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The effects of ketamine on the mismatch negativity (MMN) in humans – A meta-analysis

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HIGHLIGHTS

- Schizophrenia has been linked to a hypofunction of the glutamatergic N-methyl-D-aspartate (NMDA) receptor.
- Administration of ketamine as an NMDA antagonist consistently leads to diminished amplitudes of the auditory mismatch negativity (MMN), similar to findings in schizophrenia patients.
- There is no evidence by previous research that the MMN to duration deviants is more impaired by ketamine than the MMN to frequency deviants.

ABSTRACT

Objective: To investigate whether effects of the glutamatergic N-methyl-D-aspartate (NMDA) receptor antagonist ketamine on the mismatch negativity (MMN) vary between duration and frequency deviants, as suggested by clinical studies on schizophrenia patients.
Methods: Our meta-analysis included previous studies that used ketamine in order to induce psychotic experiences in healthy participants and that recorded the MMN either by electroencephalography or magnetoencephalography.
Results: The analysis revealed systematic MMN amplitude decreases and, with a lower effect size, latency increases after ketamine administration. However, the observed amplitude and latency effects did not vary between duration and frequency deviants.
Conclusion: Across studies, there is no evidence that ketamine effects on the MMN are larger for duration than frequency deviants.
Significance: Our findings tentatively suggest that, in addition to an NMDA receptor hypofunction, other factors might contribute to the sometimes observed pattern of impaired MMN responses to duration deviants, but unimpaired MMN responses to frequency deviants in schizophrenia.

1. Introduction

Investigations of the pathophysiological mechanisms behind schizophrenia are important for an understanding of this disease, but also for the development of novel pharmaceutical treatment strategies. On the level of biochemical neurotransmission, a number of receptors and neurotransmitters have been considered to contribute to the symptoms of schizophrenia. Historically, dopamine was the first neurotransmitter that was presumed to play a crucial role in schizophrenia. The so-called dopamine hypotheses were primarily based on to two observations: first, the administration of dopaminergic agonists (such as high doses of amphetamines) transiently induces psychotic symptoms in healthy subjects similar to those observed in patients with schizophrenia (Angrist et al., 1974; Lieberman et al., 1987). Second, the administration of dopaminergic antagonists, such as haloperidol, alleviates symptoms in schizophrenia patients whereby the dopamine receptor binding properties of such antipsychotics predict their clinical and pharmacological potencies (Creese et al., 1976). Comprehensive recent reviews of the presumed role of

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dopaminergic neurotransmission in schizophrenia are found in Brisch (2014) and Howes et al. (2015).

Similar to dopaminergic agonists, glutamatergic antagonists, blocking the N-methyl-D-aspartate (NMDA) receptor, induce transient psychotic symptoms in healthy subjects and even cause prolonged psychotic states after excessive abuse (Luby et al., 1959; Jacob et al., 1981; Javitt and Zukin, 1991; Krystal et al., 1994; Vollenweider et al., 1997; Domino and Luby, 2012). Moreover, such drugs worsen symptoms in schizophrenia patients (Lahti et al., 1995). Further evidence for an NMDA hypofunction in schizophrenia stems from glutamatergic drug treatments for schizophrenia (e.g. from treatments with glycine, D-serine, or glycine transporter inhibitors) and in vivo imaging studies in such patients (for review: Howes et al., 2015). For completeness, it should be noted at this point that other receptors, such as acetylcholine, γ-aminobutyric acid (GABA), and serotonin have been implicated in schizophrenia as well (Benes, 2001; Meltzer and Massey, 2011; Rowe et al., 2015).

For clinical neurophysiologists, the NMDA receptor hypofunction hypothesis in schizophrenia has gained importance because event-related potential (ERP) research showed that the mismatch negativity (MMN), an ERP component elicited by deviant sounds interspersed in an otherwise uniform auditory stimulation, is reduced in amplitude and, less consistently, delayed in latency in patients with schizophrenia (for review: Michie, 2001; Rosburg et al., 2004; Umbricht and Krljes, 2005; Näätänen and Kähkönen, 2009; Näätänen et al., 2015). These alterations have been linked to NMDA receptor hypofunction: the MMN amplitudes, recorded from the primary auditory cortex in macaques, decreased after the focal infusion of a potent NMDA antagonist (phencyclidine, PCP) (Javitt et al., 1996). Such an MMN amplitude reduction was also found in non-invasive recordings in healthy humans after administration of ketamine, which acts primarily as an NMDA antagonist (Umbricht et al., 2000; Kreitschmann-Andermahr et al., 2001). Additionally, ketamine led to an increase of the MMN latency (Umbricht et al., 2000; Kreitschmann-Andermahr et al., 2001). It was also found that the MMN amplitude before ketamine administration predicts the extent of psychotic experience induced by the drug, with smaller MMN amplitudes at baseline being associated with stronger psychotomimetic effects of ketamine, leading to the hypothesis that the MMN amplitude might index the functional state of NMDA receptor-mediated neurotransmission (Umbricht et al., 2002). The association between the NMDA receptor functionality, MMN, and psychotic experience/behavior was further strengthened by a study that investigated the effects of N-acetyl-cysteine (NAC), a glutathione precursor, in schizophrenia patients: NAC administration as add-on medication led to an increase of the MMN amplitude (Lavoie et al., 2008), as well as to an improvement of schizophrenia symptoms (Berk et al., 2008).

More recently, this deficient MMN response in patients with schizophrenia has been characterized as a "break-through biomarker in predicting psychosis onset" (Näätänen et al., 2015, see also Belger et al., 2012). Indeed, in one study with individuals clinically at high risk for developing a psychosis, the MMN amplitude to duration deviants (but not to frequency deviants) could predict the conversion to a full-blown psychosis (Bodatsch et al., 2011; see also Atkinson et al., 2012; Jahshan et al., 2012; Shaikh et al., 2012; Higuchi et al., 2013). There are also reports that schizophrenia patients with a short illness duration show deficits in the MMN to duration deviants but not to frequency deviants (Todd et al., 2008; see also Brockhaus-Dumke et al., 2005; Domján et al., 2012). Whereas Näätänen et al. (2015) emphasize that in particular the MMN to change in tone duration is of relevance as potential biomarker and the authors also highlight the association between MMN generation and NMDA receptor functionality, little attention has been paid to the question of whether the administration of NMDA receptor antagonists actually leads to a specific or more pronounced disruption of the MMN to duration deviants, as compared to frequency (and other kinds of) deviants.

In the current meta-analysis, we aimed at clarifying whether the effects of ketamine as an NMDA antagonist on the MMN amplitude varies between the different kinds of deviants used for eliciting it. For that purpose, we analyzed ERP studies with healthy participants who received ketamine doses strong enough to evoke psychotic experiences. We analyzed the ketamine effects on the MMN amplitudes and latencies. Our analysis aimed at providing an estimate of the general effect sizes (does the administration of ketamine result in strong, medium or weak effects?) and at assessing whether the effects vary between different kinds of deviants. More specifically, we addressed the question of whether the administration of ketamine leads to a more pronounced disruption of the MMN elicited by duration deviants as compared to frequency deviants.

2. Methods

2.1. Study selection: inclusion and exclusion criteria

In our meta-analysis, we included only studies that used either ketamine or S-ketamine as psychoactive drugs in healthy participants and recorded the MMN either by electroencephalographic or magnetoencephalographic (MEG) recordings. Pharmaceutical preparations of ketamine are racemats of S-ketamine and R-ketamine (1:1 mixtures). S-ketamine exhibits a voltage- and use-dependent blockade of NMDA receptor currents twice as large as R-ketamine (Zeilhofer et al., 1992). R-ketamine was reported not to induce psychotic symptoms (Vollenweider et al., 1997). A literature search was conducted in MEDLINE using the following key words ("MMN" or "mismatch negativity") and "ketamine". In studies detected by this search, the reference lists were checked for additional studies.

Inclusion criteria: Included studies needed to report the MMN amplitude at midfrontal/central electrodes (±standard deviations, SD, or standard errors, SE) or another measure of the MMN magnitude, such as the dipole moment of the underlying MMN generator. For electroencephalographic studies, preference was given for unrefined amplitude measures of the MMN, also in order to reduce the methodological heterogeneity across studies. For the investigation of the effects of ketamine on the MMN latency, studies needed to report the MMN peak latency (±SD/SE). In case of missing values or inconsistent reports, we sought to contact the authors of the studies. In almost every case, the contacted authors were willing and able to provide the requested information.

Exclusion criteria: Studies that used other NMDA antagonists than ketamine and recorded the MMN were not considered. Specifically, we did not include the study of Korostenskaja et al. (2007) using memantine (an NMDA antagonist also used in the treatment of patients with Alzheimer's disease) because the administration of memantine (30 mg) did, as expected, not result in any psychotic experiences. For the same reason, we did not consider the study of Knott et al. (2012) that administered ketamine, but in rather low, explicitly non-psychotomimetic doses. When studies used more than one ketamine dosage (Heekeren et al., 2008), the data of the lower drug doses were not considered. Conditions in which ketamine was administered in combination with other drugs were not considered for the meta-analysis either. Furthermore, we did not include animal studies in our analysis even though we acknowledge that such research provides complementary information to human studies.

We identified 8 studies that fulfilled our inclusion criteria. All studies but one recorded the MMN by electroencephalography

(EEG). The one study using MEG recordings was our previous own study where we investigated the effects of ketamine on the neuromagnetic MMN (Kreitschmann-Andermahr et al., 2001). Overall, frequency, duration, and intensity deviants were used in the identified studies for eliciting the MMN, whereby some studies used just a single kind of deviant and others used several kinds of deviants. For the purpose of the current analysis, the MMN to each kind of deviant and its modulation by ketamine was considered as an independent observation. For the analysis of ketamine effects on the MMN latency, data of one study using frequency deviants were not at hand (Oranje et al., 2000). All included studies manipulated the factor drug in within-subject designs.

The selected articles were reviewed to extract the following data: the sample size, the kind of deviance, number of trials, percentage of deviants, the mean MMN amplitude (±SD) after administration of ketamine and the mean MMN amplitude (±SD) either before ketamine administration or after administration of a placebo, as well as the peak MMN latencies (±SD) in these two test conditions (ketamine vs. baseline/placebo). Effect sizes were calculated on the basis of ERP data from frontal electrodes or, for the MEG study, on the basis of the reconstructed left-temporal dipole source (Table 1). For the analysis of the drug effects, the mean amplitudes and latencies (±SD) of each study were entered into OpenMeta Analyst (Brown University, Wallace et al., 2012) and effects sizes of the ketamine effects were calculated. Mean effects sizes were assessed by using a random effect model. The kind of deviance (DEVIANCE) was used as moderator variable in a meta-regression in order to reveal whether the effects sizes varied between frequency and duration deviants. The ketamine effects on the MMN to intensity deviants were not considered for the latter analysis, as only two studies used such deviants.

3. Results

The eight studies collected data in 120 (99 male, 21 female) healthy participants. There were seven studies that used frequency deviants, six that used duration deviants, and two that used intensity deviants (Table 1). Five of the eight studies were placebo-controlled. The other studies used baseline recordings either collected in separate recording sessions or directly before the ketamine administration, for evaluating the ketamine effects. Umbricht et al. (2000) reported MMN data from both a placebo condition and a within-session baseline recording as control conditions; for this study, we selected the within-session baseline recording for calculating the effect sizes. The used ketamine dosages showed some variance between studies as well (Table 2).

3.1. MMN amplitude

Across all deviants, studies showed a significant decrease of the MMN amplitude after administration of ketamine (pooled standard mean difference, SMD: 0.490, 95% CI: 0.300–0.618, SE: 0.097, $p < 0.001$). There was no statistical indication that heterogeneity was present ($\tau^2 < 0.001$, $I^2 = 0\%$, $Q_{14} = 8.063$, n.s.). Inclusion of DEVIANCE as moderator variable did not reveal an influence of the kind of stimulation on the ketamine effects on the MMN amplitude either. Ketamine effects on the MMN amplitude were significant for duration and frequency deviants, when analyzed separately (pooled SMD: 0.369, 95% CI: 0.061–0.677, SE: 0.157, $p = 0.019$; pooled SMD: 0.545, 95% CI: 0.278–0.813, SE: 0.137, $p < 0.001$, respectively, Fig. 1).

Aside from the kind of deviance, effects of ketamine on the MMN amplitude could also be modulated by the size of the MMN amplitude at baseline. It might be argued that the impact of ketamine could be larger for deviants that are easily detectable and result in large MMN responses. In an additional analysis, we only included the EEG studies and entered the amplitude of the MMN at baseline as moderator variable into the meta-analysis. However, this analysis did not reveal a significant influence of the MMN amplitude on the observed effect sizes ($\beta = 0.055$, SE 0.084, n.s.).

3.2. MMN latency

Across all deviants, studies showed a significant increase of the MMN latency after administration of ketamine (pooled SMD: −0.280, 95% CI: −0.476 to −0.083, SE: 0.100, $p = 0.005$). There was no statistical indication that heterogeneity was present ($\tau^2 < 0.001$, $I^2 = 0\%$, $Q_{13} = 9.889$, n.s.). Inclusion of DEVIANCE as moderator variable did not reveal an influence of the kind of stimulation on the ketamine effects on the MMN amplitude either. However, ketamine effects on the MMN were significant only for frequency deviants, but not for duration deviants, when analyzed separately (pooled SMD: −0.389, 95% CI: 0.678 to −0.101, SE: 0.147, $p = 0.008$; pooled SMD: −0.199, 95% CI: −0.553–0.155, SE: 0.180, $p = 0.270$, respectively, Fig. 2).

4. Discussion

Our meta-analysis across eight studies revealed decreased MMN amplitudes and increased MMN latencies after ketamine. Studies showed on average a strong effect for the MMN amplitude (pooled SMD: 0.490), whereas the ketamine effects on the MMN latency were less pronounced (pooled SMD: −0.280). Moreover, our study found no evidence that the MMNs to duration deviants were more affected by ketamine administration than the MMNs to frequency deviants. For both the MMN amplitudes and the MMN latencies, the effects were across studies numerically larger (and consequently more significant) for frequency deviants than for duration deviants.

In general, the current findings support the assumption that an NMDA receptor hypofunction leads to a decrease and delay of the MMN response. This evidence stems not just from the reported human MMN recordings but such reductions were also found in a range of animal models, including recordings in mice (Umbricht et al., 2005; Ehrlichman et al., 2008), rats (Tikhonravov et al., 2008), monkeys (Javitt et al., 1996; Gil-da-Costa et al., 2013), and even pigeons (Schall et al., 2015). Thus, the relationship between potent NMDA antagonists and the MMN can be considered as established. However, contrasting results, such as a lack of significant alterations of the MMN after ketamine (e.g. Roser et al., 2011) or a reversed pattern (significantly shorter MMN latencies after ketamine, Mathalon et al., 2014) have been published. Furthermore, this general picture of delayed and decreased MMN after ketamine administration may be obscured at times by the variance of the drug's effects between MMNs elicited by different kinds of deviants, as reported in individual studies, with drug effects present for the MMN to one kind of deviant and absent for another. Umbricht et al. (2000), for example, found a significant latency delay after ketamine for the MMN to duration deviants, whereas the delay was insignificant for frequency deviants.

Such a stronger impact of ketamine on the MMN to duration deviants is in line with observations from clinical studies showing that schizophrenia patients with a short illness duration exhibit deficits in the MMN to duration deviants but not to frequency deviants (Todd et al., 2008) or that the MMN amplitude to duration deviants (but not to frequency deviants) could predict the conversion to a full-blown psychosis in individuals at risk (Bodatsch et al., 2011). However, it still needs to be shown how systematically and

Table 1
Details of the studies included in the current meta-analysis.

Authors and year	Participants (male, female)	Auditory stimulation				Trials % dev SOA	MMN quantification
		Standard	Frequency deviant	Duration deviant	Intensity deviant		
Oranje et al. (2000)	18 (18 M, 0 F)	1000 Hz 50 ms 95 dB SPL	1100 Hz 50 ms 95 dB SPL	–	–	600 20% 1800–2200 ms	Fz
Umbricht et al. (2000)	20 (14 M, 6 F)	1000 Hz 100 ms 75 dB SPL	1500 Hz 100 ms 75 dB SPL	1000 Hz 250 ms 75 dB SPL	–	6068 5%/each 300 ms	Fz
Kreitschmann-Andermahr et al. (2001)	10 (10 M, 0 F)	1000 Hz 50 ms 90 dB SPL	1050 Hz 50 ms 90 dB SPL	1000 Hz 100 ms 90 dB SPL	1000 Hz 50 ms 80 dB SPL	594 10%/each 1050 ms	Left-hemispheric dipole moment
Heekeren et al. (2008)	9 (7 M, 2 F)	1000 Hz 50 ms 75 dB SPL	1200 Hz 50 ms 75 dB SPL	1000 Hz 100 ms 75 dB SPL	–	3000 10%/each 550 ms	Fz
Roser et al. (2011)	20 (20 M, 0 F)	1000 Hz 100 ms 75 dB SPL	1500 Hz 100 ms 75 dB SPL	1000 Hz 250 ms 75 dB SPL	–	3000 10% 300 ms	Fz
Gunduz-Bruce et al. (2012)	16 (13 M, 3 F)	500–1500 Hz 75 ms 76 dB SPL	550–1650 Hz & 450–1350 Hz 75 ms 76 dB SPL	500–1500 Hz 125 ms 76 dB SPL	500–1500 Hz 75 ms 66/86 dB SPL	1800 16.7%/each 500 ms	Fz
Schmidt et al. (2012)	19 (12 M, 7 F)	500 to 800 Hz (in 50 Hz steps) 70 ms	Roving standard procedure	–	–	~1600 ~14% 570 ms	Mean Fz, F3, F4
Mathalon et al. (2014)	8 (5 M, 3 F)	633 Hz 50 ms 80 dB SPL	–	633 Hz 100 ms 80 dB SPL	–	1740 10% 510 ms	Fz

The table provides information about the number of participants investigated in each study and the auditory stimulation (tone stimuli used as standards and deviants, as well as the total number of presented tones [Trials], percentage of deviant tone trials [% dev], and stimulus onset asynchrony [SOA]). The right column documents how the MMN was quantified for the current study purpose, which might vary from the originally presented data analysis.

Table 2
Ketamine administration and used baseline.

Authors and year	Substance	Bolus [mg/kg]	Continuous injection [mg/kg per hour]	Approximate time point of MMN recording [minutes after bolus]	Baseline[a]
Oranje et al. (2000)	Ketamine	0.30	0.213	60–135	Placebo
Umbricht et al. (2000)	Ketamine	0.24	0.9[b]	20–35	Session baseline
Kreitschmann-Andermahr et al. (2001)	Ketamine	0.30	–	0–15	Session baseline
Heekeren et al. (2008)	Esketamine	0.15–0.20	0.6–0.9	20–50	Baseline (separate session)
Roser et al. (2011)	Ketamine	0.24	0.5	20–40	Baseline (separate session)
Gunduz-Bruce et al. (2012)	Ketamine	0.23	0.29[c]	35–50	Placebo
Schmidt et al. (2012)	Esketamine	10 mg bolus	0.36		Placebo
Mathalon et al. (2014)	Ketamine	0.26	0.65	5–35	Placebo

[a] The baseline as used for the current meta-analysis.
[b] The dose was further reduced by 10% every 15 min.
[c] At the time point of MMN recording.

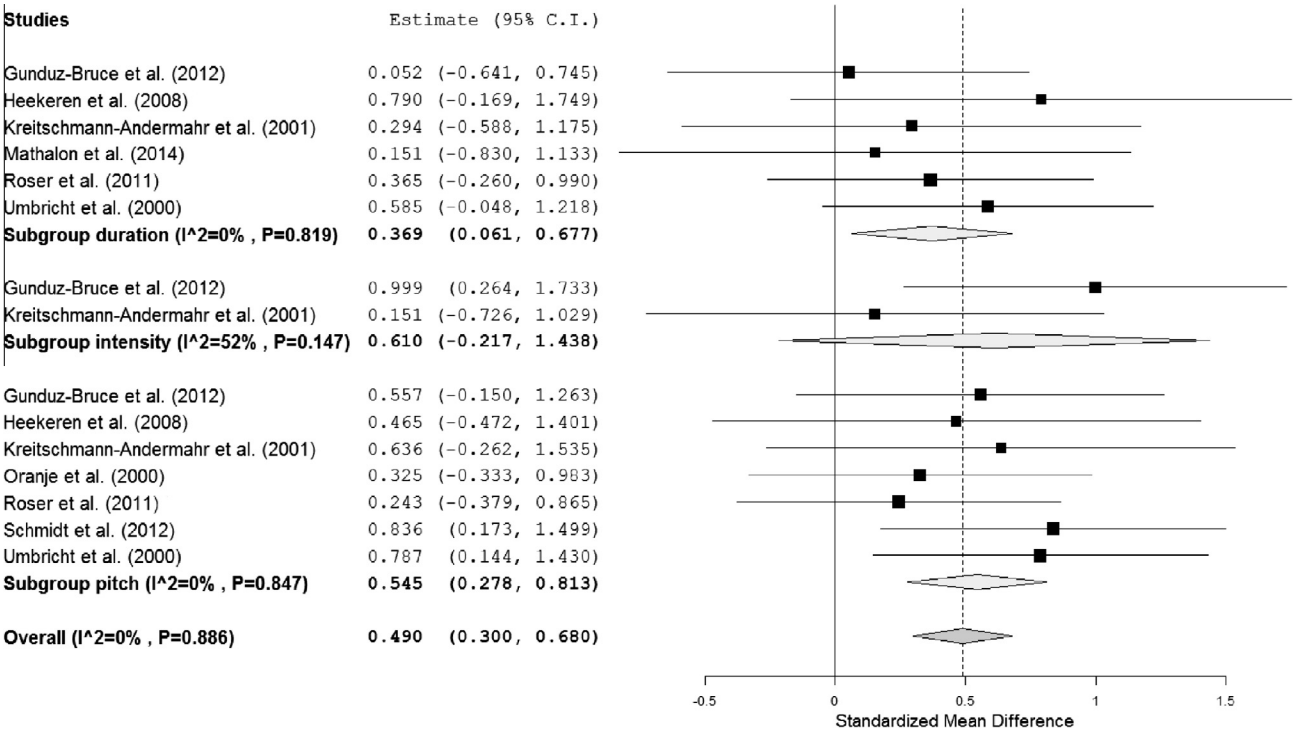

Fig. 1. The forest plot illustrates the effect sizes of ketamine on the MMN amplitudes, separately for the MMN to duration deviants (top), intensity (middle), and frequency deviants (bottom). Positive effect sizes indicate smaller MMN amplitudes after ketamine.

reliably this specific impairment of the MMN to duration deviants (as opposed to frequency deviants) occurs in schizophrenia patients. The meta-analysis of Umbricht and Krljes (2005) on the MMN in schizophrenia reported numerically, but not statistically, larger effect sizes for the duration MMN than for the frequency MMN. One aspect that might confound this observed variance between MMN deficits to different deviants in schizophrenia patients is the comparative size of the MMN amplitudes, as also discussed by Todd et al. (2008). For frequency deviants, the MMN deficit in patients with schizophrenia was more pronounced for large as opposed to small frequency deviants (Javitt et al., 1998). On the basis of this study, one might expect generally larger MMN reductions in patients for deviants that elicit larger MMNs and, in consequence, differences in the MMN amplitudes to duration and frequency deviants in controls might have an impact on the findings obtained in patients. Whereas this might provide an explanation for some of the differential findings for frequency and duration MMN reductions in schizophrenia patients (Todd et al., 2008; Domján et al., 2012), other studies also found such differences even though the MMN amplitudes to different deviants in controls were highly comparable (Brockhaus-Dumke et al., 2005; Bodatsch et al., 2011). For the ketamine studies, we did not observe a coherent pattern between the MMN amplitudes and effect sizes either. The mean peak MMN amplitudes were larger for frequency deviants than for duration deviants (3.8 ± 1.5 μV vs. 3.2 ± 1.3 μV). However, the MMN amplitude at baseline did not modulate the size of the ketamine effects on the MMN amplitude. The effects were sometimes present even though the amplitudes at baseline were low (e.g. Heekeren et al., 2008); sometimes the effects were absent even though the MMN amplitudes were pronounced (e.g. Mathalon et al., 2014).

In patients with schizophrenia, there is some evidence of progression of the MMN deficit in the course of the disease, as provided by the meta-analysis of Umbricht and Krljes (2005) and by a longitudinal study (Salisbury et al., 2007). Studies investigating patients with chronic schizophrenia usually find a clear MMN reduction, but it is yet unclear to what extent this reduction is present at the onset of disease: Umbricht et al. (2006), Salisbury et al.

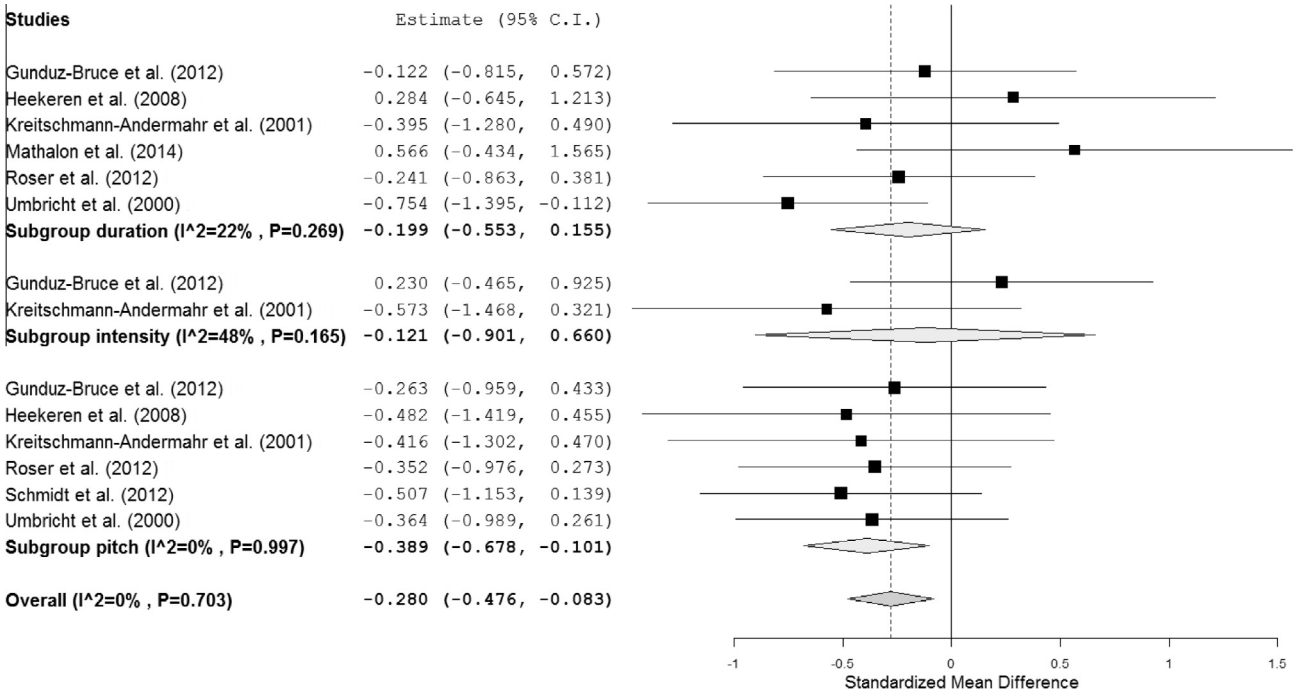

Fig. 2. The forest plot illustrates the effect sizes of ketamine on the MMN latencies, separately for the MMN to duration deviants (top), intensity (middle), and frequency deviants (bottom). Negative effect sizes indicate longer MMN latencies after ketamine.

(2002), and Magno et al. (2008) did not find MMN reductions in first-episode schizophrenia patients (independently of the kind of deviant used), whereas others reported such a reduction (Atkinson et al., 2012; Kaur et al., 2011). However, the progression of the MMN deficit over the course of the disease on the basis of cross-sectional comparisons might be overestimated since only a proportion of the first-episode patients develop chronic schizophrenia (an der Heiden and Häfner, 2000). Findings in first-degree relatives of patients with schizophrenia are also somewhat mixed with some studies reporting MMN reductions in such relatives (Jessen et al., 2001; Michie et al., 2002; Şevik et al., 2011), whereas other studies reported an unimpaired MMN in this group (Ahveninen et al., 2006; Magno et al., 2008; Hong et al., 2012). The lack of a difference in the study of Hong et al. (2012) is particularly noteworthy because a large sample of relatives was recruited ($n = 71$) and duration deviants were used for eliciting the MMN. Thus, in this study, neither the lack of statistical power nor the choice of the deviant can be blamed for the absence of significant group differences.

The magnitude of the effects of ketamine analyzed here on the MMN amplitude in healthy participants is more comparable to the pronounced effects observed in patients with chronic schizophrenia (Umbricht and Krljes, 2005) than to the apparently weak effects in first-episode patients and first-degree relatives. In addition, ketamine effects are equally found for different kinds of deviants. The latter finding indicates that the NMDA receptor hypofunction model of schizophrenia does not provide an explanation for differential MMN deficits to duration and frequency deviants in schizophrenia patients, as observed in some studies (Brockhaus-Dumke et al., 2005; Todd et al., 2008; Bodatsch et al., 2011; Domján et al., 2012), and implies that other factors contribute to such differential pattern. It has for example been suggested that the cannabinoid receptor CB1 system interacts with the NMDA neurotransmission. In healthy participants, the administration of ketamine in combination with the CB1 antagonist rimonabant led to somewhat more pronounced reductions of the MMN to duration deviants as compared to the MMN to frequency deviants (Roser et al., 2011). However, at the current time point, the influence of additional factors, either triggering the NMDA receptor hypofunction or interacting with it, has to remain speculative, due to the lack of empirical data.

On a theoretical account, NMDA receptor hypofunction has been linked to inhibitory GABAergic interneurons (Deutsch et al., 2001; Coyle, 2004). Premedication with benzodiazepines as GABAergic agonists is used to reduce dysphoric symptoms emerging from ketamine anesthesia. Yet, in a study investigating the psychotropic effects of ketamine alone and in combination with lorazepam, the benzodiazepine failed to reduce positive symptoms elicited by ketamine (Krystal et al., 1998). There are very few MMN studies that investigated the effects of ketamine in interaction with a second drug. The two previous studies that aimed at blocking the ketamine effects on the MMN by a second drug were not successful: Contrary to what has been suggested by animal data, neither the pre-treatment of N-acetylcysteine (NAC) nor the mentioned pre-treatment of rimonabant reversed the ketamine effects in humans (Roser et al., 2011; Gunduz-Bruce et al., 2012).

5. Conclusion

Ketamine reduces the MMN amplitude and increases the MMN latency, widely independent of the kind of deviance used for eliciting the MMN. This pattern resembles the MMN deficits found in chronic schizophrenia patients. Other factors might contribute to MMN reductions specific to duration deviants, as observed in schizophrenia patients with a short illness duration (Todd et al., 2008) or in individuals at risk that later on convert to psychosis (Bodatsch et al., 2011).

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References

Ahveninen J, Jääskeläinen IP, Osipova D, Huttunen MO, Ilmoniemi RJ, Kaprio J, et al. Inherited auditory-cortical dysfunction in twin pairs discordant for schizophrenia. Biol Psychiatry 2006;60:612–20.

an der Heiden W, Häfner H. The epidemiology of onset and course of schizophrenia. Eur Arch Psychiatry Clin Neurosci 2000;250:292–303.

Angrist B, Sathananthan G, Wilk S, Gershon S. Amphetamine psychosis: behavioral and biochemical aspects. J Psychiatr Res 1974;11:13–23.

Atkinson RJ, Michie PT, Schall U. Duration mismatch negativity and P3a in first-episode psychosis and individuals at ultra-high risk of psychosis. Biol Psychiatry 2012;71:98–104.

Belger A, Yucel GH, Donkers FCL. In search of psychosis biomarkers in high-risk populations: is the mismatch negativity the one we've been waiting for ? Biol Psychiatry 2012;71:94–5.

Benes F. GABAergic interneurons implications for understanding schizophrenia and bipolar disorder. Neuropsychopharmacology 2001;25:1–27.

Berk M, Copolov D, Dean O, Lu K, Jeavons S, Schapkaitz I, et al. N-acetyl cysteine as a glutathione precursor for schizophrenia-A double-blind, randomized. Placebo-Controlled Trial Biol Psychiatry 2008;64:361–8.

Bodatsch M, Ruhrmann S, Wagner M, Mller R, Schultze-Lutter F, Frommann I, et al. Prediction of psychosis by mismatch negativity. Biol Psychiatry 2011;69:959–66.

Brisch R. The role of dopamine in schizophrenia from a neurobiological and evolutionary perspective: old fashioned, but still in vogue. Front Psychiatry 2014;5:1–11.

Brockhaus-Dumke A, Tendolkar I, Pukrop R, Schultze-Lutter F, Klosterkötter J, Ruhrmann S. Impaired mismatch negativity generation in prodromal subjects and patients with schizophrenia. Schizophr Res 2005;73:297–310.

Coyle JT. The GABA-glutamate connection in schizophrenia: which is the proximate cause? Biochem Pharmacol 2004;68:1507–14.

Creese I, Burt DR, Snyder SH. Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. Science 1976;192:481–3.

Deutsch SI, Rosse RB, Schwartz BL, Mastropaolo J. A revised excitotoxic hypothesis of schizophrenia: therapeutic implications. Clin Neuropharmacol 2001;24:43–9.

Domino EF, Luby ED. Phencyclidine/schizophrenia: one view toward the past, the other to the future. Schizophr Bull 2012;38:914–9.

Domján N, Csifcsák G, Drótos G, Janka Z, Szendi I. Different patterns of auditory information processing deficits in chronic schizophrenia and bipolar disorder with psychotic features. Schizophr Res 2012;139:253–9.

Ehrlichman RS, Maxwell CR, Majumdar S, Siegel SJ. Deviance-elicited changes in event-related potentials are attenuated by ketamine in mice. J Cogn Neurosci 2008;20:1403–14.

Gil-da-Costa R, Stoner GR, Fung R, Albright TD. Nonhuman primate model of schizophrenia using a noninvasive EEG method. Proc Natl Acad Sci USA 2013;110:15425–30.

Gunduz-Bruce H, Reinhart RMG, Roach BJ, Gueorguieva R, Oliver S, D'Souza DC, et al. Glutamatergic modulation of auditory information processing in the human brain. Biol Psychiatry 2012;71:969–77.

Heekeren K, Daumann J, Neukirch A, Stock C, Kawohl W, Norra C, et al. Mismatch negativity generation in the human 5HT2A agonist and NMDA antagonist model of psychosis. Psychopharmacology 2008;199:77–88.

Higuchi Y, Sumiyoshi T, Seo T, Miyanishi T, Kawasaki Y. Mismatch negativity and cognitive performance for the prediction of psychosis in subjects with at-risk mental state. PLoS One 2013;8:e54080.

Hong L Elliot, Moran LV, Du X, O'Donnell P, Summerfelt A. Mismatch negativity and low frequency oscillations in schizophrenia families. Clin Neurophysiol 2012;123:1980–8.

Howes O, Mccutcheon R, Stone J. Glutamate and dopamine in schizophrenia: an update for the 21st century. J Psychopharmacol 2015;29:97–115.

Jacob MS, Carlen PL, Marshman JA, Sellers EM. Phencyclidine ingestion: drug abuse and psychosis. Int J Addict 1981;16:749–58.

Jahshan C, Cadenhead KS, Rissling AJ, Kirihara K, Braff DL, Light GA. Automatic sensory information processing abnormalities across the illness course of schizophrenia. Psychol Med 2012;42:85–97.

Javitt DC, Zukin SR. Recent advances in the phencyclidine model of schizophrenia. Am J Psychiatry 1991;148:1301–8.

Javitt DC, Steinschneider M, Schroeder CE, Arezzo JC. Role of cortical N-methyl-D-aspartate receptors in auditory sensory memory and mismatch negativity generation: implications for schizophrenia. Proc Natl Acad Sci USA 1996;93:11962–7.

Javitt DC, Grochowski S, Shelley AM, Ritter W. Impaired mismatch negativity (MMN) generation in schizophrenia as a function of stimulus deviance, probability, and interstimulus/interdeviant interval. Electroencephalogr Clin Neurophysiol 1998;108:143–53.

Jessen F, Fries T, Kucharski C, Nishimura T, Hoenig K, Maier W, et al. Amplitude reduction of the mismatch negativity in first-degree relatives of patients with schizophrenia. Neurosci Lett 2001;309:185–8.

Kaur M, Battisti RA, Ward PB, Ahmed A, Hickie IB, Hermens DF. MMN/P3a deficits in first episode psychosis: comparing schizophrenia-spectrum and affective-spectrum subgroups. Schizophr Res 2011;130:203–9.

Knott V, Shah D, Millar A, McIntosh J, Fisher D, Blais C, et al. Nicotine, auditory sensory memory, and sustained attention in a human ketamine model of schizophrenia: moderating influence of a hallucinatory trait. Front Pharmacol 2012;3:1–13.

Korostenskaja M, Nikulin VV, Kičić D, Nikulina AV, Kähkönen S. Effects of NMDA receptor antagonist memantine on mismatch negativity. Brain Res Bull 2007;72:275–83.

Kreitschmann-Andermahr I, Rosburg T, Demme U, Gaser E, Nowak H, Sauer H. Effect of ketamine on the neuromagnetic mismatch field in healthy humans. Brain Res Cogn Brain Res 2001;12:109–16.

Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, et al. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry 1994;51:199–214.

Krystal JH, Karper LP, Bennett A, D'Souza DC, Abi-Dargham A, Morrissey K, et al. Interactive effects of subanesthetic ketamine and subhypnotie lorazepam in humans. Psychopharmacology 1998;135:213–29.

Lahti AC, Koffel B, LaPorte D, Tamminga CA. Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. Neuropsychopharmacology 1995;13:9–19.

Lavoie S, Murray MM, Deppen P, Knyazeva MG, Berk M, Boulat O, et al. Glutathione precursor, N-acetyl-cysteine, improves mismatch negativity in schizophrenia patients. Neuropsychopharmacology 2008;33:2187–99.

Lieberman JA, Kane JM, Alvir J. Provocative tests with psychostimulant drugs in schizophrenia. Psychopharmacology 1987;91:415–33.

Luby ED, Cohen BD, Rosenbaum G, Gottlieb JS, Kelley R. Study of a new schizophrenomimetic drug; sernyl. AMA Arch. Neurol. Psychiatry 1959;81:363–9.

Magno E, Yeap S, Thakore JH, Garavan H, De Sanctis P, Foxe JJ. Are auditory-evoked frequency and duration mismatch negativity deficits endophenotypic for schizophrenia? high-density electrical mapping in clinically unaffected first-degree relatives and first-episode and chronic schizophrenia. Biol Psychiatry 2008;64:385–91.

Mathalon DH, Ahn KH, Perry EB, Cho HS, Roach BJ, Blais RK, et al. Effects of nicotine on the neurophysiological and behavioral effects of ketamine in humans. Front Psychiatry 2014;5:7–13.

Meltzer HY, Massey BW. The role of serotonin receptors in the action of atypical antipsychotic drugs. Curr Opin Pharmacol 2011;11:59–67.

Michie PT. What has MMN revealed about the auditory system in schizophrenia? Int J Psychophysiol 2001;42:177–94.

Michie PT, Innes-Brown H, Todd J, Jablensky A. Duration mismatch negativity in biological relatives of patients with schizophrenia spectrum disorders. Biol Psychiatry 2002;52:749–58.

Näätänen R, Kähkönen S. Central auditory dysfunction in schizophrenia as revealed by the mismatch negativity (MMN) and its magnetic equivalent MMNm: a review. Int J Neuropsychopharmacol 2009;12:125–35.

Näätänen R, Shiga T, Asano S, Yabe H. Mismatch negativity (MMN) deficiency: a break-through biomarker in predicting psychosis onset. Int J Psychophysiol 2015;95:338–44.

Oranje B, Van Berckel BNM, Kemner C, Van Ree JM, Kahn RS, Verbaten MN. The effects of a sub-anaesthetic dose of ketamine on human selective attention. Neuropsychopharmacology 2000;22:293–302.

Rosburg T, Kreitschmann-Andermahr I, Sauer H. Mismatch negativity in schizophrenia research. An indicator of early processing disorders of acoustic information. Nervenarzt 2004;75:633–41.

Roser P, Haussleiter IS, Chong HJ, Maier C, Kawohl W, Norra C, et al. Inhibition of cerebral type 1 cannabinoid receptors is associated with impaired auditory mismatch negativity generation in the ketamine model of schizophrenia. Psychopharmacology 2011;218:611–20.

Rowe AR, Mercer L, Casetti V, Sendt K-V, Giaroli G, Shergill SS, et al. Dementia praecox redux: a systematic review of the nicotinic receptor as a target for cognitive symptoms of schizophrenia. J Psychopharmacol 2015;29:197–211.

Salisbury DF, Shenton ME, Griggs CB, Bonner-Jackson A, McCarley RW. Mismatch negativity in chronic schizophrenia and first-episode schizophrenia. Arch Gen Psychiatry 2002;59:686–94.

Salisbury DF, Kuroki N, Kasai K, Shenton ME, McCarley RW. Progressive and interrelated functional and structural evidence of post-onset brain reduction in schizophrenia. Arch Gen Psychiatry 2007;64:521–9.

Schall U, Müller BW, Kärgel C, Güntürkün O. Electrophysiological mismatch response recorded in awake pigeons from the avian functional equivalent of the primary auditory cortex. NeuroReport 2015;26:239–44.

Schmidt A, Bachmann R, Kometer M, Csomor PA, Stephan KE, Seifritz E, et al. Mismatch negativity encoding of prediction errors predicts S-ketamine-induced cognitive impairments. Neuropsychopharmacology 2012;37:865–75.

Şevik AE, Anil Yağcğoilu AE, Yağcğoğlu S, Karahan S, Gürses N, Yildiz M. Neuropsychological performance and auditory event related potentials in schizophrenia patients and their siblings: a family study. Schizophr Res 2011;130:195–202.

Shaikh M, Valmaggia L, Broome MR, Dutt A, Lappin J, Day F, et al. Reduced mismatch negativity predates the onset of psychosis. Schizophr Res 2012;134:42–8.

Tikhonravov D, Neuvonen T, Pertovaara A, Savioja K, Ruusuvirta T, Näätänen R, et al. Effects of an NMDA-receptor antagonist MK-801 on an MMN-like response recorded in anesthetized rats. Brain Res 2008;1203:97–102.

Todd J, Michie PT, Schall U, Karayanidis F, Yabe H, Näätänen R. Deviant matters: duration, frequency, and intensity deviants reveal different patterns of mismatch negativity reduction in early and late schizophrenia. Biol Psychiatry 2008;63:58–64.

Umbricht D, Krljes S. Mismatch negativity in schizophrenia: a meta-analysis. Schizophr Res 2005;76:1–23.

Umbricht D, Schmid L, Koller R, Vollenweider FX, Hell D, Javitt DC. Ketamine-induced deficits in auditory and visual context-dependent processing in healthy volunteers: implications for models of cognitive deficits in schizophrenia. Arch Gen Psychiatry 2000;57:1139–47.

Umbricht D, Koller R, Vollenweider FX, Schmid L. Mismatch negativity predicts psychotic experiences induced by NMDA receptor antagonist in healthy volunteers. Biol Psychiatry 2002;51:400–6.

Umbricht D, Vyssotki D, Latanov A, Nitsch R, Lipp H. Deviance-related electrophysiological activity in mice: is there mismatch negativity in mice ? Clin Neurophysiol 2005;116:353–63.

Umbricht DSG, Bates JA, Lieberman JA, Kane JM, Javitt DC. Electrophysiological indices of automatic and controlled auditory information processing in first-episode, recent-onset and chronic schizophrenia. Biol Psychiatry 2006;59:762–72.

Vollenweider FX, Leenders KL, Øye I, Hell D, Angst J. Differential psychopathology and patterns of cerebral glucose utilisation produced by (S)- and (R)-ketamine in healthy volunteers using positron emission tomography (PET). Eur Neuropsychopharmacol 1997;7:25–38.

Wallace BC, Dahabreh IJ, Trikalinos TA, Lau J, Trow P, Schmid CH. Closing the gap between methodologists and end-users: R as a computational back-end. J Stat Softw 2012;49:5.

Zeilhofer HU, Swandulla D, Geisslinger G, Brune K. Differential effects of ketamine enantiomers on NMDA receptor currents in cultured neurons. Eur J Pharmacol 1992;213:155–8.