Title: The Many Facets of Mismatch Negativity

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The brain's responses to deviant stimuli continues to pose an important question for both basic and clinical research. Mismatch Negativity (MMN), an event-related potential (ERP) that occurs when a sequence of standard auditory stimuli, for example, is interrupted by a stimulus that differs in certain stimulus dimensions, such as pitch or duration, continues to attract particular attention. This is because deciphering the mechanisms underlying MMN-responses may hold wider clues into how the brain implements algorithms for cortical computations as well as provide insights into circuit dysfunctions in clinical conditions, such as schizophrenia (ScZ). Specifically, evidence has accumulated over the last decades suggesting that MMN-impairments may constitute a biomarker in ScZ that allows important links with alterations in glutamatergic neurotransmission, especially N-methyl-D-aspartate (NMDA) receptors [1]. Accordingly, furthering the understanding of the circuitry that gives rise to MMN-response is of crucial importance for both basic and clinical research.

The paper by Lakatos et al. [2] provides intriguing and novel evidence on the mechanisms of MMN-generation that is obtained through a combination of surface electroencephalographic (EEG) and laminar-recordings from primary auditory cortex (A1) and thalamic areas in awake-behaving monkeys, careful control of stimulus-parameters and a pharmacological manipulation targeting NMDA-receptors. The recordings from thalamic sites are particularly noteworthy for the following reasons: 1) Generating mechanisms of the MMN-response have been so far largely confined to auditory areas and the contributions of thalamic generators is unclear and 2) The authors tested distinct, thalamic projection systems (leminiscal projection, non-leminiscal system, pulvinar) and their role in the generation of the MMN-response that allowed to address different models of MMN-generation. Specifically, the authors tested whether MMN-responses can be fully explained by a difference in sensory stimulus-specific adaption (SSA), a response decrement that would be larger to the repeated standard than the rare deviant stimulus presentation.

Interestingly, SSA was found for responses to standard sounds in A1 but not in the thalamus while both A1 and thalamic multi-unit activity (MUA) were characterized by enlarged responses to deviant stimuli. Furthermore, whereas the SSA response in A1 was frequency-specific, the deviance-related (MMN) A1-MUA response was not. Importantly, SSA occurred only in A1 layer 4 regions receiving core leminiscal thalamocortical input, whereas the deviance-related A1-MUA was present mostly in supra- and infra-granular layers receiving input from the matrix (non-leminiscal) projection system. Thus, SSA and MMN responses were clearly separable at multiple levels.

The authors also recorded surface MMN responses, which are important for translation of the current findings to human EEG-research. Comparisons between surface EEG and laminar data suggested a particularly strong contribution from supra-granular A1 responses to MMN generation. Moreover, analysis of intertrial-phase coherence (ITC) and amplitude differences indicated the contribution of a theta-band (6-9 Hz) phase-reset mechanism of ongoing oscillations as the driving component of deviant detection. Finally, following administration of a subanesthetic dose of ketamine, a significant suppression of MMN-amplitudes was found in A1 and dorsal and medial nuclei of the medial geniculate body (MGBd/m) and diminished theta-band ITC responses were observed. Together, these data support a strong contribution of non-leminiscal thalamic and supra-granular A1 layer 1 contribution to surface MMN responses.

These data have important implications for both our understanding of MMN-generation in general as well as for understanding MMN deficits in clinical populations. In terms of MMN generation, basic science so far has highlighted the contribution of auditory cortex, in particular Heschl's gyrus and superior temporal gyrus, as the primary source of the scalp-recorded MMN, with some contribution from right frontal cortex regions. However, the potential contribution from subcortical sources, such as the thalamus, has remained unclear. In

part, this is because thalamic sources are difficult to detect with conventional EEG/MEG-approaches because of their closed-field orientations and their distant location from surface-recordings.

The findings by Lakatos and colleagues, however, suggests a strong contribution of thalamic nuclei, especially those projecting through the non-leminiscal MGBd/m system to supra- and infra-granular layers of the cortex. Thus, MMN-signals observed in human EEG-data are likely to reflect a more extensive network than previously assumed. These data are also consistent with the re-evaluation of the thalamus as a crucial node involved in higher cognitive processes, such as attention, as opposed to earlier formulations that viewed the thalamus as a passive relay station [3].

The stronger contribution of the non-leminiscal matrix compared to core leminiscal thalamocortical circuitry and the clear separation of SSA and deviance responses have potential implications for current models of MMN generation. An alternative account to the SSA-model is the predictive coding account which assumes that the MMN is not a passive response to incoming stimuli but instead involves active predictions [4]. From this perspective, the MMN is thought to reflect the prediction and prediction error response that occurs when the input differs from the learned predictions. In a recent study [5], we provided importance evidence for this hypothesis by demonstrating that the ScZ-patients did not show MMN-responses to omitted standard tones that were embedded in an oddball-paradigm, suggesting a failure in inferential mechanisms as one important component of MMN-deficits in ScZ.

Importantly, error signals and internal model adjustments involve distinct cortical layers, with error signal associated mostly with input layer 4 and the model adjustment activity most strongly with layers 2/3 of auditory cortex [6]. However, as shown by Lakatos and colleagues,

not only is SSA a frequency-specific effect that is separable from the MMN deviance-response, the authors also did not find any deviance-related response in either core leminiscal thalamic nuclei or input layer 4 of the auditory cortex. The main contribution was the matrix thalamocortical input to supragranular cortical layers. Although the current data do not suggest that the mechanisms underlying the generation of MMN-response are completely independent from SSA, MMN-mechanisms might be much less dependent on bottom-up signals than previously proposed.

In the current study, MMN-responses were shown to be closely correlated with phase-locking of theta-band oscillations that are consistent with recent findings from visual MMN-data [7]. Given the importance of oscillatory signatures for message passing in hierarchical networks, it would be potentially important to further extend this line of investigation to incorporate investigations into layer-specific functional connectivity between A1 and thalamus. In visual cortex, for example, there is consistent evidence that feedforward (FF) mediated activity (carried by gamma oscillations) arrive predominantly in layers 3/4 while feedback (FB) processes that reflect top-down mediated predictions (communicated through alpha/beta oscillations) arise predominantly in infragranular layers and preferentially terminate in superficial outer layers and infragranular deep layers [8]. Indeed, while the majority of the work on neural signatures of FF vs. FB processing has been in the visual modality, layer-specific information flow and distinct spectral signatures of FF vs. FB activity extend also to auditory networks. The current findings could thus inspire new directions in studying circuit-level aspects of auditory MMN responses in humans.

Both MMN-amplitude and theta-band ITPC were prominently reduced by administration of Ketamine, an antagonist of the NMDA-receptor, that is also crucially involved in the pathophysiology of schizophrenia. While these findings thus provide further evidence for the crucial role of glutamatergic mechanisms in deviance detection, future studies may also

investigate the role of distinct GABAergic interneurons in MMN-generation. Major contribution of somatostatin-containing (SOM+)-interneurons to MMN-responses and associated theta-band oscillations have been shown in rodent visual cortex [7]. Importantly, both SOM- and parvalbumin-containing (PV+) - interneurons are prominently affected in ScZ [9]. Since MMN-responses were primarily generated in superficial layers that are particularly densely populated by SOM+-interneurons [10], in contrast to PV+ interneurons that are most prominent in layer 4, the current study provides further evidence for the role of SOM-interneurons in MMN-generation and its impairment in ScZ.

Finally, the impressive work by Lakatos et al. also highlights the importance of linking electrophysiological research in humans with invasive recordings. A fundamental advantage of electrophysiological research over other imaging modalities is the fact that the neural signatures obtained can be mapped one-to-one onto the underlying circuitry and thus allow a mechanistic understanding of the signals obtained in human electrophysiological recordings. This is a crucial pre-requisite for translational research aimed at identifying neurobiologically informed treatment approaches. The data by Lakatos et al. impressively shows that detailed mapping of circuit dynamics underlying MMN-response reveals unknown complexities and phenomena that can only be indirectly accessed using conventional EEG/MEG-recordings. With this novel information, it may be possible in the future to uncover more precise explanatory models of MMN-deficits in ScZ and other mental disorders that could pave the way for a truly mechanistic understanding of circuit dysfunction in psychiatry.

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