instructions. This is why the within-individual sensitivity of the local-global paradigm and any single-purpose paradigms should be assessed in a healthy sample and under controlled, optimal testing conditions.

1.2 | MMN versus local effect and P3b versus global effect

It was proposed in the seminal work by Bekinschtein et al. (2009) that the local effect captures the typical MMN response and the global effect captures the typical P3b response without any direct comparison with previously published MMN/P3b responses. This is particularly regrettable in the case of the MMN because the MMN response is very sensitive to stimulus parameters such as deviance type, magnitude, statistical regularity, and perceptual grouping (Ritter et al., 2000; Sussman et al., 1998). Given the rather unusual quintlet structure of the stimuli in the local-global paradigm, one might be justified in expecting the local effect to be different from more traditional MMN responses. It has not been characterized, however, to what extent this is the case. If the purpose of a future study is to evoke MMN responses similar to, for example, Fischer et al. (2004) or Kotchoubey et al. (2005), one should know in advance if or to what extent the local-global paradigm is suited for that.

The aim of this study is to address the above-described concerns about the local-global paradigm by

comparing it with two separate paradigms optimized for MMN or P3b assessment, respectively. We do this in a sample of healthy participants in order to establish a baseline to which clinical populations can be compared in the future.

1. First, we assess the sensitivity of all three paradigms on a single participant level. Given that a recording was successfully performed under controlled conditions (i.e., the EEG data quality is good, the session was concluded under reproducible conditions without any unusual events, and without reason to assume that the participant was not following task instructions) we expect to find 100% within-individual sensitivity for all paradigms. If these criteria are fulfilled, there is no reason to expect that MMN/P3b would be absent for a healthy participant.
2. Second, we directly compare the local/global effects to the traditional MMN/P3b effects obtained by dedicated single-purpose paradigms within the same sample of participants and provide a thorough characterization of their commonalities and/or differences.

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.

2 | METHODS

2.1 | Participants

Fifteen participants took part in the study (six male; three 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).

2.2 | Auditory oddball paradigms

2.2.1 | Optimum-1 (for MMN)

A slightly adapted version of the Optimum-1 paradigm (Näätänen et al., 2004; Pakarinen et al., 2007) 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. “The paradigm is based on the assumptions that the MMNs can be independently elicited for different auditory attributes, and that the deviant tones can still strengthen the memory trace of the standard with respect to the stimulus attributes they have in common (Nousak et al., 1996).” (Pakarinen et al., 2007). Optimum-1 is therefore very economical and increases the chance of finding an MMN response for at least one type of deviant sound. Most importantly, the MMNs of the Optimum-1 paradigm correspond very well to the MMNs evoked by one-deviant paradigms (Näätänen et al., 2004). Therefore, even though this particular paradigm has not been previously used in DoC research, it should be fully comparable with the more simplistic one-deviant paradigms with the added benefit of potentially increasing MMN sensitivity.

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. Half of the frequency deviants were higher than the standards (a chord of 609, 1218, and 1827 Hz) and the other half were lower than the standards (a chord of 450, 900, and 1350 Hz). The intensity deviants were 15% softer compared with the standards. The duration deviants were 27 ms shorter than the standards. The location deviants consisted of sounds coming either from the left or the right (with equal probability) whereas the standards always came from the front. The deviant sound parameters correspond to the highest level of deviance tested by Pakarinen et al. (2007).

All sounds were separated by a fixed ISI of 500 ms. Standard and deviant sounds were presented alternately.

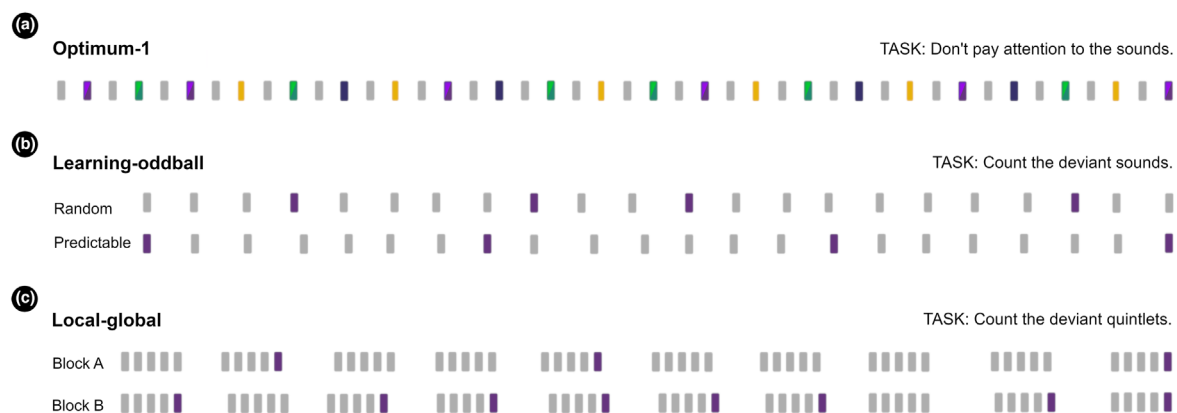


FIGURE 1 Three oddball paradigms for MMN/P3b assessment. **A.** The Optimum-1 paradigm is designed for reliable multi-dimensional MMN assessment. Standard sounds (gray bars) are interleaved with different deviant sounds (colored bars). Four types of deviant sounds are tested — frequency deviants, intensity deviants, duration deviants, and location deviants. The intensity deviants are quieter and the duration deviants are shorter compared with the standard sounds. The frequency deviants are higher or lower compared with the standard sounds, and the location deviants come either from the left or the right instead of the front (with equal probability). This is signified by two-color bars. 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. This paradigm also contains a cyclical predictability manipulation. The first eight deviant sounds are randomly dispersed between standard sounds (top row), followed by eight deviant sounds that are always separated by exactly six standard sounds (bottom row). This cycle of unpredictable and predictable deviants is repeated six times. 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, that is, 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.

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. The total number of sounds for this paradigm was 1450. 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 13.38 min.

2.2.2 | 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 in addition to evoking a robust P3b response, this paradigm is designed to also evoke transient pre-stimulus CNV and a P3b modulation, but only in some trials (see below). Our aim was to use this top-level dynamic to obtain one additional marker of regularity/deviance detection that supersedes the P3b in terms of cognitive engagement (not related to the aim of this study). Since these additional effects are supposed to occur gradually in some trials, their effect on the overall ERP of the deviant condition should be negligible. More importantly, we were not able to replicate the gradual inducement of these effects in our sample (see Figure SI.1 for a comparison of random and predictable deviants). Therefore, the CNV 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 frequency deviants. They were of higher pitch 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 and 1200 ms.

Although all deviants were interleaved with at least two standards the occurrence of deviants was not always unpredictable. The paradigm started out with eight deviants randomly separated by two to 10 (with the exception of six) standards. The following eight deviants were always separated by six 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 eight unpredictable and eight predictable deviants was repeated six 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. The total number of sounds for this paradigm was 682. 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 11.53 min on average.

2.2.3 | 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 five 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 (eight 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 were 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 number of global deviants varied randomly between 22 and 30 per block, and the average number of quintlets was 140 per block (sd = 13.6; range = 120–164). Thus, there were a total of 207 global deviants and 914 global standards, on average, for the entire local–global task. All global deviants were

separated by at least two standards. Each block began with the presentation of at least 10 standard quintlets to establish their regularity. The total number of quintlets for this paradigm was 1121 on average and the total number of sounds was therefore 5605 on average. Experimental blocks were separated by 5 s of silence to signify block change. There was also an additional break between blocks 4 and 5 (after ca. 15 min 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 four blocks. The total duration of the local-global task was 33.33 min on average (including a short break).

2.3 | Overall procedure

The paradigms were written in Matlab, using the Psychophysics Toolbox extensions (Brainard, 1997; Kleiner et al., 2007; Pelli, 1997) and the PSYCHOACOUSTICS toolbox (Soranzo & Grassi, 2014), 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 three 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 three oddball paradigms took ca. 70 min 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 min.

2.4 | Behavioral performance

Participants were monitored throughout the session to make sure that they remained eyes open and awake. There was no task for the Optimum-1 paradigm besides watching a movie. After the paradigm had finished, participants were asked to give a short recap of what they had seen and all participants were able to describe the movie accurately in a couple of sentences. For the learning-oddball and the local-global paradigm, participants had to count the rarely occurring deviants. Table 1 in SI.2 lists the individual deviant counts for both paradigms. For the learning-oddball, 94.6 out of the actual 96 deviants were counted on average. The average counting error was 3.5% (sd = 3.8, range = 0 to 13%). For

the local-global paradigm, the average counting error was 8.9% (sd = 6, range = 1 to 22%). It can be concluded that all participants followed the task instructions and paid attention to the rare deviants in the learning-oddball and the local-global paradigms. It should be noted, however, that one participant had a relatively high counting error in both tasks and it is therefore likely that they did not follow the task instructions well enough. Although it is impossible to determine what exactly this participant was doing differently.

2.5 | EEG

2.5.1 | 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, in line with previous EEG acquisitions performed by our group. Horizontal eye movements were recorded by two additional electrodes placed at the outer canthi of the eyes. Impedances were kept below 10 k Ω whenever possible. Data were sampled at 2500 Hz and filtered between 0.1 and 250 Hz.

2.5.2 | 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 20,221,118), 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. No additional high-pass filter besides the hardware filter of 0.1 Hz was applied for the learning-oddball and the local-global paradigms. All data were subsequently down-sampled to 1000 Hz and low-pass filtered with a 30 Hz cutoff.

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 were baseline-corrected for 100 ms before stimulus onset.

2.5.3 | Experimental conditions

We planned to conduct four contrasts between standard and deviant conditions: one for the Optimum-1, one for the learning-oddball, and two for the local-global paradigm. 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-individual 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 out of 720 trials on average; SD = 22; range = 633–706, corresponding to 88–98% of all available trials). The deviant condition was composed of all trials where a deviant sound – irrespective of deviant type – was played (664 out of 720 trials on average; SD = 23; range = 625–705, corresponding to 87–98% of all available trials). The four different deviant types were aggregated into one overall deviant condition for the main analysis because the MMN responses were generally very similar across deviant types (see SI.4 for a detailed investigation of the differences/similarities between deviant types). It is however possible to also perform an MMN analysis for each of the four deviant types separately albeit with weaker within-individual sensitivity due to the reduced number of trials. The results of these separate analyses are detailed in SI.3.

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 ($m = 88$ out of 96; SD = 6; range = 74–94, corresponding to 77–98% of all available trials). The standard condition was composed of all trials where the standard sound was

played ($m = 520$ out of 576; SD = 33; range = 457–560, corresponding to 79–97% of all available trials).

Four conditions were available from the local-global paradigm: local standard global standard condition (LSGS; $m = 405/453$, SD = 31, range = 343–445, 79–94%), local deviant global standard condition (LDGS; $m = 412/460$, SD = 32, range = 320–456, 75–97%), local standard global deviant condition (LSGD; $m = 93/103$, SD = 8, range = 74–103, 74–97%) and local deviant global deviant condition (LDGD; $m = 94/104$, SD = 9, range = 70–105, 73–99%). 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.

2.5.4 | Inferential analysis

Nonparametric cluster-based permutation tests (Maris & Oostenveld, 2007) were carried out for each paradigm and each participant separately. For within-individual 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. For example, 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 10,000 random permutations of the data. All alpha levels were set at 0.05 (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. For MMN, it is classically even recommended to record EEG with the nose reference in order to verify the obligatory reversal of the component over mastoids (André-Obadia et al., 2018; Duncan et al., 2009). We chose to record data with the forehead reference and re-reference to the average because we wanted to stay as close as possible to the local–global methodology. To our knowledge, the local–global data has never been acquired with a nose reference but the data is always average-referenced during preprocessing. As a consequence of this choice, all auditory ERPs are approximately half the amplitude of their mastoid-referenced equivalents. Nevertheless, the obligatory mastoid reversal is clearly visible for the MMN/local effect in this study. Second, because of 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.

In addition to the cluster-based permutation tests we also performed paired t-tests and Pearson correlation analysis on peak amplitudes and peak latencies of the effects of interest on electrode “Fz” or “Pz”. Most of these results are detailed in the SI.

3 | 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-individual sensitivity. Then the paradigms are compared in terms of the neural dynamics they evoke.

3.1 | Individual effects

3.1.1 | MMN

The Optimum-1 paradigm evoked a traditional MMN effect, which is well exemplified by the group-level analysis (Figure 2A). The MMN consisted of a systematically more negative response to deviant sounds compared with standard sounds on a cluster of frontal electrodes with a concurrent inversion at the mastoids. The peak latency of the group-level MMN at electrode “Fz” was 136 ms with

a peak amplitude of $-0.84 \mu\text{V}$. SI.3 contains the MMN analyses for each of the four different deviant types of the Optimum-1 paradigm separately. These analyses confirm that the paradigm evokes a very similar MMN effect for each deviant type within the normal latency range of 100–250 ms.

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 (Figure 2C). Additional analyses (C panels in SI.3 figures) 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-individual sensitivity for the MMN effect. The average peak latency of the individual participants’ MMN at electrode “Fz” was 133 ms ($SD = 28$, range = 82–176), and the average peak amplitude was $-1.09 \mu\text{V}$ ($SD = 0.33$, range = -0.62 to -1.76). 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 six participants (Figure 2C).

3.1.2 | 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 with a concurrent inversion at the mastoids. The peak latency of the grand average local effect at electrode “Fz” was at 105 ms with a peak amplitude of $-1.9 \mu\text{V}$. This early negative effect was swiftly followed by a prominent P3a on central electrodes. The group-level comparison exemplifies both effects (Figure 2D).

Within-individual 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 (Figure 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 $-2.12 \mu\text{V}$ ($SD = 0.8$, range = -1 to -4). Figure 2E illustrates the individual values. We conclude that the local–global paradigm

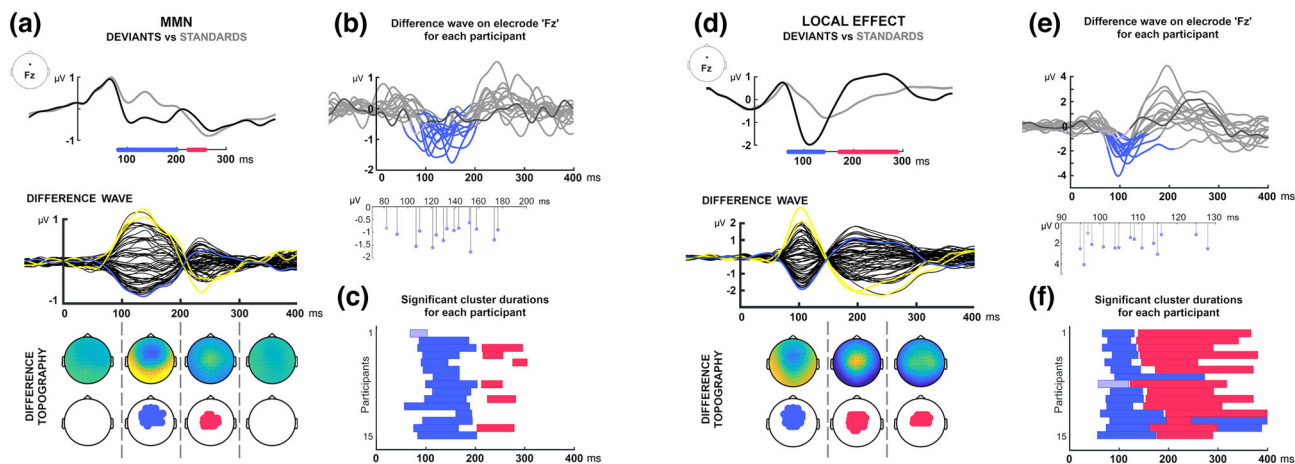


FIGURE 2 MMN and the local effect. **A. & D.** Group-level comparisons between the deviant and standard conditions of the Optimum-1 paradigm (A) and the local deviant and local standard conditions, that is, the local effect of the local–global paradigm (D). The upper panel shows the grand average deviant 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. Electrode “Fz” is highlighted with blue and the mastoids are highlighted with yellow to demonstrate polarity reversal. 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 participants with a marginally significant result are highlighted by a darker trace. 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.

exhibited satisfactory within-individual sensitivity for the local effect. Even though the P3a is not considered a part of the local effect per se, it is worth noting that in this paradigm it was very strong. On the single-participant level, this effect was reliably observed for 14 out of 15 participants (Figure 2F).

3.1.3 | P3b

The learning-oddball paradigm evoked a traditional P3b component for the deviant sounds compared with the standard sounds. This late effect on parietal electrodes is well exemplified by the group-level results (Figure 3A). The grand average P3b started between 200 and 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-individual comparisons between deviants and standards revealed a reliable P3b for 14 out of

15 participants (Figure 3C). Visual inspection of the outlier participant’s ERP confirmed that a P3b was indeed completely absent for this individual. This could potentially be related to the fact that this participant had relatively low task performance compared with other participants in this task, that is, error in the number of deviants counted (13%; see SI.2). It is therefore possible that the participant did not pay attention to the task consistently enough to evoke a reliable P3b. The other participants’ P3b components were very reliable and 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 and 500 ms (SD = 1.72, range = 0–6.86) and 2.34 μV between 500 and 700 ms (SD = 1.61, range = 0.51–6.51). Figure 3B and C illustrate the individual values. We conclude that if objective task performance is not taken into account, the learning-oddball paradigm did not exhibit satisfactory within-individual sensitivity for the P3b effect, because the P3b could not be evoked for

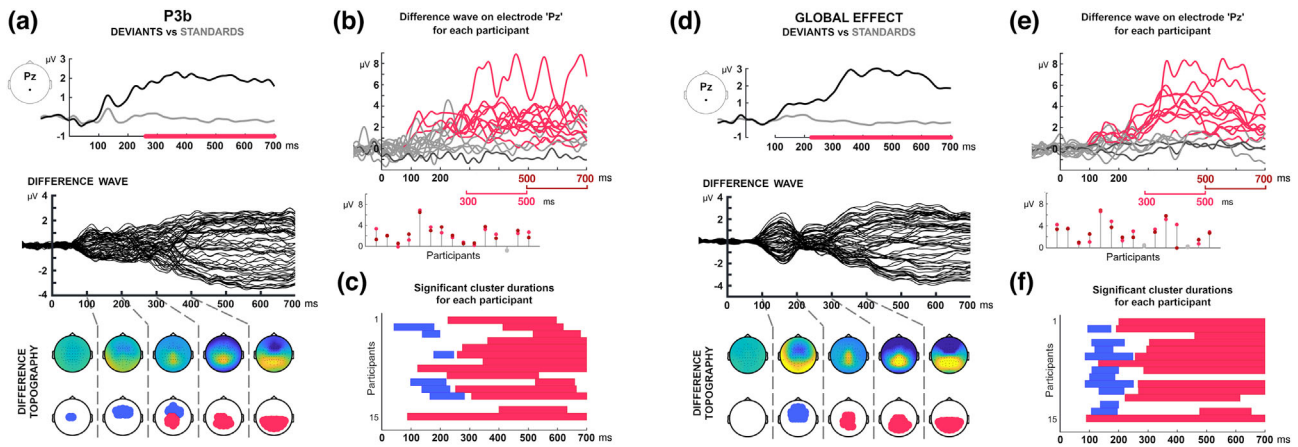


FIGURE 3 P3b and the global effect. **A. & D.** Group-level comparisons between the deviant and standard conditions of the learning-oddball paradigm (A) and the global deviant and global standard conditions, that is, the global effect of the local–global paradigm (D). The upper panel shows the grand 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 participants without a significant result are highlighted by a darker trace. 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.

one participant with this paradigm. If objective task performance were to be taken into account, however, then the learning-oddball paradigm would exhibit satisfactory within-individual sensitivity in this sample.

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. On the single-participant level, this frontal negative effect reliably preceded the P3b in only six out of 15 participants (Figure 3C).

3.1.4 | 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 and 300 ms after stimulus onset and continued until the end of the tested time period (Figure 3D). Its mean amplitude on electrode “Pz” was 2.69 μV between 300 and 700 ms.

Within-individual comparisons between global deviants and standards revealed a reliable global effect for 13 out of 15 participants (Figure 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. Again, the task performance for this participant was low in the local–global task as well (see SI.2). The other participant, however, had good task performance on both tasks. Their lack of a P3b is therefore unlikely to be due to poor or inconsistent attention. The other 13 participants’ global effects were very reliable and 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 and 500 ms (SD = 1.83, range = 0.74–6.62) and 2.89 μV between 500 and 700 ms (SD = 1.87, range = 0–6.85). Figure 3E and F illustrate the individual values. We conclude that the local–global paradigm did not exhibit satisfactory within-individual sensitivity for the global effect, because the global effect could not be evoked for two participants with this paradigm. Some of it is likely due to low task performance, that is, if task

performance were to be taken into account then within-individual sensitivity would be better. This may not be the only limiting factor however because one participant did not have a reliable P3b response despite good objective task performance.

Similar to the learning-oddball paradigm, the group-level comparison revealed an additional early negative effect very similar to the MMN on frontal electrodes for the local-global paradigm. On the single-participant level, this frontal negative effect reliably preceded the global effect in 10 out of 15 participants (Figure 3F).

3.2 | Comparisons between effects

3.2.1 | 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 13 out of 15 participants (by an average of 25 ms, $SD = 30$, range = -29 to 76 ms). Second, the local effect seems to be overshadowed by a very strong P3a component. The P3a is considerably smaller in amplitude for the Optimum-1 paradigm and it occurs later. 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 35–125 ms after stimulus onset. This is followed by a positive difference on frontal electrodes between 136 and 304 ms. There is also no correlation between the individual MMN peaks and local effect peaks — neither in terms of latency nor amplitude ($r = -0.02$, $p = 0.96$ and $r = 0.08$, $p = 0.77$, respectively; see SI.5). One possible reason for these striking differences between the Optimum-1 MMN and the local effect might be that the former effect is an aggregate of four different types of deviants whereas the latter was only evoked by frequency deviants. Perhaps the local effect is only similar to the frequency deviants in the Optimum-1 paradigm but not the other three deviant types. A comparison between each of the four MMNs with the local effect separately might partially support this possibility (SI.6). Whereas the local negative effect is much stronger in the early time window around 100 ms compared to the other three deviant types, this difference is only marginally significant compared to the frequency deviants (but this may be due to one outlier participant; see upper right panel in figure SI.6.2). Nevertheless, there is still no correlation between the individual MMN peaks and local effect peaks — even if only the frequency deviants are

considered (SI.6.2). But perhaps most importantly, the prominent P3a response that promptly follows the early negativity in the local effect is clearly much stronger compared to all Optimum-1 deviant types already in the typical MMN time window of 100–200 ms. It can therefore be concluded that the local effect from the local-global paradigm is generally not very well comparable to the MMN evoked by the purpose-built Optimum-1 paradigm, but this difference is likely amplified by the very strong P3a response that overshadows the local effect.

3.2.2 | 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; see figure SI.5). 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 MMN effects in this comparison seem not to be systematically different across participants.

4 | DISCUSSION

Both MMN and P3b are well-described ERP components with a potential for clinical application in DoC. 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 was not yet clear whether the responses evoked by the local–global paradigm indeed reflect the more traditional MMN and P3b components previously described in the literature in terms of within-individual sensitivity and effect characteristics. Verifying these aspects was the primary aim of the present study.

First, the within-individual sensitivity was assessed for the local–global paradigm and two separate oddball paradigms optimized for evoking MMN or P3b, respectively. We were most interested in its sensitivity for the local effect because previously published data (e.g., Faugeras et al., 2012) and the above-outlined discrepancies concerning optimal MMN paradigm design gave cause to question whether the local–global paradigm is as good as a dedicated MMN paradigm in evoking this early negative effect. Similarly, we wanted to check whether the relatively more complicated design of the active oddball task in the local–global paradigm may be detrimental to P3b sensitivity compared to a simpler task. Contrary to our expectations, the results indicate that the within-individual sensitivity of the local–global paradigm is comparable to a single-purpose MMN paradigm. Both the local effect and the MMN were evoked for all participants in the current sample (although the effect of interest was marginally significant for one participant with each paradigm). The within-individual sensitivity for the P3b was not as good. A reliable P3b was evoked for only 13 out of 15 participants with the local–global paradigm and for 14 out of 15 participants with the single-purpose P3b paradigm. Possible reasons for the relatively low P3b sensitivity are discussed below. 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., Bekinschtein et al., 2009; Faugeras et al., 2012; Jongsma et al., 2013). 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.

The second set of analyses in this study directly compared the local effect to the more common MMN and the global effect to the more common P3b within the same sample of participants. We were most interested to see to what extent the local and global effects might differ from more common MMN/P3b effects in terms of effect characteristics such as peak amplitude and latency. This would help to better compare the different results reported in previously published studies. Because the MMN is very sensitive to stimulation parameters, systematic differences between the local effect and a MMN from a different paradigm should be expected (we thank both Reviewers for pointing this out). This was indeed the

case, but the results also demonstrate the rather large extent of differences between the two paradigms (discussed in more detail below). The P3b effect, on the other hand, was virtually identical for the local–global paradigm and the other single-purpose paradigm tested.

The fact that the local–global paradigm and the learning-oddball paradigm evoke very similar P3b responses once again confirms the domain-general nature and high test–retest reliability of P3b (Perez et al., 2017; Williams et al., 2005). 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 should be good news for DoC research where the recording conditions are challenging and prolonged EEG experiments are often not feasible. However, any paradigm worth considering for clinical application should at least evoke the signal of interest reliably in healthy control participants provided adequate testing conditions. The results of this study indicate that P3b paradigms may not perform sufficiently well in that regard, that is, their baseline within-individual sensitivity is difficult to determine.

Probably the main reason why some participants may not exhibit a reliable P3b effect has to do with task engagement. It has been repeatedly shown that a P3b response can be completely abolished if attention is directed away from the critical stimuli (Bekinschtein et al., 2009; Duncan et al., 2009; Polich, 2007). In healthy participants, covert task engagement can be verified to some extent by asking them to report how many deviants they counted during the experiment. If a participant's objective task performance (i.e., the correctness of the reported trial count) is very poor, likely, they may not exhibit a reliable P3b. This was demonstrated by one participant in our study who had relatively poor task performance on both active oddball tasks and also did not exhibit a P3b for either paradigm. All participants who exhibited a reliable P3b had comparably better objective task performance. However, the opposite was not quite true. There was one participant in our sample who had good objective task performance yet still, no reliable P3b could be found for the local–global paradigm. This raises the question of how well objective indicators of task engagement really reflect covert attention. Or put differently, how much attention is effectively necessary to obtain a P3b response? This study is not equipped

to address this point. A targeted investigation in a larger sample would be needed to conclusively answer the question.

There is also an alternative, related reason why at least one participant did not exhibit a P3b response for the local–global paradigm. The stimulus design plus block structure of this task is a bit more complicated compared to typical active oddball tasks in DoC research. Participants may be more likely to sometimes get confused by this paradigm and if even healthy young participants may have trouble following the task, the issue is likely to be even more consequential in patients with DoC. Future studies should therefore carefully consider the precise aim and target participant/patient group, and deliberate whether the local–global task may suffer from too complicated task requirements. In addition to the more common oddball tasks such as the learning-oddball paradigm (the predictability manipulation can safely be removed) there are new and improved alternatives with simpler task instructions available. The Act-Pass protocol (Morlet et al., 2023), for example, makes use of attentional EEG markers to assess compliance with verbal task instructions directly, constituting a promising new avenue in DoC research.

The MMN does not require an active task and participants do not need to pay attention to the experimental stimuli (Näätänen, 1990). This is an advantage, particularly in DoC research. On the other hand, MMN is not domain-general like the P3b and the response can be influenced by many factors of the stimulation protocol. The choice of paradigm and stimulus parameters is therefore much more relevant. The results of this study indicate that even though both the local–global and the Optimum-1 paradigms have good within-individual sensitivity for MMN, the respective MMN responses are evidently quite different from each other. The MMN evoked by the Optimum-1 paradigm is more common compared to previously published DoC studies (although as rightly pointed out by Reviewer 1 “there is not such a thing as a typical MMN response”). The MMN evoked by the local–global effect is somewhat more unusual because it peaks very early (although still within the typical MMN range) and is promptly followed by a prominent P3a.

There are potentially several explanations for these differences. One possibility is that the quintlet grouping of the sounds in the local–global paradigm induces stronger habituation of the standard sound and therefore the MMN response to the deviant sound is larger in magnitude. Increasing deviance magnitude typically decreases MMN latency, which is why the local effect may peak so early (Pakarinen et al., 2007). On the other hand, the quintlet grouping might also have a different consequence. MMN is known to operate on the basis of objects

(Ritter et al., 2000) and thus is influenced by perceptual grouping. Sussman et al. (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. But if the local effect is not a MMN, what is it? We propose that it could potentially reflect an N1 effect of selective attention or processing negativity (PN; Näätänen, 1990). The current study is however in no way equipped to test this hypothesis and so it remains a speculation. Note also that the differentiation between N1 and MMN has been put into question (Heilbron & Chait, 2018; May, 2021), so it is possible that they reflect the same neural processing steps despite differences in latency.

Finally, one possible reason for not observing a more common 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 so well visible in the final ERPs. The very prominent P3a component following the local effect corroborates this possibility. This is to some extent also expected. The local–global paradigm incorporates an active oddball task and it is implied that participants have to pay attention to the quintlets. Perhaps the design idea of orthogonality between the local and global deviance levels does not work perfectly in practice. Note, for example, that in addition to having a strong P3a in the local contrast, there is also a MMN effect in the global contrast (the same is true for the learning-oddball contrast between deviants and standards). Together, these observations suggest that MMN and P3b should perhaps not be conceptualized as orthogonal effects but rather as intricately intertwined hierarchical markers of unexpected deviance processing in the brain. For practical reasons, it may therefore make sense to also include the P3a as part of the expected local effect and not only concentrate on the early frontal negativity. Be as it may, this study demonstrates the extent of differences between a more common MMN in DoC research and the local effect. The results suggest that care should be taken when comparing the local effect to other studies employing more standard oddball sequences.

5 | CONCLUSIONS

The results of this study indicate that the within-individual sensitivity of the local–global paradigm for the MMN (i.e., the local effect) is comparable to a single-purpose oddball sequence. Both paradigms evoked the

MMN reliably in all participants. The local effect of the local–global paradigm was notably different from a more traditional MMN response, however. Thus, caution should be exercised when comparing the local effect with earlier MMN literature. 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 within-individual sensitivity of these paradigms with regard to the P3b component may constitute a serious limiting factor for research — especially in the clinical context.

AUTHOR CONTRIBUTIONS

RR: conceptualization, methodology, investigation, project administration, software, data curation, resources, formal analysis, visualization, writing – original draft, writing – review & editing; CF: investigation, project administration, formal analysis, writing – review & editing; MM: conceptualization, methodology, funding acquisition, resources, supervision, writing – review & editing; SS: conceptualization, methodology, funding acquisition, resources, supervision, writing – review & editing.

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CONFLICT OF INTEREST STATEMENT

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.

DATA AVAILABILITY STATEMENT

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

PEER REVIEW

The peer review history for this article is available at <https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/ejn.16302>.

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