Impairment in Predictive Processes during Auditory Mismatch Negativity in ScZ: Evidence from Event-Related Fields

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Abstract

Patients with schizophrenia (ScZ) show pronounced dysfunctions in auditory perception but the underlying mechanisms as well as the localization of the deficit remain unclear. To examine these questions, the current study examined whether alterations in the neuromagnetic mismatch negativity (MMNm) in ScZ-patients could involve an impairment in sensory predictions in local sensory and higher auditory areas. Using a whole-head MEG-approach, we investigated the MMNm as well as P300m and N100m amplitudes during a hierarchical auditory novelty paradigm in 16 medicated ScZ-patients and 16 controls. In addition, responses to omitted sounds were investigated, allowing for a critical test of the predictive coding hypothesis. Source-localization was performed to identify the generators of the MMNm, omission responses as well as the P300m. Clinical symptoms were examined with the Positive and Negative Syndrome Scale (PANSS). Event-related fields (ERFs) to standard sounds were intact in ScZ-patients. However, the ScZ-group showed a reduction in the amplitude of the MMNm during both local (within trials) and global (across trials) conditions as well as an absent P300m at the global level. Importantly, responses to sound omissions were reduced in ScZ-patients which overlapped both in latency and generators with the MMNm sources. Thus, our data suggest that auditory dysfunctions in ScZ involve impaired predictive processes that involve deficits in both automatic and conscious detection of auditory regularities.

Keywords: Schizophrenia, Auditory Perception, Magnetoencephalograpghy, Sensory Predictions

Introduction

Current theories of perception suggest that neural circuits are not passive recipients for information from the external world but actively predict the causes of sensory inputs (Rao and Ballard 1999; Friston 2010). From this perspective, internal models that represent the knowledge and beliefs about the outer world are used to generate predictions that are compared with novel incoming inputs (Friston 2008). Only the difference between the incoming sensory inputs and the predictive signal, the prediction error, is transmitted to the next stage of processes where it leads to an adjustment of the internal model (Winkler, Cowan et al. 1996; Winkler and Czigler 2012).

One prediction error signal that is particular suited to examine predictive coding and its impairments is mismatch negativity (MMN), an event-related potential (ERP), which is elicited when the brain detects that an established pattern in sensory input has been violated. According to predictive coding models, the MMN is thought to reflect the prediction error response that occurs when the input differs from a predicted event (Garrido, Friston et al. 2008; Wacongne, Changeux et al. 2012). In line with the idea of a hierarchy of internal models which transmit predictions in a top-down fashion to lower sensory areas (Friston 2008), empirical evidence shows the existence of several auditory MMN generators, localized in primary and secondary auditory cortices, as well as in temporal, parietal, and frontal regions (Garrido, Friston et al. 2008; Recasens, Grimm et al. 2014).

A critical test of the predictive coding account of MMN-responses is the use of experimental conditions that include the unexpected omission of an auditory stimulus in a sequence of standard tones. For the omitted tone, an electrophysiological response should be similar to that of a deviant tone as the omitted sound violates the internal model of an upcoming auditory event. Because of the lack of active generation of stimulus-specific sensory representation in this scenario, omission responses are more difficult to accommodate within a passive adaption model of MMN responses (Wacongne, Changeux et al. 2012).

Understanding the neural mechanisms underlying predictive coding is not only relevant for normal brain functioning but may also offer novel perspectives on psychiatric conditions, such as schizophrenia (ScZ) (Adams, Stephan et al. 2013). Recent evidence suggests that impairments in predictive processes can parsimoniously explain several features of ScZ (Fletcher and Frith 2009). Specifically, behavioral (Shergill, Samson et al. 2005), electrophysiological (Ford and Mathalon 2004) and neuroimaging evidence (Shergill, White et al. 2014) highlight that ScZ-patients are impaired in the generation of forward models during sensory-motor tasks. Such a deficit could lead to experiences where self-generated actions are experienced as being of alien origin (Blakemore, Wolpert et al. 2002) or the misperception of self-generated speech as an auditory hallucination (Heinks-Maldonado, Mathalon et al. 2007). Currently, the potential relevance of impairments in predictive processes for the explanation of deficits in sensory processing in ScZ has been less investigated (Ford and Mathalon 2012; Lakatos, Schroeder et al. 2013).

In ScZ-patients, MMN(m)-amplitudes have been consistently found to be reduced (Umbricht and Krljes 2005) and correlate with impaired social functioning (Light and Braff 2005), cognitive deficits (Kiang, Light et al. 2007) and reductions in gray matter (GM) (Rasser, Schall et al. 2011). More recently, MMN-deficits have also been shown to be present in participants at-risk for the development of ScZ (Bodatsch, Ruhrmann et al. 2011; Perez, Woods et al. 2014), suggesting that MMN could be potentially used for early detection and diagnosis (Nagai, Tada et al. 2013). Together, these data therefore highlight the need to further identify the nature and mechanisms of MMN-impairments in ScZ.

To address this question, we employed an auditory hierarchical two-level oddball task which is based on local (within tone series) and global (across tone series) violations of temporal regularities (Wacongne, Labyt et al. 2011). Specifically, local violations were elicited through a series of standard sequences (five identical tones) that are interspersed with deviant sequence (four identical tones followed by a different tone). To examine global regularities

encoding and generation of higher-order responses as reflected by a global MMNm and P300m, rare sequences were compared to frequently presented sequences. In addition, analysis of omission responses whereby unexpected omission of a fifth tone was compared to fully predictable sequences of four tones also permitted the investigation of prediction mechanism during auditory processing (Fig. 1).

Based on these findings, we expected that ScZ-patients were characterized by reduced amplitudes of MMNm-responses, replicating a large body of work in both at-risk, first-episode (FEP) and chronic ScZ-populations. Importantly, MMNm-responses were also expected to be reduced in omission trials. Findings by Wacongne et al. (2011) and others (Chennu, Noreika et al. 2016) showed that omission responses are similar in latency and topography to the MMN response elicited by deviant sequences. Finally, we expected the P300m elicited by a violation of global regularities to be reduced in ScZ. The P300m can be functionally and anatomically dissociated from the MMNm (Bekinschtein, Dehaene et al. 2009), suggesting a distributed network across sensory and higher brain areas is activated that leads to an integrated, conscious representation. As ScZ fundamentally involves a dysconnection syndrome involving large-scale networks (Friston and Frith 1995), we hypothesized that the P300m would be reduced, highlighting a comprehensive deficit of predictive mechanisms at both pre-attentive, local networks as well as in more extended, large-scale ciruits.

Enter Figure 1 about here

Methods

Participants

Sixteen ScZ-patients (all male; aged 37.38 ± 14.9 years) were recruited from Shaar-Menashe hospital in Israel and diagnosed by a trained psychiatrist with the SCID-interview for DSM-IV-R. All patients fulfilled DSM-IV criteria for ScZ and were receiving antipsychotic medication at the time of testing (ten ScZ-patients received first generation antipsychotic medication). Current psychopathology was assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein et al. 1987) and symptoms were grouped into five factors according to the model of Lindenmayer et al. (1995) including the factors "negative", "positive", "depression", "excitement", and "cognitive".

Enter Table 1 about here

The control group consisted of n = 16 participants (aged 36.38 ± 9.4 years) recruited from the local community, and were matched to the ScZ group in terms of age and sex (Table 1). Exclusion criteria were for both ScZ-patients and controls: 1) a neurological disorder or 2) current or past alcohol or substance dependence. After being given a complete description of the study, each participant provided written informed consent.

The study was carried out according to the Declaration of Helsinki and approved by both Shaar-Menashe hospital's and Bar Ilan University's ethical boards.

Stimuli

Two tones composed of three superimposed sine waves (350, 700, and 1400 Hz, tone A; or 500, 1000, and 2000 Hz, tone B) were synthesized. The tones were 50 ms long, with 7-ms rise and fall times. Series of four or five such tones were presented via headphones with a 150 ms stimulus onset asynchrony. The series could comprise five identical tones (local standard,

denoted xxxxx), four identical tones and a fifth different tone (local deviant, denoted xxxxY), or only four identical tones (omission, denoted xxxx_). Series were separated by silences of variable duration (700-1000 ms) and presented in semi-randomized blocks of ~3 min duration, during which one series was designated as frequent and the other as rare (Fig. 1). Each block started with 20 frequent series of sounds (either the local standard (block xxxxx) or the local deviant (block xxxxY) to establish the global regularity (global rule); of the next 80 occurrences, 75% were frequent series, 15% the rare series, and 10% the omission series. In the omission block only omission series were presented (expected omissions). Each participant received a total of 10 blocks of 100 trials each (two replications of the four series xxxxx and xxxxY with either x = A and Y = B, or x = B and Y = A, plus two xxxx_ omission blocks with x = A for one and x = B for the other). All stimuli were presented using E-prime v1.2 (Psychology Software Tools).

Data Acquisition

MEG recordings were conducted using a whole-head, 248-channel magnetometer array (4-D Neuroimaging, Magnes 3600 WH) in a magnetically shielded room. The 4D Neuroimaging system includes a noise cancellation package that utilizes 23 reference channels, including 18 magnetometers and 5 gradiometers, located ~30 cm above the 248 channels. MEG data were cleaned online by multiplying the values of each channel by a predetermined set of reference coil weights. Data were digitized at a sample rate of 1017.23 Hz and a 0.1 to 400 Hz online band-pass filter was applied.

Prior to the MEG-recording, the head-shape was digitized using a Polhemus Fastrack digitizer and the head position was digitally registered. Head position was registered at the beginning and end of the MEG session using 5 head position indicator (HPI) coils, and the discrepancy between head location at the beginning and end of the session was computed for all participants. No participant had a discrepancy greater than 0.7cm for any of the 5 HPI coils.

In addition, using a camera directed at the participants' heads, participants' behavior was monitored and documented at all time during the MEG session. To avoid eye movements, participants were instructed to focus on a fixation cross, and were constantly reminded by the experimenter between blocks to pay attention to the auditory stimuli as previous studies (Beckinschtein et al. 2009) have shown that attention is a prerequisit for rare sequences to elicit a P300 response. Participants were measured in a supine position.

Data Preprocessing

50 Hz line-noise and its harmonics were removed by calculating the average 50 Hz cycle on every MEG channel and then removing it from the data. Heartbeat artifacts were removed using an event-synchronous cancellation algorithm (Tal and Abeles 2013). Finally, independent component analysis was used to remove EOG artifacts. Preprocessing and analysis of the MEG data was performed with the open source Matlab toolbox "FieldTrip" (Oostenveld, Fries et al. 2011). Trials were epoched from 200 ms before to 1300 ms after the onset of the first sound of each sequence, low-pass filtered at 40 Hz and baseline corrected using the first 200 ms of each epoch. After visual rejection of any remaining artifacts, the trials were averaged per condition and per participant.

Statistical Analysis

A nonparametric mixed-design two-way ANOVA was employed based on a permutation approach with one between-subject factor GROUP (patients vs. controls), and one within-subject factor LEVEL-OF-MISMATCH (local vs. global). The analysis was performed on data containing the difference between standard and deviant tone for the local mismatch and between frequent and rare sequences for the global mismatch (i.e. the global standard comprises the 75% standard sequences in the xxxxx-block and the 75% deviant sequences in the xxxxxY-block and the global deviant comprises the 15% deviant sequences in the xxxxx-

block, the 15% standard sequences in the xxxxY block and the 10% omissions in both blocks) considering all MEG sensors. The clustering procedure was performed over adjacent time bins and data entries whose *F*-value surpassed a critical threshold corresponding to an α level of 0.05 were assigned to clusters based on their temporal and spatial adjacency and with a minimum of two sensors passing the threshold to form a cluster. Cluster-level statistics were calculated by taking the sum of the *F*-values within each cluster. The observed cluster-level statistics were then tested against the distribution of the maximum cluster-level statistics obtained from Monte Carlo simulations with 1000 permutations for each main effect and the interaction. For each permutation, group and condition assignments were shuffled and the estimation of *F*-values and the clustering procedure were repeated on the resampled data. The resulting maximum cluster values were used to construct the maximum cluster-level distribution under the null hypothesis of no experimental effect. Clusters were considered to be significant at an α level of 0.05 if the initially observed cluster was greater than the 95th percentile of the maximum cluster-level statistic distribution.

To examine differences between experimental conditions, i.e. differences between standard and deviant tones on the local level or rare vs. frequent tone series on the global level, non-parametric *t*-tests based on a permutation approach (1000 permutations) as implemented in Fieldtrip were performed.

Cluster-based statistics were computed between 50 and 250 ms for the MMNm, between 50 and 700 ms for the global effect, and between 50 and 500 ms after the omission of the fifth tone for omission effects based on prior findings (Wacongne, Labyt et al. 2011). For the omission effects, the difference of unexpected and expected omissions was calculated for each block separately. In addition, we analyzed the P300m effect at the local level between 200 and 400 ms after the onset of the deviant tone. For all analyses, we only report the most significant cluster for each effect.

Source-level analysis and statistics

We implemented a source-reconstruction approach to localize generators of MMNm, P300m and omission responses to identify commonalities and differences in the underlying networks of these responses.

Source estimation of evoked brain activity for the MMNm, P300m and omission responses was performed using the linearly constrained minimum variance (LCMV) (Van Veen, van Drongelen et al. 1997) beamformer technique as implemented in Fieldtrip. Since no individual subject MRIs were available, we used a generic brain for source reconstruction. Participant-specific source power values were normalized to a three-dimensional template grid (5 mm resolution) in Montreal Neurological Institute (MNI) coordinates and co-registered to the MEG coordinates system specific to the generic brain.

Sources were estimated for each condition using common filter weights based on a combination of standard and deviant responses in each condition, thus ensuring that differences in source activity were not related to spatial filter differences. Therefore, the covariance matrix was computed on all single trials derived from that combination. Subsequently, we projected averaged sensor-level data in each condition through the common spatial weights. The LCMV beamformer was independently applied on the statistically significant time intervals derived from the sensor-space analysis and centered around the statistical peak time point of the group difference of the individual effect with ± 10 ms.

In order to assess group-differences in MMNm, P300m and omission responses, non-parametric *t*-tests based on a permutation approach (1000 permutations) as implemented in Field-trip were performed. Group-differences were considered to be statistically significant at an α level of 0.05 and were corrected with a false-discovery-rate (FDR) procedure.

Effect-sizes for MMNm-amplitudes

We computed effect sizes (Cohen's *d*) for differences between standard and deviant tones, i.e. the MMNm, within each group for the local and global effect as well as for the difference for each effect across groups and for the P300m effect as well as for omission responses. Effect sizes were calculated by dividing the difference between the mean MMNm-amplitude of two conditions or groups respectively by the pooled standard deviation.

Results

Sensor-level data

The 2 x 2 permutation ANOVA with factors GROUP and LEVEL-OF-MISMATCH showed a main effect of group ($p < 0.01$), a main effect of LEVEL-OF-MISMATCH ($p = 0.001$), and a GROUP x LEVEL-OF-MISMATCH interaction ($p < 0.01$), allowing us to test for differences between experimental conditions and groups.

Local MMNm: Control participants showed an early MMNm effect, i.e. the difference between the fifth sound of standard and deviant sequences within each block (either xxxxx or xxxxY), peaking at around 120 ms after the onset of the fifth deviant tone. The local MMNm response was significant and with the same sign in each block type (block xxxxx: 98-196 ms, $p < 0.005$, $d = 4.64$; block xxxxY: 76-148 ms, $p < 0.005$, $d = 2.56$; Fig. 2). Similarly, ScZ-patients showed MMNm responses to local deviance in both xxxxx and xxxxY blocks (block xxxxx: 110-158 ms, $p < 0.005$, $d = 3.41$; block xxxxY: 96-153 ms, $p < 0.005$, $d = 2.56$; Fig. 2). Importantly, these responses were significantly reduced compared to controls (block xxxxx: 98-167 ms, $p < 0.005$, $d = 1.61$; block xxxxY: 91-125 ms, $p < 0.005$, $d = 1.19$; Fig. 2).

Global MMNm: The analysis of the second-level novelty response induced by the presentation frequency of the overall sequence revealed that in controls rare sequences differed from frequent sequences (126-185 ms, $p < 0.005$, $d = 0.94$; Fig. 2). In ScZ, the

MMNm elicited by rare sequences was absent. However, the group differences did not reach statistical significance (Fig. 2).

Omission Responses: The analysis of omission responses revealed an early effect at around 120 ms after the omission of the fifth tone in the control group which was significant in the xxxxx block (110-140 ms, $p < 0.005$, $d = 3.28$; Fig. 2). No significant difference between unexpected and expected omissions was found in ScZ-patients. Compared to healthy controls, the omission response in ScZ-patients was absent in the xxxxx block (110-135 ms, $p < 0.01$, $d = 0.78$; Fig. 2).

Enter Figure 2 about here

Local P300m: Control participants showed an effect of local deviance, i.e. the difference between the fifth sound of standard and deviant sequences within each block, in both xxxxx and xxxxY blocks during the time interval of the P300m (block xxxxx: 200-358 ms, $p < 0.005$, $d = 4.13$; block xxxxY: 200-338 ms, $p < 0.005$, $d = 2.81$; Fig. 3). The local P300m effect was also found in ScZ-patients (block xxxxx: 200-400 ms, $p < 0.005$, $d = 2.89$; block xxxxY: 200-325 ms, $p < 0.005$, $d = 1.89$; Fig. 3), which was significantly reduced compared to controls in the xxxxY block (200-340 ms, $p < 0.05$, $d = 0.68$; Fig. 3).

Global P300m: Rare sequences differed from frequent ones in controls, with responses over temporal and midline sensors (248-428 ms, $p < 0.005$, $d = 2.30$; Fig. 3). ScZ-patients did not show a P300m response to global deviance whose amplitude was reduced compared to controls over left temporal and midline sensors in a time window between 210-338 ms ($p < 0.005$, $d = 1.14$; Fig. 3).

Omission responses: In a later P300m time window, differences between unexpected and expected omissions were significant in both blocks for the controls (block xxxxx: 261-341 ms, $p < 0.005$, $d = 2.18$; block xxxxY: 240-313 ms, $p < 0.005$, $d = 2.67$; Fig. 3), and the ScZ-

patient group (block xxxxx: 226-276 ms, $p < 0.005$, $d = 2.43$; block xxxxY: 255-290 ms, $p < 0.005$, $d = 1.89$; Fig. 3). However, no significant differences were observed between groups.

Enter Figure Figure 3 about here

N100m Responses: To exclude that differences in MMNm and omission-responses were solely driven by group differences to standard tones, we compared the ERF-response to the first tone of each sequence. The comparison revealed that there was no significant difference between the two groups in the N100m (80-120 ms, $p > 0.05$). In addition, we compared the adaptation of the ERF-responses from the first to the fourth tone of each sequence. The comparison revealed that the reduction in ERF-responses across standard trials between the two groups were similar ($p > 0.05$; see Fig. 4).

Enter Figure Figure 4 about here

Source-level data

None of the between-group analyses in any condition nor time-intervals survived FDR-correction (see Supporting Information eFig.1 and eFig.2). Therefore we report here only the grand average source-maps for each group, condition and time-interval.

Local MMNm: Source generators of the local MMNm (120-140 ms) in the xxxxx-block were located bilaterally in both groups in temporal and frontal regions, with peak activation localized in the right superior temporal gyrus (STG). Activity in frontal cortices was localized in medial regions of the superior frontal cortex (SFG), and the medial (MFG) and inferior gyri (IFG) bilaterally (Fig. 5, first column). In the xxxxY-block (105-125 ms), source activity was notably reduced as compared to the xxxxx-block. Only some regions in the left STG and MTG showed enhanced activity to local deviants, specifically in the control group.

Pronounced activity in both groups was observed bilaterally in STG and MTG, and SFG in controls for local standards, thus reflecting increased activity to stimulus repetitions presented infrequently (Fig. 5).

Global MMNm: In line with sensor-level data, generators of the second-level novelty responses in the MMNm interval (151-171 ms) showed source-activity to rare sequences strongly attenuated as compared to local MMNm and omission sources. Both groups showed bilateral activation in auditory sources, with peak activations located in the right STG, suggesting overlapping generators with local MMNm. Opposite to local MMNm sources in the xxxxx-block, bilateral regions in the STG and MTG showed stronger responses to frequent as compared to rare events in both groups. Right MFG and precentral gyrus showed enhanced activity to repetitive sequences in controls, but increased activity to rare events in the ScZ-patient group (Fig. 5).

Omission Responses: Sound omissions (115-135 ms) elicited stronger activity in frontal and auditory areas in both groups. Similar to local MMNm, peak activation was localized in the right superior temporal gyrus (STG) suggesting overlapping generators. Compared to the control omission block, unexpected omission responses elicited strong activation in HG, STG, and posterior portions of the MTG. In frontal cortices, both groups showed activation of regions analogous to those observed in the local MMNm condition, overlapping right SFG, and MFG bilaterally (Fig. 5).

Enter Figure 5 about here

Local P300m: In the xxxxx-block, generators of the P300m response to local deviants (200-300 ms) were localized bilaterally in auditory regions with peak activation localized in left and right STG for the control and ScZ-patient groups, respectively. As opposed to MMNm sources, local P300m showed a strong contribution from sources in the anterior cingulum,

medial SFG, MFG, precentral and postcentral regions (Fig. 6). Similarly to local MMNm effects, in the xxxxY-block infrequently presented local standards elicited stronger activation in STG and MTG, bilaterally. Only regions in MTG, and STG in controls showed enhanced responses to rare sequences (Fig. 6, middle column).

Global P300m: P300m anatomical generators to rare sequences (248-268 ms) showed a similar, but weaker configuration than those observed during local P300m effects. Peak activation localized in left and right STG for the control and ScZ-patient groups, respectively. In addition to the bilateral activation of STG and MTG, P300m to global violations showed the involvement of anterior cingulum, medial SFG, and MFG (Fig. 6).

Enter Figure 6 about here

Discussion

The purpose of the present study was to investigate the hypothesis that MMNm-deficits in ScZ-patients reflect an impairment in sensory predictions, thus providing a potentially novel perspective on auditory-perceptual dysfunctions in the disorder. Currently, predictive coding deficits have been demonstrated during sensory-motor tasks (Shergill, Samson et al. 2005), indicating a failure in forward models which lead to impaired attribution and monitoring of self-generated actions and sensory events (Blakemore, Wolpert et al. 2002; Ford, Perez et al. 2012; Naatanen, Shiga et al. 2015). Currently, it is less clear whether dysfunctional auditory processing, which reflect a core component of the disorder (Javitt 2009), could also be explained in terms of a predictive coding account.

MMN-deficits represent one of the most promising biomarkers for the early detection and diagnosis of ScZ (Bodatsch, Ruhrmann et al. 2011; Naatanen, Shiga et al. 2015; Chennu, Noreika et al. 2016). Accordingly, identifying the underlying processes could be important for developing mechanistic models of dysfunctional sensory processing in ScZ. One possible

mechanism underlying the generation of the MMN during normal brain functioning is a sensory prediction process (Wacongne, Changeux et al. 2012).

Consistent with prior findings (Wacongne, Labyt et al. 2011), we observed overlapping ERF-responses and generators for the local MMNm and omission responses that support the hypothesis that the MMN reflects prediction error-signaling. Moreover, violations of global regularities elicited an MMNm at around 150 ms and a P300m in controls, suggesting the occurrence of predictions at different levels of the auditory processing stream. The latter is supported by the involvement of higher brain areas, such as the anterior cingulate, medial superior frontal gyrus and middle frontal cortex, in the network underlying the P300m generated during the global condition consistent with the initiation of a global workspace (Dehaene and Changeux 2011), while the MMNm likely reflects automatic encoding of global auditory regularities.

In ScZ-patients, the MMNm-responses to local deviants were reduced over right fronto-temporal sensors while we also observed absent ERF-responses to expected sound-omissions with a similar latency and source-configuration. The reduction in the neuromagnetic MMN replicates previous findings with MEG (Kircher, Rapp et al. 2004; Yamasue, Yamada et al. 2004; Thonnessen, Zvyagintsev et al. 2008) as well as extensive evidence on frequency induced MMN-deficits in EEG-data (Salisbury, Shenton et al. 2002; Umbricht, Bates et al. 2006). As the MMNm and omission responses overlapped both in latency, topography and underlying sources, it is likely that both the MMNm as well as the omission response resulted from an impaired predictive signaling in ScZ that leads to a reduced MMNm-amplitude as well as to a failure to “fill-in” an omitted sound.

In addition to an impairment in local predictive processes, our data support the notion that impairments in ScZ extend to the detection of global regularities. In ScZ-patients, MMNm response to global rules were reduced, suggesting a deficiency in the detection of global

regularities at an automatic level that was accompanied by an absence of the P300m response relative to controls.

Previous research with EEG has indicated that the global deviant response is both anatomically and functionally distinct from the classical MMN-response and consistent with the topography of a P300 as evidenced by studies in sleep and coma which leads to the reduction of the global response while the local MMN-amplitude is largely intact (Bekinschtein, Dehaene et al. 2009; Strauss, Sitt et al. 2015). Accordingly, this deficit could indicate a failure to sustain activity in a global workspace (Dehaene and Changeux 2011) involving a dysfunction in recurrent interactions between cortical regions in ScZ, consistent with a notion of dysconnectivity syndrome (Friston and Frith 1995).

The specific impairment in sensory predictions at both local and global levels in ScZ is furthermore supported by the analysis of ERFs to standard sounds which were intact as well as their attenuation across repeated presentations of standards in ScZ-patients. Impaired encoding of sensory sounds could lead to reduced MMN-responses as the difference of the deviant tone will be perceived as smaller depending on precision with which the standard tones are encoded (Todd, Michie et al. 2012). According to the present findings, an impairment in sensory precision can therefore not account for MMN-deficits in ScZ.

In summary, the current study provides new evidence for the hypothesis that auditory-perceptual dysfunctions in ScZ involve impaired sensory predictions at both local and global levels. ScZ-patients were impaired at detecting local and global regularities in a hierarchical MMN-paradigm that has been shown to involve predictive coding at multiple levels of auditory processing (Wacongne, Labyt et al. 2011). Importantly, dysfunctional sensory processing in ScZ-patients involved reduced responses to omitted sounds which is incompatible with adaption-accounts of MMN-deficits. Previous studies have demonstrated MMN-deficits in unmedicated ScZ-patients (Catts, Shelley et al. 1995) as well as in participants meeting at-risk criteria for psychosis (Bodatsch, Ruhrmann et al. 2011). Thus, the

current findings are unlikely to be due to the confounding effects of anti-psychotic medication and instead point to a fundamental deficit in sensory predictions in ScZ.

Moreover, given the potential of MMN-deficits as a biomarker for psychosis-prediction (Nagai, Tada et al. 2013), demonstrating whether sensory predictions are already impaired prior to the onset of psychosis is crucial. Perceptual disturbances are one of the earliest manifestations of psychosis (Uhlhaas and Mishara 2007) and therefore dysfunctional predictive coding may underlie the emergence of the at-risk state. In addition, it will be important to test whether such abnormalities extend to other sensory modalities, such as vision, which has been prominently implicated in cognitive deficits in ScZ and to investigate whether shared abnormalities in sensory predictions underlie perceptual dysfunctions and the emergence of positive symptoms, such as delusions and hallucinations .

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References

Adams, R. A., K. E. Stephan, et al. (2013). "The computational anatomy of psychosis." Front Psychiatry **4**: 47.

Bekinschtein, T. A., S. Dehaene, et al. (2009). "Neural signature of the conscious processing of auditory regularities." Proc Natl Acad Sci U S A **106**(5): 1672-1677.

Blakemore, S. J., D. M. Wolpert, et al. (2002). "Abnormalities in the awareness of action." Trends Cogn Sci **6**(6): 237-242.

Bodatsch, M., S. Ruhrmann, et al. (2011). "Prediction of psychosis by mismatch negativity." Biol Psychiatry **69**(10): 959-966.

Catts, S. V., A. M. Shelley, et al. (1995). "Brain potential evidence for an auditory sensory memory deficit in schizophrenia." Am J Psychiatry **152**(2): 213-219.

Chennu, S., V. Noreika, et al. (2016). "Silent Expectations: Dynamic Causal Modeling of Cortical Prediction and Attention to Sounds That Weren't." J Neurosci **36**(32): 8305-8316.

Dehaene, S. and J. P. Changeux (2011). "Experimental and theoretical approaches to conscious processing." Neuron **70**(2): 200-227.

Fletcher, P. C. and C. D. Frith (2009). "Perceiving is believing: a Bayesian approach to explaining the positive symptoms of schizophrenia." Nat Rev Neurosci **10**(1): 48-58.

Ford, J. M. and D. H. Mathalon (2004). "Electrophysiological evidence of corollary discharge dysfunction in schizophrenia during talking and thinking." J Psychiatr Res **38**(1): 37-46.

Ford, J. M. and D. H. Mathalon (2012). "Anticipating the future: Automatic prediction failures in schizophrenia." Int J Psychophysiol **83**(2): 232-239.

Ford, J. M., V. B. Perez, et al. (2012). "Neurophysiology of a possible fundamental deficit in schizophrenia." World Psychiatry **11**(1): 58-60.

Friston, K. (2008). "Hierarchical models in the brain." PLoS Comput Biol **4**(11): e1000211.

Friston, K. (2010). "The free-energy principle: a unified brain theory?" Nat Rev Neurosci **11**(2): 127-138.

Friston, K. J. and C. D. Frith (1995). "Schizophrenia: a disconnection syndrome?" Clin Neurosci **3**(2): 89-97.

Garrido, M. I., K. J. Friston, et al. (2008). "The functional anatomy of the MMN: a DCM study of the roving paradigm." Neuroimage **42**(2): 936-944.

Heinks-Maldonado, T. H., D. H. Mathalon, et al. (2007). "Relationship of imprecise corollary discharge in schizophrenia to auditory hallucinations." Arch Gen Psychiatry **64**(3): 286-296.

Javitt, D. C. (2009). "When doors of perception close: bottom-up models of disrupted cognition in schizophrenia." Annu Rev Clin Psychol **5**: 249-275.

Kay, S. R., A. Fiszbein, et al. (1987). "The positive and negative syndrome scale (PANSS) for schizophrenia." Schizophr Bull **13**(2): 261-276.

Kiang, M., G. A. Light, et al. (2007). "Cognitive, neurophysiological, and functional correlates of proverb interpretation abnormalities in schizophrenia." J Int Neuropsychol Soc **13**(4): 653-663.

Kircher, T. T., A. Rapp, et al. (2004). "Mismatch negativity responses in schizophrenia: a combined fMRI and whole-head MEG study." Am J Psychiatry **161**(2): 294-304.

Lakatos, P., C. E. Schroeder, et al. (2013). "Predictive suppression of cortical excitability and its deficit in schizophrenia." J Neurosci **33**(28): 11692-11702.

Light, G. A. and D. L. Braff (2005). "Mismatch negativity deficits are associated with poor functioning in schizophrenia patients." Arch Gen Psychiatry **62**(2): 127-136.

Lindenmayer, J. P., S. Grochowski, et al. (1995). "Five factor model of schizophrenia: replication across samples." Schizophr Res **14**(3): 229-234.

Naatanen, R., T. Shiga, et al. (2015). "Mismatch negativity (MMN) deficiency: a break-through biomarker in predicting psychosis onset." Int J Psychophysiol **95**(3): 338-344.

Nagai, T., M. Tada, et al. (2013). "Mismatch negativity as a "translatable" brain marker toward early intervention for psychosis: a review." Front Psychiatry **4**: 115.

Oostenveld, R., P. Fries, et al. (2011). "FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data." Comput Intell Neurosci **2011**: 156869.

Perez, V. B., S. W. Woods, et al. (2014). "Automatic auditory processing deficits in schizophrenia and clinical high-risk patients: forecasting psychosis risk with mismatch negativity." Biol Psychiatry **75**(6): 459-469.

Rao, R. P. and D. H. Ballard (1999). "Predictive coding in the visual cortex: a functional interpretation of some extra-classical receptive-field effects." Nat Neurosci **2**(1): 79-87.

Rasser, P. E., U. Schall, et al. (2011). "Gray matter deficits, mismatch negativity, and outcomes in schizophrenia." Schizophr Bull **37**(1): 131-140.

Recasens, M., S. Grimm, et al. (2014). "Encoding of nested levels of acoustic regularity in hierarchically organized areas of the human auditory cortex." Hum Brain Mapp **35**(11): 5701-5716.

Salisbury, D. F., M. E. Shenton, et al. (2002). "Mismatch negativity in chronic schizophrenia and first-episode schizophrenia." Arch Gen Psychiatry **59**(8): 686-694.

Shergill, S. S., G. Samson, et al. (2005). "Evidence for sensory prediction deficits in schizophrenia." Am J Psychiatry **162**(12): 2384-2386.

Shergill, S. S., T. P. White, et al. (2014). "Functional magnetic resonance imaging of impaired sensory prediction in schizophrenia." JAMA Psychiatry **71**(1): 28-35.

Strauss, M., J. D. Sitt, et al. (2015). "Disruption of hierarchical predictive coding during sleep." Proc Natl Acad Sci U S A **112**(11): E1353-1362.

Thonnessen, H., M. Zvyagintsev, et al. (2008). "Optimized mismatch negativity paradigm reflects deficits in schizophrenia patients. A combined EEG and MEG study." Biol Psychol **77**(2): 205-216.

Todd, J., P. T. Michie, et al. (2012). "Mismatch negativity (MMN) reduction in schizophrenia-impaired prediction--error generation, estimation or salience?" Int J Psychophysiol **83**(2): 222-231.

Uhlhaas, P. J. and A. L. Mishara (2007). "Perceptual anomalies in schizophrenia: integrating phenomenology and cognitive neuroscience." Schizophr Bull **33**(1): 142-156.

Umbricht, D. and S. Krljes (2005). "Mismatch negativity in schizophrenia: a meta-analysis." Schizophr Res **76**(1): 1-23.

Umbricht, D. S., J. A. Bates, et al. (2006). "Electrophysiological indices of automatic and controlled auditory information processing in first-episode, recent-onset and chronic schizophrenia." Biol Psychiatry **59**(8): 762-772.

Van Veen, B. D., W. van Drongelen, et al. (1997). "Localization of brain electrical activity via linearly constrained minimum variance spatial filtering." IEEE Trans Biomed Eng **44**(9): 867-880.

Wacongne, C., J. P. Changeux, et al. (2012). "A neuronal model of predictive coding accounting for the mismatch negativity." J Neurosci **32**(11): 3665-3678.

Wacongne, C., E. Labyt, et al. (2011). "Evidence for a hierarchy of predictions and prediction errors in human cortex." Proc Natl Acad Sci U S A **108**(51): 20754-20759.

Winkler, I., N. Cowan, et al. (1996). "Interactions between Transient and Long-Term Auditory Memory as Reflected by the Mismatch Negativity." J Cogn Neurosci **8**(5): 403-415.

Winkler, I. and I. Czigler (2012). "Evidence from auditory and visual event-related potential (ERP) studies of deviance detection (MMN and vMMN) linking predictive coding theories and perceptual object representations." Int J Psychophysiol **83**(2): 132-143.

Yamasue, H., H. Yamada, et al. (2004). "Abnormal association between reduced magnetic mismatch field to speech sounds and smaller left planum temporale volume in schizophrenia." Neuroimage **22**(2): 720-727.

Figure Legends

Figure 1. Experimental design. Three auditory stimuli could be presented: local standard (a series of five identical tones, denoted xxxxx), local deviant (four identical tones followed by a different tone; denoted xxxxY), and omission (four identical tones; denoted xxxx_). These stimuli were presented in three types of blocks in which one series (local standard, local deviant or omission) was presented with a high frequency (initially 100%, then 75%) and the other two series were rare (15% and 10% respectively). This design thus separated the local deviancy of the fifth sound in a single tone sequence from the global deviance which is dependent on the overall frequency of a sequence in a given block and also allowed us to probe whether the omission effect differed when a standard or a deviant tone was expected.

Figure 2. Sensor-level topography and time-courses of ERFs for the MMNm response. Topographies for the local effect show the spatial distribution of the difference between deviant and standard tones, for the global effect the spatial distribution of the difference between rare and frequent tone series, and for the omission response the spatial distribution of the difference between unexpected and expected sound omissions, at the statistical peak time point indicated by the vertical dotted line in the graph which shows the time course for the individual sensor (statistical peak sensor; marked by a white dot on the corresponding topographical map). Black dots on the maps indicate cluster-corrected significant sensors. The grey bars indicate the statistical significant time window. Bilateral auditory areas show a rapid response to the fifth deviant tone, whether it is rare (xxxxx blocks) or frequent (xxxxY blocks). StaXX, local standard block xxxxx; DevXX, local deviant block xxxxx; StaXY, local standard block xxxxY; DevXY, local deviant block xxxxY; OmiXX, omission block xxxxx; OmiXY, omission block xxxxY; OmiExp., expected omission.

Figure 3. Sensor-level topography and time-courses of ERFs for the P300m response. Topographies for the local effect show the spatial distribution of the difference between deviant and standard tones, for the global effect the spatial distribution of the difference between rare and frequent tone series, and for the omission response the spatial distribution of the difference between unexpected and expected sound omissions, at the statistical peak time point indicated by the vertical dotted line in the graph which shows the time course for the individual sensor (statistical peak sensor; marked by a white dot on the corresponding topographical map). Black dots on the maps indicate cluster-corrected significant sensors. The grey bars indicate the statistical significant time window. Bilateral auditory areas show a P300m response to the fifth deviant tone in both groups. StaXX, local standard block xxxxx; DevXX, local deviant block xxxxx; StaXY, local standard block xxxxY; DevXY, local deviant block xxxxY; OmiXX, omission block xxxxx; OmiXY, omission block xxxxY; OmiExp., expected omission.

Figure 4. Analysis of N100m responses to the standard tones in each sequence. (A) The graph shows the time course for the corresponding sensors marked on the topography. (B) The histograms show the averaged N100m response to each tone for controls and ScZ-patients (top) and the differences of the first three tones with the fourth tone for both groups (bottom). (C) Topographies show the spatial distribution of the N100m response to each tone of the sequence for both controls and ScZ-patients.

Figure 5. LCMV source-reconstruction of the MMNm effect at the local and global level as well as for the omission response. Effects are separately shown for control subjects (top row) and ScZ-patients (bottom row) and displayed on axial-view slices. Grand average source-maps show activation to local deviance (first column), i.e. the difference between deviant and standard tones, to the second-level novelty response (second column) and to the difference

between unexpected and expected sound omissions (third column) during time intervals centered around the statistical peak time point of the group difference at sensor-level of the individual effect with ± 10 ms.

Figure 6. LCMV source-reconstruction of the P300m effect at the local and global level. Effects are separately shown for control subjects (top row) and ScZ-patients (bottom row) and displayed on axial-view slices. Grand average source-maps show activation to local deviance (first column), i.e. the difference between deviant and standard tones, during a late P300m time interval (200 - 300 ms) and to the second-level novelty response (second column) during a time interval centered around the statistical peak time point of the group difference at sensor-level with ± 10 ms.

eFigure 1. LCMV source-reconstruction of the MMNm effect. Axial-view slices showing significant (uncorrected for multiple comparisons) clusters of activity between control and patient group related to local deviance (first column), i.e. the difference between deviant and standard tones, to the second-level novelty response (second column) and to the difference between unexpected and expected sound omissions (third column) during time intervals centered around the statistical peak time point of the group difference at sensor-level of the individual effect with ± 10 ms. Functional maps display independent *t*-values tresholded at $p < 0.01$ (uncorrected).

eFigure 2. LCMV source-reconstruction of the P300m effect. Axial-view slices showing significant (uncorrected for multiple comparisons) clusters of activity between control and patient group related to local deviance (first column), i.e. the difference between deviant and standard tones, during a late P300m time interval (200 - 300 ms) and to the second-level novelty response (second column) during a time interval centered around the statistical peak

time point of the group difference at sensor-level with ± 10 ms. Functional maps display independent *t*-values tresholded at $p < 0.01$ (uncorrected).

Table 1. Demographic data, and symptom scores for ScZ-patients

	Controls (n = 16)		Patients (n = 16)	
	Mean	SD	Mean	SD
Age (years)	36.38	9.38	37.38	14.89
Education (years)	16.75	4.49	10.31	2.15
Handedness, left	0		0	
Duration of Illness (years)	—	—	18.75	15.47
GAF	—	—	42	19.12
PANSS				
Negative	—	—	14.81	1.97
Excitement	—	—	4.5	0.73
Cognitive	—	—	7.43	0.51
Positive	—	—	5.25	1.34
Depression	—	—	5.93	0.92