Mismatch Negativity Encoding of Prediction Errors Predicts S-ketamine-Induced Cognitive Impairments

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Psychotomimetics like the *N*-methyl-D-aspartate receptor (NMDAR) antagonist ketamine and the 5-hydroxytryptamine_{2A} receptor (5-HT_{2A}R) agonist psilocybin induce psychotic symptoms in healthy volunteers that resemble those of schizophrenia. Recent theories of psychosis posit that aberrant encoding of prediction errors (PE) may underlie the expression of psychotic symptoms. This study used a roving mismatch negativity (MMN) paradigm to investigate whether the encoding of PE is affected by pharmacological manipulation of NMDAR or 5-HT_{2A}R, and whether the encoding of PE under placebo can be used to predict drug-induced symptoms. Using a double-blind within-subject placebo-controlled design, S-ketamine and psilocybin, respectively, were administered to two groups of healthy subjects. Psychological alterations were assessed using a revised version of the Altered States of Consciousness (ASC-R) questionnaire. As an index of PE, we computed changes in MMN amplitudes as a function of the number of preceding standards (MMN memory trace effect) during a roving paradigm. S-ketamine, but not psilocybin, disrupted PE processing as expressed by a frontally disrupted MMN memory trace effect. Although both drugs produced positive-like symptoms, the extent of PE processing under placebo only correlated significantly with the severity of cognitive impairments induced by S-ketamine. Our results suggest that the NMDAR, but not the 5-HT_{2A}R system, is implicated in PE processing during the MMN paradigm, and that aberrant PE signaling may contribute to the formation of cognitive impairments. The assessment of the MMN memory trace in schizophrenia may allow detecting early phases of the illness and might also serve to assess the efficacy of novel pharmacological treatments, in particular of cognitive impairments.

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INTRODUCTION

Dissociative *N*-methyl-D-aspartate receptor (NMDAR) antagonists such as ketamine and classic hallucinogens like psilocybin, which activate 5-hydroxytryptamine_{2A} receptors (5-HT_{2A}R), constitute two models of psychosis that are used to study the neurobiology of psychotic symptom formation in schizophrenia (González-Maeso and Sealfon, 2009; Javitt and Zukin, 1991; Vollenweider and Geyer, 2001). Although administration of ketamine to healthy volunteers reproduces both positive and negative symptoms of schizophrenia (Adler *et al*, 1999; Malhotra *et al*, 1996; Vollenweider *et al*, 1997a), psilocybin engenders positive symptoms that are highly reminiscent of those observed in

schizophrenia (Geyer and Vollenweider, 2008; Gouzoulis-Mayfrank *et al*, 1998). In neuroimaging studies, both ketamine and psilocybin altered the activity in fronto-temporal regions associated with depersonalization and thought disorder (Vollenweider *et al*, 1997a, b). Furthermore, ketamine infusion in schizophrenia patients transiently exacerbated positive symptoms (Lahti *et al*, 1995b) associated with an activation of PFC and thalamic structures (Lahti *et al*, 1995a). Although ketamine- and psilocybin-like drugs differ in their primary mechanism of action, both classes of drugs increase extracellular glutamate in PFC (Moghaddam *et al*, 1997; Muschamp *et al*, 2004), which may explain some of the common psychotic symptoms. However, while the pharmacological properties of these psychotomimetics are well documented (Fantegrossi *et al*, 2008; Nichols, 2004), the neuronal and cognitive mechanisms underlying ketamine- and psilocybin-induced symptoms are less well understood.

Recent works suggest that the formation of symptoms induced by psychomimetics could be understood within the framework of predictive coding models (Corlett *et al*,

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2009, 2011). These suggestions followed from predictive coding models of learning and inference (Friston, 2005; Rao and Ballard, 1999) and their specific application to schizophrenia (Stephan *et al*, 2006). Predictive coding assumes a hierarchical neural architecture where each level provides predictions about the state of the level below and evaluates the discrepancy with the actual inputs from the lower level, that is, prediction error (PE) (Friston, 2005; Rao and Ballard, 1999). Predictions and PE are conveyed via synaptic connections instantiating a Bayesian message passing scheme. Simply speaking, both perceptual inference and learning rely on minimization of PE throughout the hierarchy. Neuronal states and connection strengths are adjusted during inference and learning, respectively, to minimize PE at all levels of the hierarchy.

It has repeatedly been proposed that aberrant PE processing might be involved in the formation of psychosis, originally in the context of associative learning theory (Gray *et al*, 1991; Hemsley, 1993) and more recently in terms of Bayesian concepts (Fletcher and Frith, 2009; Murray *et al*, 2008; Stephan *et al*, 2006). Broadly speaking, these theories constitute two non-exclusive classes that stress either (i) inappropriate timing of PE signals (King *et al*, 1984; Shaner, 1999) or (ii) inadequate magnitude or precision (inverse variance) of PE estimates during hierarchical Bayesian inference (Corlett *et al*, 2009; Friston, 2005; Stephan *et al*, 2006). These general concepts have been used to explain a range of empirical findings about schizophrenia, such as interpreting fMRI data in terms of a disruption of PE processing in the PFC of schizophrenia patients with delusions (Corlett *et al*, 2007). Critically, the extent of this PE disruption was related to an individual's propensity to delusion formation. Another example is that in the early stage of psychosis, schizophrenia patients often describe how irrelevant stimuli capture their attention (Chapman, 1966). This has been framed in terms of 'aberrant salience', a phenomenological concept originally developed without explicit reference to PEs (Kapur, 2003). More recent proposals (Roiser *et al*, 2009) have speculated about a link of aberrant salience to contextually irrelevant or 'chaotic' PEs (King *et al*, 1984), which may underlie formation of inappropriate statistical associations, leading to maladaptive inference about the causes of sensory inputs. In summary, abnormal PEs may represent a general mechanism for the emergence of psychotic symptoms in schizophrenia and understanding these symptoms requires formal models that link cognitive impairments to psychopathology.

A commonly used physiological paradigm to estimate PE signaling is the mismatch negativity (MMN) event-related potential (ERP) (Garrido *et al*, 2009b; Todd and Robinson, 2010), which is most relevant to psychotic symptoms in naturally occurring and drug-induced psychosis (Corlett *et al*, 2011; Kantrowitz and Javitt, 2010). MMN is an electrophysiological event-related response to unexpected sensory (typically auditory) stimuli, the so-called 'deviants', that differ in one physical stimulus dimension from a sequence of preceding identical 'standards' (Näätänen *et al*, 1978). Indeed, deficits in MMN amplitude have been repeatedly reported in schizophrenic patients (Umbricht and Krljes, 2005), and a comparable deficit was found in healthy volunteers after exposure to ketamine (Heekeren

et al, 2008; Umbricht *et al*, 2000). Furthermore, the MMN amplitude assessed under placebo correlated positively with the ketamine-induced positive-like symptoms as indexed by the global score of the Altered State of Consciousness rating scale (5D-ASC) and the BPRS psychosis score in healthy subjects (Umbricht *et al*, 2002). This correlation was significant over frontal electrodes, suggesting that the integrity of PFC is crucial for PE processing in MMN. Another study using a different modality (fMRI) and different paradigm (an associative learning task) suggested that this role of the PFC for PE processing may generalize, reporting that ketamine disrupted PE-dependent activity in the right PFC of healthy volunteers (Corlett *et al*, 2006).

In this study, we investigated how PE processing is altered under NMDAR antagonist and/or 5-HT_{2A}R agonist manipulation, and whether ketamine- and psilocybin-induced symptoms can be predicted by the MMN. Instead of a classical oddball paradigm, we use a 'roving' MMN paradigm and examine the formation and strengthening of memory traces (by quantifying the amplitude of the MMN as a function of the number of preceding standards) (Haenschel *et al*, 2005; Imada *et al*, 1993). A notable advantage of the roving paradigm is that physical stimulus differences between standards and deviants are varied independently of the number of standard repetitions in the roving paradigm. This ensures that the ensuing MMN memory trace effect is entirely due to learning and cannot result from differential states of frequency-specific auditory neurons in the temporal cortex.

MATERIALS AND METHODS

This study was approved by the Ethics Committee of the University Hospital of Psychiatry, Zurich, Switzerland. After receiving a written and oral description of the aim of this study, all participants gave written informed consent statements before inclusion. The use of psychoactive drugs was approved by the Swiss Federal Health Office (BAG), Department of Pharmacology and Narcotics (DPN), Bern, Switzerland.

Subjects

Healthy subjects were recruited at the local university and technical college through advertisement and were then divided into two groups, either receiving S-ketamine or psilocybin (ketamine group: $N=19$ (male: 12), mean age = 26 ± 5.09 years; psilocybin group: $N=20$ (male: 12), mean age = 23 ± 2.27 years).

Before the inclusion, subjects' physical health was confirmed by medical history, clinical examination, electrocardiography, and blood analysis. To ascertain the subjects' mental status, all subjects were screened by the DIA-X diagnostic expert system (Wittchen and Pfister, 1997), a semi-structured psychiatric interview, and the Hopkins Symptom Checklist (SCL-90-R) (Derogatis, 1994). Furthermore, subjects replied to the Mini-International Neuropsychiatric Interview (MINI), a short, structured psychiatric interview (Sheehan *et al*, 1998). We verified the absence of a history of drug dependence or present drug abuse by urine drug screening and a questionnaire of drug consumption.

Drug Administration

In both groups, subjects underwent two sessions (placebo/active drug) in a counterbalanced order. Both subjects and principal investigator were blind to drug order. Subjects stayed monitored and under constant supervision until all drug effects had worn off, and were then released into the custody of a partner or immediate relative.

For the S-ketamine/placebo infusion, an in-dwelling catheter was placed in the antecubital vein of the non-dominant arm. The infusion scheme can be summarized as BET (Krüger-Thiemer, 1968). Once the subject was ready, a bolus injection over 5 min with 10 mg of ketamine was given (B). Following 1 min break, a continuous infusion with 0.006 mg/kg per min was started (E). To keep S-ketamine levels fairly constant and prevent accumulation in the brain, the dose was reduced by titrating (T). In the placebo session, the same procedure was followed. Instead of S-ketamine, an infusion of physiological sodium chloride solution and 5% glucose was given. Psilocybin was given per os at a dose of 115 µg/kg. The specific doses were chosen based on previous studies (Kometer *et al*, 2011; Vollenweider and Kometer, 2010).

Psychometric Assessment of S-Ketamine- and Psilocybin-Induced States (ASC-R)

A revised form of the Altered State of Consciousness (ASC-R) questionnaire, a visual analogue and self-rating scale, was used to assess the subjective effects of ketamine and psilocybin (Dittrich, 1975, 1998). This revised scale (ASC-R) (Studerus *et al*, 2010) comprises three primary dimensions and their respective subscales: (i) 'oceanic boundlessness', referring to positively experienced ego-dissolution associated with changes in the sense of time and emotions, ranging from heightened mood to sublime happiness and feelings of unity with the environment, subsuming the subscales disembodiment, blissful state, spiritual experience, and experience of unity and insightfulness; (ii) 'anxious ego-disintegration', comprising the subscales anxiety and impaired control and cognition,

including items for disordered thought and loss of control over body and thought; and (iii) visionary restructuralization, including the subscales elementary and complex imagery, audio-visual synesthesias, changed meaning of percepts, and auditory alterations.

Auditory Test Paradigm (MMN)

Electroencephalographic (EEG) activity was measured during an auditory 'roving' oddball paradigm (Baldeweg *et al*, 2004; Boly *et al*, 2011; Garrido *et al*, 2008; Haenschel *et al*, 2005), originally developed by Cowan *et al* (1993). Acoustic stimuli were generated by the E-prime software (Schneider *et al*, 2002), and applied binaurally through headphones (TDH-39-P; Maico, Minneapolis, MN).

Stimuli comprised a structured train of pure sinusoidal tones, with a roving changing tone (Figure 1). Within each stimulus train, all tones were of one frequency and were followed by a train of a different frequency. The first tone of a train represents the deviant (red), which becomes the standard tone after a few repetitions (blue). Hence, the deviants and standard tones have exactly the same physical properties within one stimulus train, differing only in the number of times they have been presented in the recent past (in a previous stimulus train). The number of times the same tone was presented within one stimulus train varied pseudo-randomly between 1 and 11 ($t = 1-11$). The probability that the same tone was presented in one stimulus train (i) was 2.5% for trains with 1 or 2 identical tones, (ii) 3.75% for trains with 3 or 4 identical tones, and (iii) 12.5% for trains with 5-11 identical tones. In other words, 5% of all stimulus trains consisted of 1-2 identical tones, 7.5% of all stimulus trains consisted of 3-4 identical stimuli, and 87.5% of all stimulus trains consisted of 5-11 identical stimuli. The frequency of the tones varied from 500 to 800 Hz in random steps with integer multiples of 50 Hz, tone duration was set at 70 ms, and the inter-stimulus interval was 500 ms.

In parallel, subjects performed a distracting visual task and were instructed to ignore the sounds. It has been argued

Figure 1 Stimulus design is characterized by a sporadically changing standard stimulus. The first presentation of a novel tone is a deviant ($D/t(1)$; circle) that becomes a standard (triangle), through repetition ($t(6)$). Standard repetition varied between 1 and 11 ($i = 1-11$).

that the best condition to observe an MMN is when the subject's attention is directed away from the stimulus (Näätänen, 2000). The task consisted of button-pressing whenever a fixation cross-changed its luminance, which occurred pseudo-randomly every 2–5 s (not coinciding with auditory changes). The testing session lasted approximately 15 min. The purpose of the additional distracting task was to ensure that the participant's attention was not focused on the tones.

EEG/ERP Recording

EEG recordings were made from 64 scalp electrodes using the ActiveTwo system (Biosemi, Amsterdam, The Netherlands). The horizontal electrooculogram (EOG) was recorded from electrodes attached on the outer canthus of each eye. Similarly, vertical EOG was recorded from electrodes attached infraorbitally and supraorbitally to the left eye. Data were recorded at a sampling rate of 512 Hz. All electrodes were active silver/silver chloride electrodes and were referenced during recording to a common-mode signal electrode between POz and PO3 (see <http://www.biosemi.com/faq/cms&drl.htm> for more details on this setup); the offset of all electrodes was below 25 mV, indicating good recording quality.

For ERP analysis, independent component analysis (ICA) was used to remove artifacts due to eye movements and blinks. Following ICA, epochs with a 200-ms prestimulus baseline and a 500-ms poststimulus interval were constructed. Epochs with amplitudes that exceeded $\pm 100 \mu\text{V}$ at any electrode were excluded from further averaging. Following artifact rejection, epochs were averaged offline for each subject and were digitally filtered with a band-pass filter (1–30 Hz). MMN was measured as the peak negativity within the 100–200 ms window latency of difference waveform (deviant–standard waveforms). Here, we followed previous studies of the roving paradigm (eg, Garrido et al, 2008) in focusing only on deviants preceded by at least 6 standards. Waveforms were mathematically referenced to an average-mastoid reference before peak detection, analogously analyzed as previous studies (Umbricht et al, 2000, 2002, 2003). Based on previous studies, a set of fronto-central (Fz, F3, and F4) and -temporal electrodes (TP7 and TP8) were preselected (Alho et al, 1996; Sato et al, 2000; Tiitinen et al, 1993; Waberski et al, 2001).

Statistical Analysis

All statistical analysis was conducted using Statistica 7.1 for Windows (Statsoft, Tulsa, OK, USA). Results of the distracting visual task were evaluated according to signal detection theory (Macmillan and Creelman, 1991) to determine sensitivity indexes (d') under placebo and following drug administration, which were entered into a repeated-measures analysis of variance (repeated-measures ANOVA) with between-subjects factor group (ketamine group vs psilocybin group). Furthermore, averaged means of MMN difference wave amplitude and latency were subjected to a repeated-measures ANOVA using the within-subjects factors, electrode (frontal vs temporal), treatment (placebo vs drug), and standard repetition ($t=6, 8$, and 10), and the between-subjects factor group

(ketamine group vs psilocybin group). Where the ANOVA null hypothesis of equal means was rejected, we used *post-hoc* tests (Fisher's least significant difference (LSD) test). In addition, correlations were conducted to examine the effect of the distracting visual task (d' values) on the MMN difference wave amplitudes. Another repeated-measures ANOVA was carried out to study ketamine- and psilocybin-induced symptoms.

For further analysis, the relative increase of the MMN difference waveform from $t(6)$ to $t(8)$ and further from $t(8)$ to $t(10)$ was computed and the average of these values expressed as 'MMN slope'. To assess the relationship between MMN slope under 'baseline' (drug-free) conditions and drug-induced psychopathology, we correlated (over subjects) the MMN slope under placebo with each symptom rating in the ASC-R questionnaire and Bonferroni corrected the significance level for multiple testing.

RESULTS

Distracting Visual Vigilance Test

Repeated-measures ANOVA revealed that both drugs produced significantly prolonged reaction times ($F(1, 37) = 31.4$, $P < 0.0000$, $\eta^2 = 0.46$) as well as reduced sensitivity indices (d') ($F(1, 37) = 20.8$, $P < 0.00001$, $\eta^2 = 0.36$) (Table 1). Drug effects did not differ from each other, as indicated by the lack of interaction with the between-subjects factor group.

MMN Memory Trace Effect (PE Processing)

A significant main effect for *standard repetition* revealed the systematic increase in MMN amplitude with increasing number of standard tones (memory trace effect) ($F(2, 74) = 3.58$, $P < 0.05$, $\eta^2 = 0.1$). In general, both overall MMN amplitude and MMN trace effect were more pronounced over frontal than temporal electrodes ($P < 0.000001$), as indicated by a significant main effect for *electrode* ($F(1, 37) = 145$, $P < 0.000001$, $\eta^2 = 0.8$) and a significant *electrode* $\times$ *standard repetition* interaction ($F(2, 74) = 5.1$, $P < 0.01$, $\eta^2 = 0.12$). Furthermore, a main effect of treatment was found ($F(1, 37) = 8.35$, $P < 0.01$, $\eta^2 = 0.18$) reflecting an overall attenuation of the MMN amplitude, irrespective of standard repetition, following drug administration. Furthermore, a *treatment* $\times$ *electrode* interaction ($F(1, 37) = 5$, $P < 0.05$, $\eta^2 = 0.12$) revealed that this treatment effect occurred only over frontal electrodes ($P < 0.00000$). However, the *electrode* $\times$ *treatment* $\times$ *group*

Table 1 Behavioral Results of the Distracting Visual Vigilance Task

	Ketamine group			Psilocybin group		
	Placebo	Ketamine	P-value	Placebo	Psilocybin	P-value
RT (ms)	331 $\pm$ 4.3	350 $\pm$ 5.2	0.001	340 $\pm$ 4.6	360 $\pm$ 5.1	0.001
d'	1.9 $\pm$ 0.27	1.1 $\pm$ 0.22	0.01	1.6 $\pm$ 0.28	0.8 $\pm$ 0.12	0.01

Mean reaction times (RT) and sensitivity indices (d') $\pm$ SE. Both measures were significantly worsened by both drugs, but did not differ significantly between drugs.

interaction revealed that this treatment effect depended on the location of the electrodes and on the specific drug used ($F(1, 37) = 10.5$, $P < 0.01$, $\eta^2 = 0.22$). Although psilocybin did not affect the MMN over frontal or temporal electrodes, ketamine did disrupt the MMN, but only at frontal electrodes ($P < 0.00001$) (Figure 2). A subsequent ANOVA of the ketamine group revealed that ketamine disrupted the MMN memory trace effect over frontal electrodes, indicated by a triple *electrode* $\times$ *treatment* $\times$ *standard repetition* interaction ($F(2, 36) = 4.7$, $P < 0.05$, $\eta^2 = 0.21$). *Post-hoc* analysis showed that for the frontal electrodes Fz, F3, and F4 shown in Figure 2, the *treatment* $\times$ *standard repetition* interaction was also significant (P at $t(6) < 0.0001$; P at $t(8) < 0.0001$; P at $t(10) < 0.000001$), indicating that the difference in the effect of ketamine vs placebo on the MMN trace effect became more pronounced with longer trace length. The corresponding MMN difference waves for the ketamine group were plotted in Figure 3. Finally, as shown by a significant *treatment* $\times$ *group* interaction (Figure 3), ketamine but not psilocybin caused a latency shift of the MMN, irrespective of standard repetition ($F(1, 37) = 5.29$, $P < 0.05$, $\eta^2 = 0.13$).

Notably, no significant correlations between the behavioral results of the distracting visual vigilance task (d' values) and the MMN slope in either group were found, suggesting a functional dissociation.

S-Ketamine- and Psilocybin-Induced Symptoms (ASC-R Questionnaire)

At the dose tested, both ketamine and psilocybin produced similar alterations on the global ASC score that were characterized by derealization and depersonalization phenomena, affective changes, cognitive impairments, and perceptual alterations, reflected by a main effect for *treatment* ($F(1, 37) = 69.5$, $P < 0.000001$, $\eta^2 = 0.65$).

Subsequent ANOVA with *treatment* and *subscale* as repeated measures and *group* as between-subject factor revealed that both drugs significantly increased all subscale scores (all P 's < 0.01), with the exception of the anxiety score ($F(11, 407) = 4.6$, $P < 0.00001$, $\eta^2 = 0.11$). In addition, psilocybin-induced auditory alterations were not

Figure 3 Corresponding mismatch negativity (MMN) difference waveforms following placebo (solid line) and ketamine administration (dashed line) at frontal electrodes (Fz, F3, and F4) for $t(6)$ (above), $t(8)$ (middle), and $t(10)$ (below).

Figure 2 Mean amplitudes $\pm$ SE of mismatch negativity (MMN) difference waveforms across standard repetitions ($t = 6-10$) at frontal electrodes (Fz, F3, and F4) following placebo (green) or drug administration (red: ketamine; blue: psilocybin), respectively. Note: Significant differences between treatment conditions at $*P < 0.0001$ and at $**P < 0.000001$.

Figure 4 Means $\pm$ SE of ketamine- (solid line) and psilocybin-induced (dashed line) symptoms relative to placebo (dotted line) measured with the revised form of the Altered State of Consciousness (ASC-R). Note: Significant differences (least significant difference (LSD) test) between drugs at $*P < 0.05$ and at $**P < 0.01$. Symptoms scores were expressed as the percent of scale maximum. The abbreviation VR comprised 'visionary restructuring', OB means 'oceanic boundlessness', and AED stands for 'anxious ego-disintegration'. Both ketamine and psilocybin increased the global ASC score relative to placebo, but did not differ from each other. Ketamine produced higher score than psilocybin for auditory alterations, disembodiment, and impaired control and cognition. Otherwise, psilocybin produced higher score for elementary imagery than ketamine. No correlation between drug-induced cognitive impairments (impaired control and cognition) and drug-induced perceptual alterations (auditory and visual) was found.

significantly higher than that under placebo. Moreover, *post-hoc* analysis showed that ketamine produced significantly higher scores than psilocybin for auditory alterations ($P < 0.05$), for depersonalization as indexed by disembodiment ($P < 0.000001$) and for cognitive impairments as indexed by impaired control and cognition ($P < 0.05$) (Figure 4). Otherwise, psilocybin produced more severe elementary imagery ($P < 0.01$), including visual illusions and (pseudo-) hallucinations than ketamine. Notably, no correlation was found between drug-induced cognitive impairments (impaired control and cognition) and drug-induced perceptual alterations (auditory and visual). This speaks against the possibility that drug-induced perceptual aberrations induced cognitive impairments.

Linking MMN Slope and Drug-Induced Symptoms

We assessed the relation between MMN slope under 'baseline' (drug-free) conditions at frontal electrodes and drug-induced psychopathology by correlating the MMN slope under placebo with each symptom rating from the ASC-R questionnaire (under Bonferroni correction for multiple testing). We found a significant correlation between the MMN slope under placebo and ratings pertaining to *impaired control and cognition* (which includes items for disordered thought and loss of control over body and thought). Critically, this correlation was significant under ketamine ($r = -0.67$; $P < 0.05$ Bonferroni corrected), but not under psilocybin ($r = -0.11$; $P = \text{NS}$) (Figure 5). Those subjects who showed the greatest MMN slope under placebo experienced the lowest ketamine-induced cognitive impairments. No other correlations

between the MMN slope under placebo and any other drug-induced symptom was found.

DISCUSSION

Our study provides two major results: Firstly, prefrontal PE processing during the roving MMN paradigm is disrupted by the NMDAR antagonist S-ketamine, but not by the 5-HT_{2A}R agonist psilocybin. Secondly, the processing of PE under placebo predicts the severity of ketamine-induced cognitive impairments. In the following, we discuss these findings within a predictive coding framework of MMN (Baldeweg, 2006; Friston, 2005; Garrido *et al*, 2009a,b), relating them to putative neurobiological mechanisms for the emergence of cognitive impairments.

According to classical theories (Näätänen, 1992), the MMN potential originates from a network comprising the superior temporal gyrus (STG) and the inferior frontal gyrus (IFG) (Garrido *et al*, 2008; Opitz *et al*, 2002; Rinne *et al*, 2000), which detects a disruption within a regularity of preceding standards based on a comparison of the actual sensory input with the already established memory trace (Doeller *et al*, 2003; Giard *et al*, 1990). In this study, we have performed an analysis in sensor space; since EEG sensor signals result from a mixture of neuronal sources, one should be cautious about relating our findings to neural sources in specific locations. In other words, an MMN effect observed at frontal electrodes must not necessarily correspond to a frontal source, and the following discussion should be read with this caveat in mind.

Figure 5 Relationship between the mismatch negativity (MMN) slope under placebo over frontal electrodes and the subscale *impaired control and cognition*, which includes disordered thought and loss of control over body and thought, induced by ketamine (solid line) and psilocybin (dotted line). Impaired control and cognition scores are expressed as the percentage of the maximum points possible. Notably, the MMN slope under placebo was predictive of ketamine-induced cognitive impairments ($r = -0.67$; $P < 0.05$), but not of psilocybin-induced cognitive impairments ($r = -0.11$; $P = \text{NS}$).

Consistent with other reports using a ‘roving’ oddball design (Baldeweg *et al*, 2004; Haenschel *et al*, 2005), an MMN memory trace effect was found in this study over the frontal cortex; however, no comparable effect was detected over temporal cortical regions. The absence of a temporal MMN memory trace effect suggests that the adaptation hypothesis (Jääskeläinen *et al*, 2004), which posits that the MMN results from local neuronal adaptation in the auditory cortex, cannot easily explain the MMN memory trace effect found in this study. Instead, the frontal MMN memory trace effect may be more plausibly understood as a marker of PE caused by the deviation from a learned regularity. This interpretation would be in line with the model adjustment hypothesis (Näätänen and Winkler, 1999; Winkler *et al*, 1996). However, another roving MMN study in healthy volunteers (which focused on MMN amplitudes in reference to the 6th standard and did not quantify memory trace effects) used dynamic causal modeling and Bayesian model selection to suggest that the model explaining MMN amplitude best was a combination of the adaptation and model adjustment hypotheses. This model accommodates intra-areal adaptation within the STG combined with plasticity of inter-areal connections between temporal and frontal regions (Garrido *et al*, 2008). The authors explicitly interpreted their findings within the predictive coding framework, emphasizing that this theory includes both adaptation and model adjustment in the sense that ‘model adjustment’ corresponds to the adjustment of a generative model of future stimuli and ‘adaptation’ corresponds to local changes in post-synaptic gain (Garrido *et al*, 2008). Thus, from this perspective, the MMN would arise from a failure to predict bottom-up input and suppress the resulting PE (Garrido *et al*, 2008, 2009b).

As reported previously (Heekeren *et al*, 2008; Umbricht *et al*, 2000), the temporal MMN (TP7/TP8) was not significantly altered by S-ketamine in this study, although

this lack of effect may have resulted from the chosen nearby mastoid (TP9/10) reference, which might mask a drug effect on this component. However, similar to this study, no disruption of the temporal MMN was observed in schizophrenic patients *vs* healthy controls in two recent studies using the nose as reference and applying a similar ‘roving’ paradigm as used in this study (Baldeweg *et al*, 2004; Sato *et al*, 2003). In contrast to S-ketamine’s lack of effect on temporal MMN, our study found that S-ketamine did disrupt the frontal MMN, which is consistent with previous human studies using different MMN paradigms (Heekeren *et al*, 2008; Umbricht *et al*, 2000). Here we extend these previous findings by showing that S-ketamine not only reduced the MMN amplitude, but also disrupted the frontally generated MMN memory trace effect compared with placebo. A similar reduction of the frontal memory trace effect was observed in schizophrenic patients (Baldeweg *et al*, 2004). This finding, together with the established importance of the NMDAR for synaptic plasticity during perceptual learning (Kandel, 2001; Morris *et al*, 1986), fits nicely to the role that neurobiologically specific predictive coding theories of MMN have assigned to NMDAR-dependent plasticity. In these theories (Friston, 2005; Stephan *et al*, 2006), NMDAR-dependent short-term plasticity is critical for adjusting the strength of glutamatergic synapses connecting hierarchically related cortical areas during perceptual learning. Computationally, this synaptic adjustment is driven by the magnitude of trial-wise PEs in lower-level structures, leading to adjustment of predictions generated by higher-level structures. From this perspective, our finding of a reduced frontal MMN memory trace may reflect the drug-induced perturbation of NMDAR-dependent plasticity of temporo-frontal (forward) connections that serves to adjust PE message passing between the STG and the IFG during MMN generation (Garrido *et al*, 2008; Opitz *et al*, 2002). In other words, the

disruption of frontal MMN by S-ketamine may result from a deficient adjustment of prefrontally generated predictions about temporal inputs due to insufficient PE-dependent plasticity of forward connections. We will examine the plausibility of this potential mechanism in future modeling studies. However, the present data cannot fully exclude that increased AMPA receptor conductance following NMDAR blockade (Shi and Zhang, 2003) or downstream effects on the dopaminergic system (Kapur and Seeman, 2001; Vollenweider *et al*, 2000) may also have contributed to the present findings. Indeed, in the context of predictive coding accounts of psychosis, it was suggested recently that both NMDAR (for backward connections) and AMPAR (for forward connections) contribute to conveying PE information (Corlett *et al*, 2009). In contrast, the empirical data from studies examining the MMN under dopaminergic manipulations indicate that dopamine does not modulate the MMN (Korostenskaja *et al*, 2008; Leung *et al*, 2007; Leung *et al*, 2010).

Some symptoms frequently observed in schizophrenia are not typically interpreted within a Bayesian framework and are usually examined from different perspectives. For example, this include deficits in early information processing as indexed by measures as prepulse inhibition of startle reflex or the P50 auditory-evoked potential suppression (Braff *et al*, 2001; Turetsky *et al*, 2007). In this context, it has been recently suggested that in schizophrenic patients, deficits in early sensory processing may explain the observed reduction in MMN (Leitman *et al*, 2010). If one accepts S-ketamine as a valid model of schizophrenic symptoms, then this may be seen as a challenge for our findings. However, given that physical differences between deviant and standard tones were independent of the number of standard tones in the roving paradigm and that the difference in the effect of ketamine *vs* placebo on the MMN trace effect became more pronounced with longer trace length, it seems unlikely that a pure deficit in early sensory processing could account for the ketamine-induced disruption of the MMN memory trace effect. This interpretation is further supported by a lack of correlation between ketamine-induced auditory alterations and the generation of the MMN memory trace effect.

Contrary to S-ketamine, the 5-HT_{2A}R agonist psilocybin neither reduced the MMN amplitude nor the MMN memory trace effect, which is consistent with a previously reported lack of psilocybin on MMN measured by a classical paradigm (Umbricht *et al*, 2003). Similarly, a recent MMN study with S-ketamine and the 5-HT_{2A}R agonist DMT showed that the frontal MMN was only affected by S-ketamine and not by DMT (Heekeren *et al*, 2008). Although 5-HT_{2A}R seems to be involved in different forms of working memory (Williams *et al*, 2002) and 5-HT_{2A}R agonists such as LSD or DOM enhanced associative learning as measured by eyeblink conditioning in rabbits (Harvey, 2003), the implicit perceptual learning as indexed by the frontal memory trace effect appeared not to be sensitive to manipulations of the 5-HT_{2A}R system (or to the dose of psilocybin used in this study). Although it has been proposed that neuro-modulators like serotonin may influence the processing of PE (Corlett *et al*, 2009) and may be one of the key modulators interacting with NMDARs to produce aberrant synaptic plasticity in schizophrenia (Stephan *et al*, 2009),

this does not necessarily contradict our findings since such a putative role of serotonin could be expressed in a regionally specific manner (ie, in other circuits than the auditory system), and may thus not be a critical factor in PE processing during the MMN paradigm (cf. Garrido *et al*, 2009b).

Furthermore, we also explored whether ketamine- or psilocybin-induced symptoms could be predicted by the MMN slope (in the absence of any drug) (ie, under placebo); in other words, we used two pharmacological models of psychosis to relate individual 'baseline' physiology to his/her predisposition to develop psychotic symptoms under pharmacological challenge. This approach is inspired by the general notion that the development of psychiatric disease may result from the interplay between the (genetically determined) susceptibility of an individual and the exposure to environmental stressors (Brown, 2011), and follows previous studies, which examined whether physiological markers can predict the individual degree of psychotic symptoms in drug-induced psychosis and schizophrenia (Corlett *et al*, 2006; Honey *et al*, 2008; Krystal *et al*, 2003; Umbricht *et al*, 2002). Here, we found that the MMN slope under placebo showed a negative correlation with the subsequent ketamine-induced extent of cognitive impairments across subjects; in contrast, no comparable relationship was found for psilocybin. Although this result is in accordance with Umbricht's MMN study (Umbricht *et al*, 2002), it may not appear to be fully consistent with the results by Corlett *et al* (2006), who found that frontal PE signals under placebo, measured during an associative learning task with fMRI, exhibited a positive correlation with the severity of positive symptoms (delusions, perceptual aberrations) under ketamine. However, the results from the two studies are not directly comparable owing to a number of major methodological differences, including different symptom rating scales, different ketamine dosage and application regimens, different measurement techniques (fMRI *vs* EEG), and, perhaps most importantly, fundamentally different cognitive paradigms. Still, one may wonder why individual MMN slope under placebo should predict ketamine-induced cognitive impairments (rather than other symptoms). This can be understood by considering that ketamine disrupts (short- and long-term) NMDAR-mediated synaptic plasticity, which is a crucial mechanism for PE-dependent learning (for a review, see Stephan *et al* (2006)). This is relevant for understanding cognitive impairments or 'negative symptoms', such as thought disorder, in schizophrenia because 'many, if not all, of them can also be understood as a consequence of aberrant modulation of synaptic plasticity' (Stephan *et al*, 2009). In brief, if one is endowed with inadequate PE-dependent learning (due to NMDAR-related deficiencies), one may be impaired in learning about the statistical structure of the (social and physical) environment and adapting one's beliefs and behavior accordingly. This could explain a wide range of symptoms, from social withdrawal and apathy to thought disorders and aberrant perceptual inference (see Stephan *et al* (2009) for details). On the other hand, the magnitude of the MMN slope can be seen as expressing the individual capacity for PE-dependent learning, that is, how trial-wise 'surprise' about a deviant induces NMDAR-dependent short-term plasticity to update predictions about the next trial.

In other words, MMN slope may serve as an index of individual capacity of utilizing PEs for adaptive cognition through NMDAR-dependent plasticity. From this perspective, one would predict that the higher this individual capacity in the drug-free state (ie, the higher the MMN slope under placebo), the less pronounced the effects of ketamine on PE-dependent learning and subsequent aberrations in adaptive cognition. This is what we found.

To conclude, these results suggest that the frontal MMN memory trace effect may provide a useful approach to study NMDAR-dependent PE processing during the MMN as a form of implicit perceptual learning. Unraveling the role of NMDAR function in predictive coding may provide valuable insights into pathophysiological mechanisms of schizophrenia in general and the emergence of cognitive impairments in psychosis in particular. This may particularly benefit from a computational modeling approach, which uses physiologically interpretable model parameters for clinical predictions (Stephan *et al*, 2006). In relation to this, recent studies demonstrated that a reduction of MMN can predict the transition of 'ultra-high risk' to first-episode psychosis (Bodatsch *et al*, 2010; Shin *et al*, 2009). Finally, the assessment of the MMN memory trace effect may also provide a promising tool to assess the efficacy of novel pharmacological treatment, in particular for treatment of cognitive impairments.

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DISCLOSURE

The authors declare no conflict of interest.

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