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Mismatch negativity indexes illness-specific impairments of cortical plasticity in schizophrenia: A comparison with bipolar disorder and Alzheimer's disease

Torsten Baldeweg [a,b,*], Steven R. Hirsch [c]

[a] University College London, Institute of Child Health, London, United Kingdom
[b] Great Ormond Street Hospital for Children NHS Foundation Trust, Great Ormond Street, London, United Kingdom
[c] Division of Neuroscience & Psychological Medicine, Imperial College School of Science, Technology and Medicine, Charing Cross Hospital, London W6 8RP, United Kingdom

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ABSTRACT

Cognitive impairment is an important predictor of functional outcome in patients with schizophrenia, yet its neurobiology is still incompletely understood. Neuropathological evidence of impaired synaptic connectivity and NMDA receptor-dependent transmission in superior temporal cortex motivated us to explore the correlation of in vivo mismatch negativity (MMN) with cognitive status in patients with schizophrenia. MMN elicited in a roving stimulus paradigm displayed a response proportional to the number of stimulus repetitions (memory trace effect). Preliminary evidence in patients with chronic schizophrenia suggests that attenuation of this MMN memory trace effect was correlated with the degree of neuropsychological memory dysfunction. Here we present data from a larger confirmatory study in patients with schizophrenia, bipolar disorder, probable Alzheimer's disease and healthy controls. We observed that the diminution of the MMN memory trace effect and its correlation with memory impairment was only found in the schizophrenia group. Recent pharmacological studies using the roving paradigm suggest that attenuation of the MMN trace effect can be understood as abnormal modulation of NMDA receptor-dependent plasticity. We suggest that the convergence of the previously identified synaptic pathology in supragranular cortical layers with the intracortical locus of MMN generation accounts for the remarkable robustness of MMN impairments in schizophrenia. We further speculate that this layer-specific synaptic pathology identified in supragranular neurons plays a pivotal computational role, by weakening the encoding and propagation of prediction errors to higher cortical modules. According to predictive coding theory such breakdown will have grave implications not only for perception, but also for higher-order cognition and may thus account for the MMN–cognition correlations observed here. Finally, MMN is a sensitive and specific biomarker for detecting the early prodromal phase of schizophrenia and is well suited for the exploration of novel cognition-enhancing agents in humans.

1. Introduction

1.1. Defining the microcircuit

Research into mismatch negativity (MMN) represents a successful translational application of cognitive electrophysiology to neuropsychiatric disorders. This is particularly true for research into schizophrenia, a disorder which so far has escaped a comprehensive description of its underlying pathophysiology. MMN deficits in patients with schizophrenia have been replicated many times since the original observations by Shelley et al. (1991), making MMN one of the most robust biological markers of this complex disorder (Umbricht and Krljes, 2005). A modern formulation suggests that schizophrenia can be understood 'as a complex genetic disorder of cortical microcircuits' (Harrison and Weinberger, 2005) where risk genes (each with relatively small impact) converge functionally on synaptic plasticity and stabilisation of microcircuitry, especially implicating NMDA receptor-mediated glutamate transmission.

In this paper we review progress made in applying MMN to characterise one important aspect of schizophrenia which until recently has not received sufficient attention — the *cognitive impairment associated with schizophrenia* (CIAS, reviewed by Michalopoulou et al., 2013), which can manifest separately from the more florid symptoms of

Abbreviations: AD, Alzheimer's disease; BD, bipolar disorder; MMN, mismatch negativity.

* Corresponding author at: UCL Institute of Child Health, 30 Guilford Street, London WC1N 1EH, United Kingdom. Tel.: +44 207 905 2756; fax: +44 207 905 2161.
E-mail address: T.Baldeweg@ucl.ac.uk (T. Baldeweg).

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psychosis and is largely not responsive to antipsychotic medication. In addition, we present empirical data which support the hypothesis that the cortical microcircuits generating MMN index illness-specific dysfunction of (NMDA receptor-dependent) auditory cortical plasticity, which extends to higher-order networks that collectively give rise to the cognitive phenotype of schizophrenia.

1.2. MMN and cognitive impairment in schizophrenia

Since the description of *dementia praecox* by Kraepelin (1913) it is recognised that cognitive deficits are an important aspect of schizophrenia (Owens and Johnston, 1980; Saykin et al., 1991). In a sizeable proportion of patients these deficits contribute to progressive and significant intellectual impairment (McKenna et al., 1990; McGlashan and Fenton, 1993), which in turn is an important predictor of functional outcome (Green, 1997; Michalopoulou et al., 2013). Cognitive impairment affects several neuropsychological domains: short- and long-term memory, attention and executive functions (Saykin et al., 1991). The 'amnesic syndrome' in schizophrenia or 'schizophrenia dementia' is characterised by disproportionate long-term memory impairment (McKenna et al., 1990; Tamlyn et al., 1992).

The aetiology of cognitive impairment in schizophrenia is currently not understood. It does not involve neuropathology characteristic for Alzheimer's disease (Purohit et al., 1998). The role of NMDA receptor dysfunction had been suggested on the basis of cognitive effects of NMDA receptor antagonists (Javitt and Zukin, 1991). Two key neuropathological findings (obtained at Charing Cross Hospital in London) were the primary motivation for our laboratory to begin exploring MMN as an in vivo biological marker of cognitive impairment (Hirsch et al., 1997). Garey et al. (1998) showed a distinct loss of dendritic spines in the superior temporal cortex (and in a smaller series also in frontal cortex) of post-mortem specimens obtained from patients with schizophrenia (Fig. 1). This loss was most pronounced in layer III pyramidal neurons in supragranular layers which receive the majority of cortico-cortical connections. NMDA receptors are particularly abundant in those dendritic spines, and a further study linked the loss of NMDA receptors in the superior temporal region (specifically gene expression for the NR1 subunit) directly to the degree of cognitive impairment which was determined prospectively (Humphries et al., 1996).

We expected that MMN could be a suitable in vivo biomarker for such dysfunction, given its main generator site in the superior temporal gyrus and its dependence on NMDA receptor mediated transmission, as shown in both monkeys and humans (Javitt et al., 1996; Umbricht et al., 2000). We predicted that impairment in MMN generation should be related to the degree of cognitive dysfunction in schizophrenia patients, independently of the severity of current psychotic symptoms.

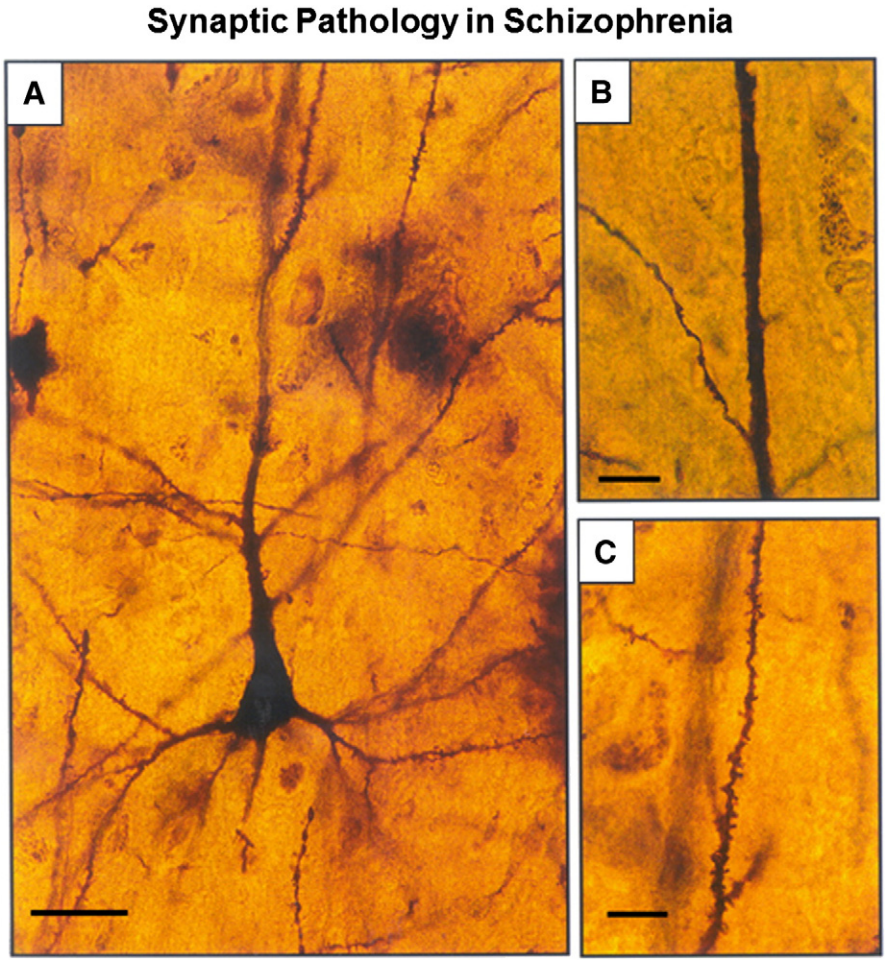

Fig. 1. Loss of dendritic spines in supra-granular layers of superior temporal gyrus and in frontal cortex in a patient with schizophrenia in comparison with age-matched healthy control. Micrographs of pyramidal cells in the cerebral cortex stained with the Golgi method. (A) A layer III pyramidal cell from a control brain, showing its morphology and spiny dendrites. (B) Smooth, spineless segment on an apical dendrite in schizophrenic cortex. (C) A higher power view of spines on an apical dendrite of a control pyramidal neuron. Scale: (A) 25 μm; (B) 15 μm and (C) 10 μm.
Reproduced with permission from: Garey LJ, Ong WY, Patel TS, Kanani M, Mortimer AM, Barnes TRE, Hirsch SR. (1998). Reduced dendritic spine density on cerebral cortical pyramidal neurons in schizophrenia. *Journal Neurology Neurosurgery Psychiatry*; 65: 446–453. See also Garey, L. (2010). When cortical development goes wrong: schizophrenia as a neurodevelopmental disease of microcircuits. *J.Anat., 217*, 324–333.

In order to probe this memory–MMN relationship more directly than is possible with the classical oddball protocol, we introduced the roving stimulus protocol (Cowan et al., 1993) into a clinical context. The continuously changing ('roving') sound input required the de novo formation of echoic memory traces and by varying the number of standard repetitions before each deviant, it was possible to probe the efficacy of echoic memory trace formation (memory trace effect). Intuitively, this memory trace effect was intended to measure the capacity for encoding novel information, i.e. to probe short-term plasticity processes. It was predicted that the degree of memory dysfunction would be proportional to the efficacy of encoding new auditory information, i.e. equivalent to a diminution of the MMN memory trace effect.

The data from a first pilot study (Baldeweg et al., 2004) supported this hypothesis, showing a diminution of the MMN memory trace effect (expressed as the relative increase or slope of MMN amplitude with number of standards) in proportion to the impairment in working memory, assessed neuropsychologically using digit span, and long-term episodic memory, tested using the Rivermead Behavioural Memory Test. MMN was negatively correlated with age and duration of illness in patients, but no correlations were found between psychometric scores, age and MMN in controls.

1.3. Further support for the correlation of MMN with cognitive status

Näätänen et al. (2011, 2012) comprehensively reviewed MMN studies which addressed this issue in patients with schizophrenia. In brief, supportive evidence was also found for a predictive relationship of MMN with global everyday functioning and independence of community-living (Light and Braff, 2005), which is closely correlated with cognitive status. Other studies also reported MMN–cognition correlations (Kawakubo et al., 2006; Kiang et al., 2007; Toyomaki et al., 2008; Turetsky et al., 2009). In addition, MMN was found correlated with indices of social cognition and functioning (Kawakubo and Kasai, 2006; Wynn et al., 2010; Rasser et al., 2011).

More recently it was shown that MMN correlated with verbal fluency scores in at-risk individuals (Higuchi et al., 2013) and with working memory performance in the early phase of the illness (Miyanishi et al., 2013), while the MMN–working memory correlation also extended to siblings of schizophrenia patients (Sevik et al., 2011). Frontal MMN reduction was also associated with executive dysfunction (Toyomaki et al., 2008), verbal learning and working memory deficits (Kaur et al., 2011), psychomotor slowing and attentional dysfunction (Hermens et al., 2010). While the evidence for a MMN–cognitive status correlation in schizophrenia reviewed above appears well replicated, the question of its specificity to this disorder has not been addressed.

1.4. The current study

It is important to note that similar MMN–cognitive status correlations were also found in other conditions, such as intellectual disability, healthy ageing and neurodegenerative diseases (reviewed in Näätänen et al., 2011, 2012), which poses important questions about the specificity of this relationship in schizophrenia. First, this relationship could be due to non-specific factors, such as the presence of global brain atrophy, a finding shared between major neuropsychiatric disorders and ageing. Secondly, while previous studies have overwhelmingly shown that MMN is intact in patients with bipolar disorder, these studies have used the classical oddball paradigm (Catts et al., 1995; Umbricht et al., 2003; Hall et al., 2007a, 2007b; Salisbury et al., 2007; Takei et al., 2010). It is conceivable, that the stimulus encoding demands of the roving stimulus paradigm poses a greater challenge in this population. More complex stimulation protocols can reveal MMN deficits which the oddball paradigm fails to show (e.g. Kujala et al., 2006). Furthermore, more recent studies have reported MMN attenuation in bipolar disorder cohorts (Andersson et al., 2008; Jahshan et al., 2012; Kaur et al., 2012). Finally, none of the previous studies have probed the MMN–cognition relationship in patients with schizophrenia and bipolar disorder in comparison with non-psychotic patients with cognitive impairments (e.g. Alzheimer's disease) using the same experimental setup.

Thus, the aims of the present study were: a) to replicate the findings made using the roving stimulus protocol in a larger patient and control sample; b) to compare the roving stimulus MMN between patients with schizophrenia and bipolar disorder; and c) to test the specificity of MMN–cognition correlation by comparison with patients with Alzheimer's disease. The methodology was kept similar to that used previously (Baldeweg et al., 2002, 2004); hence the description here will be kept brief.

2. Methods

2.1. Participants (see Table 1)

Only patients satisfying the DSM-IV criteria for the respective diagnoses were included in the study. Schizophrenia and bipolar disorder (BD) patients were recruited from in- and out-patient clinics at the Psychiatry Department, Charing Cross Hospital, while Alzheimer's disease (AD) patients were recruited from the Neurology Department, Charing Cross Hospital, and the Old Age Psychiatry Department, St Charles Hospital, all in London, UK. Exclusion criteria were a history of head injury, hearing loss, epilepsy, electro-convulsive therapy in the last 3 years, or recent drug and alcohol abuses. The study was approved by

Table 1
Demographic and clinical characteristics of study groups.

	Controls	Schizophrenia	Bipolar disorder	Alzheimer's disease
N	49	49	25	15
Gender (male/female)	25/24	28/21	12/13	9/6
Age (years)	36.4 (11.5)	38.0 (12.5)	38.1 (10.3)	71.2 (11.9)[b]
Handedness (L/R)	3/46	4/45	3/22	1/14
Parental SES (% in Social Classes I–III)	77.3%	58.3%	65.4%	69.2%
Education (years)	11.9 (2.4)	10.7 (2.2)	11.6 (2.4)	10.1 (2.4)
Employed (%)	79.6%	22.4%[a]	46.2%	–
Marital status (% married)	59.3%	18.3%	26.9%	65.3%
NART IQ	112.4 (13.9)	110.2 (8.9)	101.4 (9.28)	108.0 (6.8)
Quick Test IQ	101.3 (12.6)	94.1 (12.6)	100.0 (10.1)	–
Age of onset (years)	–	24.4 (6.5)	29.3 (7.3)[a]	68.1 (10.2)
Duration of illness (years)	–	10.4 (9.1)	8.8 (7.5)	3.1 (1.3)
Number of admissions	–	4.4 (4.4)	3.7 (2.7)	–
PANSS positive	–	19.3 (6.3)	17.3 (5.1)	–
PANSS negative	–	17.1 (5.3)	13.5 (3.4)[a]	–
PANSS general	–	36.4 (8.0)	33.3 (6.1)	–

SES = socio-economic status, IQ = intelligence quotient, NART = National Adult Reading Test, PANSS = Positive and Negative Syndrome Scale.
Significant differences ($p < 0.05$) in planned comparisons: a — schizophrenia versus bipolar disorder and b — schizophrenia compared to Alzheimer's disease.

the Riverside Research Ethics Committee and St Mary's Local Research Ethics Committee London, UK.

2.1.1. Schizophrenia patients (n = 49)

Patients with a DSM-IV diagnosis of schizoaffective disorder were excluded. All but one patient were taking neuroleptic medication. Of these, 39 (80%) were prescribed atypical anti-psychotic medications. Other medication included antidepressants (15 patients), lithium (9 patients), anticonvulsant mood stabilisers (10 patients) and anti-parkinsonian agents (9 patients). The average chlorpromazine equivalent was 337 mg/day (SD 351).

2.1.2. Control participants (n = 49)

Healthy control participants were recruited by local advertisements. Exclusion criteria were a history of neurological or psychiatric problems, hearing loss, drug or alcohol abuse, or a first-degree family member with a psychiatric disorder.

2.1.3. Bipolar disorder (BD) patients (n = 25)

Among the patients with bipolar disorder, 11 (48%) were on atypical anti-psychotic medications. Mood stabilisers were prescribed to 15, antidepressants to 8, and anti-parkinsonian agents to 1. A positive history of psychosis (hallucinations and/or delusions) was reported in 14 (56%).

2.1.4. Alzheimer's disease (AD) patients (n = 15)

Patients with a history of vascular disease were excluded. Due to practical difficulties three Alzheimer's disease patients were unable to undergo full neuropsychological assessment.

2.2. Procedures

2.2.1. Psychiatric assessment

All patients were assessed by a qualified psychiatrist using clinical interview and the severity of current symptoms was assessed using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987).

2.2.2. Neuropsychological evaluation

Patients were screened for impairment in everyday memory using the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and the Rivermead Behavioural Memory Test (RBMT) (Wilson et al., 1985), a test of memory domains relevant to everyday functioning. Working memory was tested using the WAIS-R Digit Span Forward and Backward (Wechsler, 1981). Executive control and semantic retrieval were assessed using the verbal fluency FAS score from the Controlled Oral Word Association Test (Benton and Hamsher, 1976). Pre-morbid verbal intelligence was assessed using the National Adult Reading Test (NART) (Nelson, 1982), while current intellectual functioning was estimated using the Quick Test (QT) (Ammons and Ammons, 1962). Handedness was determined using the Annett Scale (Annett, 1972).

2.2.3. ERP acquisition

EEG was recorded continuously from 30 electrodes and left and right mastoids (M1, M2) placed according to the international 10–20 system. Silver/silver chloride electrodes were attached using self-adhesive paste. The vertical electro-oculogram was recorded from electrodes placed above the right eye and the right outer canthus. System band pass was 0.1–30 Hz, with a digital sampling rate of 500 Hz and reference was placed on the bridge of the nose. The subjects were seated in a conformable chair in an acoustically shielded room and watched a silent and subtitled video. Relative hearing levels were tested binaurally using a staircase procedure at 800 and 1000 Hz before EEG recording commenced. None of the participants exhibited hearing problems.

2.2.4. Stimulation

A roving stimulus paradigm with duration and frequency deviants was used with slight modifications from that used previously (Baldeweg et al., 2002, 2004). Pure sinusoidal tones (80 dB SPL, 5 ms rise/fall) were delivered binaurally via headphones. A stimulus train consisted of a sequence of standard tones of one constant frequency and duration (25 ms) and which were followed by a deviant tone of the same pitch but differing in tone length (75 ms, duration deviant). Each train was followed by a new train of stimuli with a different frequency. The first stimulus of the new stimulus train therefore served as a frequency deviant for the preceding train (minimum frequency separation 50 Hz). Twelve different frequencies from 700 Hz to 1250 Hz were used. The number of standards in each stimulus train was either 2, 6 or 36, varied randomly from one train to the next (stimulus onset asynchrony 300 ms, inter-train interval 300 ms, total of 3194 stimuli, including 645 deviants). In modification to the original paradigm a random number of standards (ranging randomly from 1 to 4) after each duration deviant were inserted, so that duration and frequency MMN could be measured independently, without baseline contamination by the preceding duration deviant-elicited P3a.

2.2.5. ERP data processing

Data were filtered off-line with a band pass of 0.1–15 Hz. EEG data epochs were 400 ms long with a pre-stimulus baseline of 100 ms. All epochs with amplitudes exceeding +/− 100 μV in any of the derivations were excluded automatically. MMN was measured in the difference waves obtained by subtracting the ERP to the immediately preceding standard from the deviant ERP. Mean MMN amplitude was determined in the difference waveforms between 100 and 200 ms post-stimulus for frequency MMN, and between 120 and 220 ms for duration MMN. MMN peak amplitude and latency will not be reported here, for brevity.

To investigate the efficacy of auditory sensory memory encoding (memory trace effect), the increase of MMN amplitude with increasing standard repetition (MMN slope) was calculated for duration and frequency MMN amplitudes. This was done by subtracting MMN to deviants presented after n = 2 repetitions from MMN amplitudes to deviants presented after n = 36 repetitions (Baldeweg et al., 2004; Schmidt et al., 2012).

2.3. Statistical analysis

Group differences in demographic, clinical and cognitive data were tested using independent sample t-tests, analysis of variance and χ^2 or Fisher's exact tests, where appropriate. Group differences in neuropsychological scores were first evaluated using multivariate analysis of variance (MANOVA) with task as within-subject factor and group as between-subject factor. MMN amplitudes were analysed using repeated measures analysis of variance (RMANOVA) with MMN type (frequency, duration), standard repetition (n = 2, 6, 36) and electrode (Fz, F3, F4) as within-subject factors, and group as between-subject factor. Least square difference test was done for post-hoc analysis. Non-parametric correlations were computed between neuropsychological test scores and MMN amplitudes using Spearman's rank correlation. A two-tailed p value less than 0.05 was considered significant throughout. Linear regression analysis was used to determine neuropsychological correlates of MMN impairment with model selection performed in a stepwise fashion using the R^2 change statistic.

3. Results

We first investigated MMN differences between schizophrenia and bipolar disorder (BD) groups, before investigating the memory trace effect in relation to cognitive status in both schizophrenia and AD groups.

3.1. Comparison of demographical and clinical characteristics

3.1.1. Comparison of schizophrenia and bipolar disorder (BD) groups

The groups did not differ in age, gender, parental socio-economic status, pre-morbid IQ (NART) and time spent in education (Table 1). Both patient groups did not differ in duration of illness and number of hospital admissions, but patients with bipolar disorder were older at illness onset. Of note is that the two clinical groups did not differ in their positive or general psychopathology (PANSS) scores, while schizophrenia patients had higher negative PANSS scores, compatible with reports from other cohorts (Rosen et al., 2012).

3.1.2. Comparison of schizophrenia and Alzheimer's disease (AD) groups

The Alzheimer's disease group was older than controls and schizophrenia patients ($F(df = 3,127) = 32.9$, $p < 0.05$) but did not differ in gender ratio and parental socioeconomic status. While premorbid IQ and education was not different between patient groups (Table 1), the AD group was considerably more cognitively impaired (mean Mini-Mental State Examination (MMSE) score: 20.3 SD 1.8) than the schizophrenia group (MMSE score: 28.4 SD 1.8) and many AD patients were not able to complete the RBMT test (not reported here).

3.2. MMN comparison of schizophrenia and bipolar disorder groups

Systematic comparison of effect sizes across studies has established that the lowest deviant probability results in the greatest likelihood of detecting significant MMN group differences (Javitt et al., 1998; Umbricht and Krljes, 2005). Thus in order to maximise the chance of observing robust differences between psychosis groups we restricted the comparisons to the longest ($n = 36$) standard repetition condition.

3.2.1. MMN comparison of schizophrenia and bipolar disorder groups (Fig. 2)

As predicted MMN amplitude was severely reduced in the schizophrenia group compared to each other group but there was no difference between controls and BD patients (mean MMN (in μV) and standard deviation for control, schizophrenia and BD groups, respectively — duration MMN: −2.7 (1.4), −0.6 (1.2), and −2.5 (1.4) and frequency MMN: −3.5 (1.5), −0.8 (1.5), and −3.3 (1.7)). This was confirmed using a repeated-measures ANOVA with MMN type (duration, frequency) as within-subject factor and group (controls, schizophrenia, bipolar disorder) as between-subject factor showing a group effect ($F(df = 2,120) = 82.4$, $p < 0.05$), but there was no significant group by MMN type interaction. Furthermore, post-hoc tests demonstrated that schizophrenia patients differed from healthy controls and bipolar patients (all $p < 0.05$), while no difference was observed between bipolar group and healthy controls (all $p > 0.05$). The group differences reported for both deviants combined were also significant for each of them: duration deviant: $F(df = 2,120) = 42.47$, $p < 0.05$ and frequency deviant: $F(df = 2,120) = 51.09$, $p < 0.05$, with post-hoc differences (all $p < 0.05$) between schizophrenia and controls and schizophrenia and BD groups but no difference for BD and controls, for both deviant types tested separately. The group differences persisted after including negative PANSS scores as covariate of no interest.

Furthermore, MMN was compared between patients with bipolar disorder who had a positive history of psychosis ($N = 14$) and those who did not ($N = 11$). No significant difference was observed for either duration MMN ($t = 1.40$, $df = 23$, $p > 0.05$) or frequency MMN ($t = 0.21$, $df = 23$, $p > 0.05$). Finally, MMN in the bipolar disorder group was not affected by the use of mood stabilising medication and there were no correlations with PANSS symptom scores (all $p > 0.168$).

In summary, although both patient samples reported a similar level of positive psychotic symptoms at the time of testing, robust MMN deficits were observed only in patients with schizophrenia.

3.3. MMN memory trace effect in schizophrenia and Alzheimer's disease groups

Next, we examined the relationship of MMN to cognitive functions in patients with schizophrenia and subsequently tested if this relationship is similar to that of AD patients.

3.3.1. Neuropsychological evaluation and definition of schizophrenia cognition groups

The schizophrenia group was impaired relative to controls across all neuropsychological test scores (MANOVA effect of group: $F(df = 1,97) = 96.5$, $p < 0.05$). However, the impairment was not uniform as suggested by group by test interaction ($F(df = 5,92) = 11.7$, $p < 0.05$). For comparison of the different tests, the neuropsychological scores of the schizophrenia group were expressed as z-scores derived from the scores of the control group. The largest impairments were evident in long-term memory (RMBT, $z = -2.9$) and working memory (Digit Span Forward, $z = -2.1$), with least (non-significant) deficits in premorbid IQ (NART, $z = -0.5$). Since the variability in cognitive function was large, the patient sample was divided (using a median split at $z = -1.44$ on the overall performance z score) into a higher cognition group ($N = 23$, mean $z = -0.9$) and lower cognition group ($N = 26$, mean $z = -2.1$). The two cognition groups did not differ in most of their demographic and clinical characteristics (see Supplementary Table); however the lower cognition group was less likely to be employed (χ^2 ($N = 49$, $df = 1$) $= 10.80$, $p < 0.05$) and married (χ^2 ($N = 49$, $df = 3$) $= 65.5$, $p < 0.05$) than the higher cognition group.

3.3.2. MMN memory trace effect in patients with schizophrenia and Alzheimer's disease

Further to the MMN reduction for the largest number of repetitions reported above (Fig. 2), we first compared the memory trace effect between the schizophrenia and control groups. As predicted MMN

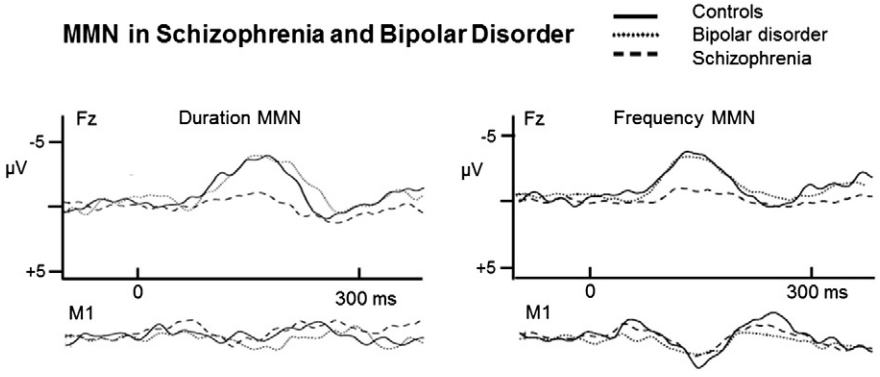

Fig. 2. MMN group comparison shows impairment in the schizophrenia but not in the bipolar disorder group in comparison with healthy controls. This is shown for duration and frequency MMN recorded after $n = 36$ standard repetitions.

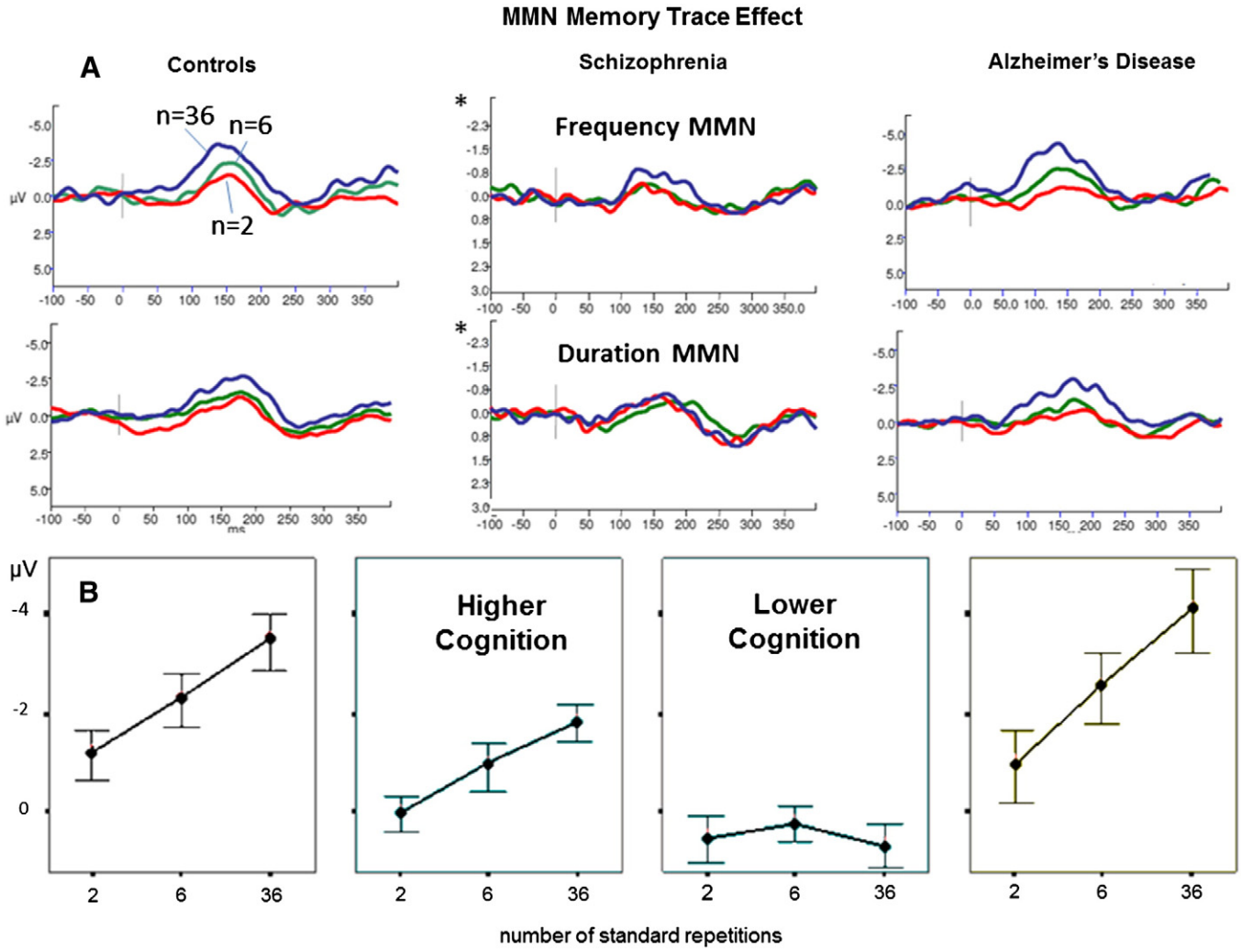

Fig. 3. Group means of the MMN memory trace effect show impairment in schizophrenia but not in patients with Alzheimer's disease in comparison with healthy controls (A). Please note that the amplitude scale was altered for the grand mean of the schizophrenia group (*) to visualise the attenuation of this effect more clearly. (B) Mean duration MMN amplitudes across groups, including the higher and lower cognition schizophrenia groups, showing preservation of MMN memory trace effect with repetition in the higher cognition group but this effect was abolished in the lower cognition group. An identical effect is seen for the frequency MMN (data not shown here).

increased with standard repetition in controls (Fig. 3A) and this effect was markedly attenuated in the schizophrenia group (group by repetition effect: $F(df = 2,95) = 17.5$, $p < 0.05$). Please note that the amplitude scale in Fig. 3A was altered for the grand mean of the schizophrenia group to visualise the attenuation of this effect more clearly.

Next we considered the MMN memory trace effect in AD patients (Fig. 3A, right column). Somewhat surprisingly, there was no visible MMN attenuation in the AD group which is supported by statistical analysis. While the overall RMANOVA group (controls, schizophrenia, AD) by repetition interaction effect was significant ($F(df = 4,216) = 8.8$, $p < 0.05$), post-hoc test demonstrated that only schizophrenia patients differed in their MMN responses from healthy controls (all $p < 0.05$). The main effects of group ($F(df = 2,108) = 71.34$, $p < 0.05$) and of repetition were also significant ($F(df = 2,107) = 17.34$, $p < 0.05$). No overall MMN difference was observed between Alzheimer's patients and healthy controls. MMN slopes of the AD group were indistinguishable from control values for duration ($t = 0.25$, $df = 50$, $p > 0.05$) and frequency MMN ($t = 0.78$, $df = 50$, $p > 0.05$), while they were larger than those of the schizophrenia group (duration: $t = 2.56$, $df = 50$, $p < 0.05$; frequency: $t = 5.72$, $df = 50$, $p < 0.05$).

In order to visualise the effect of cognitive status we plotted duration MMN amplitude separately for the two schizophrenia cognition groups (shown in Fig. 3B). This graph demonstrates that the memory trace effect was preserved in the higher cognition group, i.e. the slope of MMN change was similar to that of controls, despite an overall reduction in MMN amplitude. In contrast, the lower cognition group did not show any evidence for MMN increase with repetition.

Finally, a subgroup of 13 schizophrenia patients with the lowest MMSE scores was selected to match the AD individuals on overall cognitive status (MMSE score) and their MMN was compared to the Alzheimer's group. ANOVA again showed a main effect of group ($F(df = 1,24) = 25.3$, $p < 0.05$) and a group by repetition interaction ($F(df = 2,23) = 12.6$, $p < 0.05$), confirming the above findings from the total sample to this subgroup analysis. The two groups also differed in their MMN slopes (duration MMN: $t = 3.32$, $df = 23$, $p < 0.05$; frequency MMN: $t = 5.77$, $df = 32$, $p < 0.05$).

3.3.3. Correlations of MMN slope with neuropsychology scores

In patients with schizophrenia, MMN slopes (at electrode Fz) were correlated significantly (all $p < 0.05$) with the following neuropsychological scores: frequency MMN: Digit Span Forward ($r = -0.64$), RBMT total score ($r = -0.37$), and verbal fluency FAS score ($r = -0.34$) and duration MMN: Digit Span Forward ($r = -0.43$), RBMT ($r = -0.63$), and verbal fluency ($r = -0.35$). There were no correlations with PANSS symptom scores. Stepwise linear regression

demonstrated that independent predictor variables for frequency MMN were Digit Span Forward ($b = -0.47$) and RBMT scores ($b = -0.38$). For duration MMN the only significant predictor was RBMT score ($b = -0.43$). There were no significant correlations between MMN slopes or amplitudes and psychometric scores of the BD and AD groups (all $r < 0.28$, all $p > 0.168$).

4. Discussion

This is the first study to evaluate the diagnostic specificity of MMN in comparison with bipolar disorder and Alzheimer's disease, to address the important question of its correlation with cognitive status. The current study yielded a number of key findings. First, we replicate the correlation of the memory trace effect with neuropsychological memory scores in patients with schizophrenia in a larger sample of participants. Secondly, we show that this correlation was not observed in patients with bipolar disorder, who shared a comparable level of positive symptoms and general psychopathology. Finally, we show that patients with Alzheimer's disease, who demonstrated more severe cognitive impairment than schizophrenia patients, showed preserved MMN. Overall, this argues for a striking degree of specificity of MMN for the cognitive impairment associated with schizophrenia.

4.1. MMN and cognition across aetiological groups

In agreement with our pilot study, we found that MMN slope correlated most consistently with working and episodic memory scores. MMN therefore appears sensitive to deficits in encoding sensory information and this predicted patients' inability to store information in both working memory and long-term episodic memory, but is not related to their premorbid 'crystallised' intelligence. This suggests that the cortical dysfunction indexed by MMN is replicated in higher-order cortical networks, as sensory memory, working memory and episodic memory systems are neuropsychologically dissociable, i.e. are supported by distinct cortical networks. Auditory sensory memory is localised in the superior temporal cortex (Colombo et al., 1990) and working memory supported by fronto-parietal regions, while episodic memory is mainly dependent on hippocampal circuitry (Mishkin et al., 1998).

This is in stark contrast to AD patients, who showed preserved MMN despite exhibiting more severe memory impairments, presumably caused by the medial temporal emphasis of Alzheimer's disease pathology (Braak and Braak, 1995; Nelson et al., 2012). Our MMN findings are compatible with data of Pekkonen et al. (1994) who reported normal MMN in AD patients at short inter-stimulus intervals (1 s) but reduced MMN at longer intervals of 3 s. Reduced MMN (during active oddball) but preserved MMN to environmental sounds were reported by Kazmerski et al. (1997) but Gaeta et al. (1999) reported normal MMN to small and large frequency deviants in AD patients compared to elderly controls. We conclude that MMN reflects a severe disruption to sensory encoding in schizophrenia, while the reverse is the case in AD where preserved encoding contrasts with accelerated memory trace decay (Näätänen et al., 2011).

Given the overlap in clinical presentation and genetic influences of BD and schizophrenia there is an ongoing debate of the role of shared aetiological factors for the two major psychoses (Goldberg et al., 2009). The role of glutamatergic dysfunction in BD is under investigation using magnetic resonance spectroscopy and MMN with evidence for a moderate reduction in glutamate metabolites and MMN magnitude (Chitty et al., 2013). It is not yet known if fluctuating mood status accounts for some of the diverging findings (Kaur et al., 2012; Chitty et al., 2013). We observed that MMN clearly differed between schizophrenia and BD groups even though they were matched for some important characteristics of their psychopathology (positive and general PANSS scores). However, it is conceivable that the MMN difference is due to differences in cognitive functioning between groups. Our data do not suggest that this is the case. Patients with bipolar disorder performed significantly worse than the control group on a number of tests (data not shown) and the average neuropsychological z score indicated a general cognitive deficit of 1.4 standard deviations below the healthy control mean. This finding is in line with evidence that BD patients can show a similar profile of neuropsychological impairment, that is however less severe than in patients with schizophrenia (Vohringer et al., 2013). Furthermore, this score was significantly lower than of the higher cognition schizophrenia group ($z = -0.9$) ($t = 2.56$, $p < 0.05$); nevertheless their MMN was significantly larger than in the higher cognition group (group effect across all deviants: $F(df = 1,46) = 27.8$, $p < 0.05$). Importantly also no correlations between MMN and any of the psychometric scores were found for this group.

The discrepancy in MMN findings across studies of affective spectrum disorders (with some studies reporting MMN reduction while others do not) remains to be resolved, with a suggestion that differences between diagnostic groups are less pronounced in the early phase of the illness (Kaur et al., 2012) an issue that can only be resolved in longitudinal studies (Kaur et al., 2013).

Thus, we conclude that, much like the comparison with AD patients, the MMN difference between bipolar disorder and schizophrenia groups was not due to a difference in cognitive status. This apparent specificity of MMN to cognition in schizophrenia is complementary to the notion that the oddball MMN indexes a subtle decline across ageing (e.g. Kiang et al., 2009) and in neurodegenerative disorders (Näätänen et al., 2011). Given the limited age range of this study, we did not find robust MMN correlations with age in any group. MMN correlated inversely with duration of illness in the schizophrenia group only, as commonly reported (Umbricht and Krljes, 2005). We suggest that the combination of rapid and constantly changing stimulus input of the roving paradigm exposed a particular weakness of the auditory system in schizophrenia that exceeds the MMN sensitivity to overall cognitive decline. However, a comparison of the roving stimulus protocol with the classical oddball paradigm (e.g. Cooper et al., 2013) is needed to test this hypothesis.

4.2. Methodological considerations

It is important to acknowledge the limitations of this study. First, our study was not designed to demonstrate MMN and cognitive impairment in bipolar disorder. The effect size of MMN reduction was 0.14 and of a similar magnitude to that reported by Umbricht et al. (2003). We would have required a sample of several hundred participants per group to confirm a difference with sufficient statistical power. Data from the largest bipolar disorder sample reported so far (Hall et al., 2007a, 2007b) are in agreement with our findings which are in stark contrast to the large effect sizes commonly achieved when comparing schizophrenia groups with controls (Umbricht and Krljes, 2005).

The same limitation also applies to our comparison with Alzheimer's disease, in addition to our failure to recruit an older age-matched control group. Only a small number of eligible Alzheimer's disease patients could be included into this study, as over half of potential participants had a history of vascular disease. Other eligible patients were too impaired to cope with the testing schedule. Nevertheless, despite the larger cognitive compromise in this group (ranging from mild dysfunction in those with short duration of illness to severe dementia), the MMN findings are robustly showing intact auditory stimulus encoding at short inter-stimulus intervals, in overall agreement with literature findings. While we cannot rule out the possibility of MMN impairment in both bipolar disorder and Alzheimer's disease groups, we can firmly conclude that using the stimulation parameters of our study it appears of a qualitatively different magnitude to that observed in schizophrenia.

We admit that the division of the schizophrenia sample into two cognition groups is somewhat arbitrary and here only served to visualise the different profiles of MMN memory trace effects (Fig. 3B). It also usefully demonstrates that cognitive status is distinct from positive

symptoms of schizophrenia, as the cognition groups only differed in negative symptom scores and marital and employment status. This is in agreement with the robust association reported for MMN with general functioning (Light and Braff, 2005) with recent evidence showing a closer relationship to independence of living and work than social functioning (Wynn et al., 2010).

A major caveat is that the majority of patients were using psychotropic medication. In line with others (Jahshan et al., 2012; Kaur et al., 2012) we did not find direct evidence that mood stabilisers and neuroleptic medication affected MMN, but caution is due when interpreting this data.

Finally, this study was also not designed to address the nature of MMN impairment in schizophrenia (see Todd et al. (2012) for a detailed discussion), such as the contribution of lower precision of sound representation and increased discrimination thresholds (Javitt et al., 1997; Todd et al., 2003). First, it is worth noting that in our previous study which also failed to show frontal MMN responses in the patient group, basic tone frequency discrimination (tested behaviourally before MMN recording) was relatively intact when tested on frequency changes which were used during MMN recording. This finding supports the study by Todd et al. (2003) who reported MMN reduction in schizophrenia patients with intact discrimination thresholds. This conclusion is also supported by the relative preservation of the mastoid mismatch positivity in previous studies (Sato et al., 2003; Todd et al., 2003; Baldeweg et al., 2004), which was confirmed at the group level in the present study (data not shown, but see Fig. 2, right), suggesting that some element of sensory discrimination was intact.

Second, the adoption of the roving stimulus paradigm was intended to capture a neurophysiological signature of sound encoding deficits in schizophrenia. The putative ERP correlate, the repetition positivity (RP), was indeed found reduced in schizophrenia patients (Baldeweg et al., 2004), independently from the reduction in deviant negativity. While there is evidence that experimental manipulations (repetition, attention, timing regularity) which influence the strength of sensory memory also modulate RP (Haenschel et al., 2005; Costa-Faidella et al., 2011), a direct correlation with behavioural sensory discrimination performance has not yet been reported. Nevertheless, we confirm that patients who demonstrated a profound impairment in the memory trace effect (and by inference be impaired in sensory memory tasks) are also impaired in working and long-term memory tasks. Such presumed correlation between sensory precision and higher order cognition is made even more likely as the behavioural estimation of perceptual thresholds in turn is critically influenced by cognitive factors such as motivation, attention and intellectual abilities (e.g. Amitay et al., 2010).

4.3. Models of auditory short-term plasticity

After having documented the sensitivity of MMN to cognition in schizophrenia we now wish to review some of the progress made in uncovering putative mechanisms underlying these deficits. There is compelling evidence for the role of NMDA receptor blockade in MMN generation in monkey (Javitt et al., 1996), rodent (Ehrlichman et al., 2008) and human studies (Umbricht et al., 2000; Kreitschmann-Andermahr et al., 2001; Heekeren et al., 2008). However, it is not known if the MMN memory trace effect as employed in our studies is also sensitive to NMDA receptor blockade. This was investigated by Schmidt et al. (2012) using the roving stimulus paradigm of Garrido et al. (2008). They showed that s-ketamine, which blocks NMDA receptors, but not psilocybin, a 5-HT_{2A} receptor blocker, reduces the MMN memory trace effect, expressed as the slope of MMN amplitude over increasing numbers of standard repetitions. Although both drugs induced similar levels of positive psychosis-like symptoms in healthy volunteers, MMN slope during the placebo condition predicted perceived cognitive deficits induced by ketamine only, confirming the findings of Umbricht et al. (2002) obtained using the classical oddball MMN.

Furthermore, this group explored using dynamic causal modelling of scalp ERP the relative contribution of two putative mechanisms of MMN generation (adaptation vs. model adjustment) to the observed drug effects (Schmidt et al., 2013). Garrido et al. (2008, 2009) had previously introduced dynamic causal modelling for inferring causal relationships between neural generators of MMN. Adaptation of tonotopically organised auditory neurons (May et al., 1999) was modelled as changes in intrinsic connections of auditory cortex dipole generators (local gain control). The model adjustment hypothesis (Winkler et al., 1996) was implemented by examining short-term plasticity in long-range (extrinsic) connections between generators in primary and secondary auditory cortex. Schmidt et al. (2013) were able to replicate the findings of Garrido et al. (2009) by showing that both intrinsic auditory cortex adaptation and short-term plasticity in extrinsic connections between sources are required to explain MMN generation. Ketamine reduced estimates of synaptic plasticity but not of adaptation, and the former effect was correlated with ratings of ketamine-induced impairments of cognition. These findings are in complete agreement with another (yet unpublished) study employing the same roving paradigm as used in the present study (see Baldeweg (2007) for further information). This lends overall support for the initial intuition that the MMN memory trace effect at least partially expresses NMDA receptor-dependent cortical plasticity. Pharmacological challenge studies also support the link to cognitive impairment by showing that ketamine (but not other hallucinogens) induces impairments in both MMN and cognition (Umbricht et al., 2000; Heekeren et al., 2008; Schmidt et al., 2012).

4.4. Convergence of neuropathology and mismatch generation: prediction error detectors in supragranular cortex (Fig. 4)

Our original motivation for exploring the MMN as an in vivo marker of cognitive dysfunction was based on the discovery of synaptic pathology in supragranular neurons in the brains of patients with schizophrenia (Garey et al., 1998; Humphries et al., 1996; Glantz and Lewis, 2000). We now revisit this finding within the context of recent evidence from neurophysiology and computational neuroscience.

On the basis of the surprising observation that the MMN recorded using the roving paradigm could be completely explained by repetition effects to the standards ('repetition positivity', see Haenschel et al., 2005; Costa-Faidella et al., 2011), we invoked a novel theory of perceptual learning proposed by Friston (2003, 2005a) to account for the neurophysiological responses (Baldeweg et al., 2004, 2006). In short, during perceptual learning, hierarchical sensory systems employ 'predictive coding', where each level of the hierarchy receives bottom-up prediction errors from the level below and top-down predictions from the level above. At the lowest sensory level, this prediction error is simply the sensory input that has yet to be predicted. Deviation from the predicted sensory input (deviant) elicits error signals in lower levels (expressed physiologically as mismatch responses or prediction errors), which are propagated up the sensory hierarchy to inform higher level representations to elaborate top-down predictions. During stimulus repetition, connection strengths between hierarchical levels are adjusted, through synaptic plasticity, to suppress prediction error more efficiently. The physiological correlate of this is repetition suppression (i.e. repetition positivity). The roving stimulus paradigm is ideally suited to elicit robust ERP correlates of this process because prediction error generation and suppression are repeated with each new (roving) stimulus train. This model has been well supported by experimental data (reviewed in Baldeweg (2007) for MMN — and see Bastos et al. (2012) for a comprehensive review of the microcircuitry underlying predictive coding). We speculated that MMN generation and its deficit in schizophrenia could be understood within the framework of predictive coding (Baldeweg et al., 2004, 2006; Baldeweg, 2006, 2007; Stephan et al., 2006; see also Todd et al. (2012) for a consideration of the nature of prediction error deficit). In brief, there is remarkable

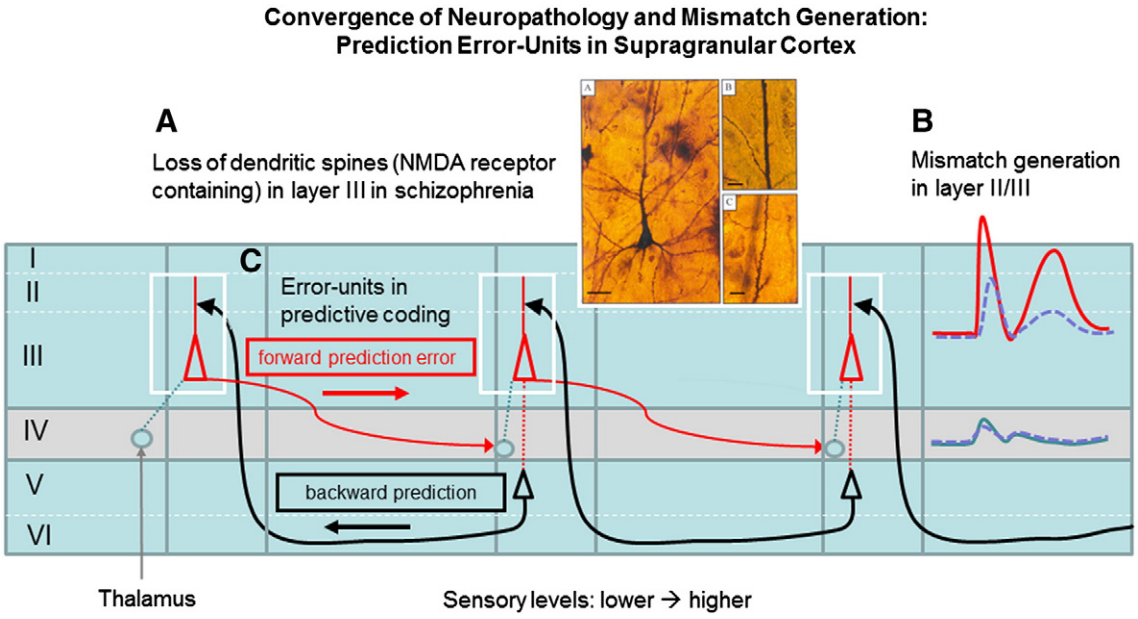

Fig. 4. Schematic showing the convergence of synaptic neuropathology (A: loss of NMDA receptor containing spines on layer III pyramidal cells (shown in white box and photomicrograph from Garey et al., 1998) with B: the intracortical locus of MMN generation (adapted from the findings of Javitt et al., 1996). Deviant-elicited potentials (red, MMN) are mainly recorded from supragranular layer II/III, where NMDA receptor blockers can suppress them without affecting input into layer IV. C: Supra-granular neurons play a strategic computational role as prediction error-units within hierarchical cortical networks that employ predictive coding (Friston, 2005a). These error-units are the source of forward (bottom-up) connections within the brain (shown in red) conveying prediction error to higher levels. Top-down predictive signals are relayed via backward projections (shown in black) from higher-level infra-granular layers to lower-level supra-granular pyramidal cells. Critical details of the intrinsic (lateral) cortical connections including inhibitory interneurons are omitted here (see Friston and Kiebel, 2009; Bastos et al., 2012 for details).

convergence on three important points (summarised in Fig. 4, see legend for further explanations):

First, the cytoarchitectural features of schizophrenia – as reviewed by Harrison (1999) – comprise of reduction of synaptic connectivity, predominantly affecting dendritic inputs to layer II/III pyramidal cells. This layer- and disease-specific arrangement has been documented for the hippocampus (Harrison and Eastwood, 1998), dorso-lateral frontal neocortex (Garey et al., 1998; Glantz and Lewis, 2000; Kolluri et al., 2005) and temporal neocortex (Garey et al., 1998). Many schizophrenia risk genes converge on the physiology of these NMDA receptor-containing synapses (Harrison and Weinberger, 2005).

Second, supra-granular cortical layers are the main source of mismatch responses — as determined from intracortical recordings (Javitt et al., 1996). Critically, NMDA receptor blockade abolished MMN in layer II/III but did not affect afferent thalamic input into layer IV.

Third, theoretical accounts of predictive coding in neocortical circuits suggest that the connectivity of layer II/III pyramidal neurons endows them with a strategic role to select the most likely interpretation of inputs (Douglas and Martin, 2004). More, specifically, layer II/III pyramidal cells have been postulated to act as error-detectors under predictive coding models of perception (Mumford, 1992; Friston, 2005a). In a more recent formulation (Bastos et al., 2012) these cells (jointly with local interneurons) encode and propagate prediction error forwards to higher cortical levels.

The concordance between the major locus of neuropathological changes in schizophrenia (Harrison, 1999; Garey, 2010) and the intracortical site of MMN generation could account for the remarkable robustness of MMN deficits in this disorder. Furthermore, it explains why the MMN indexes the degree of cognitive impairment because the specific synaptic pathology in superior temporal cortex (subserving MMN, sensory memory) is replicated in lateral frontal cortex (e.g. subserving working memory, executive functions) and hippocampus (episodic memory) as reviewed above. This is also supported by the correlation of MMN deficits with grey matter density reductions not only in the superior temporal cortex (Salisbury et al., 2007) but also in frontal cortex (Rasser et al., 2011).

The consilience of predictive coding and pathophysiology in schizophrenia provides an elegant framework to explain how a relatively subtle synaptic pathology (but situated in a critical hub) can have profound effects across cortical hierarchies, giving rise to pervasive impairments — from perception to higher-order cognition. Furthermore, abnormal prediction error processing has been implicated in psychosis more widely (Stephan et al., 2009) to account for hallucinations (Friston, 2005b) as well as delusions through impaired specification of prior expectations and aberrant signalling of their violations (Corlett et al., 2007, 2011; Adams et al., 2013).

5. Conclusions and implications

We reviewed the evidence that MMN deficits are correlated with cognitive impairment in patients with schizophrenia. We also presented confirmatory data using the roving stimulation protocol to show that this correlation is reproducible and robust. In addition, we found no evidence for MMN–cognition correlations in patients with bipolar disorder and Alzheimer's disease, which suggests illness-specific disruption of MMN networks in schizophrenia. These findings require replication and clarification, for example, if they are dependent on the specific stimulation parameters used here to elicit MMN. If confirmed, they will inform the debate on the aetiological overlap of schizophrenia and bipolar disorder (Goldberg et al., 2009).

Our findings add to the growing literature suggesting that MMN can be used not only for identification of at-risk individuals (Baker et al., 2005; Bodatsch et al., 2011) but importantly also for the preclinical evaluation of novel therapeutic agents (Korostenskaja and Kahkonen,

2009). The collective evidence ranging from the phencyclidine model of schizophrenia to MMN findings over the last 20 years has provided a clear rationale for the development of NMDA receptor agonists (Javitt et al., 2012) with clinical trials now under way (e.g. Umbricht et al., 2010; Harvey and Yee, 2013). Based on our own experience we suggests that MMN recorded using the roving stimulus paradigm can serve as a sensitive translational biomarker to evaluate neuropharmacological effects of cognition-enhancing agents in humans, for example with reference to nicotine which exerts a positive effect on MMN (Baldeweg et al., 2006) and ketamine with the opposing effect (Schmidt et al., 2012).

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