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An acute dose, randomized trial of the effects of CDP-Choline on Mismatch Negativity (MMN) in healthy volunteers stratified by deviance detection level

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Abstract

Background: Alpha 7 nicotinic acetylcholine receptors (α7 nAChR) are prioritized molecular targets for the development of new pharmacological treatments for impaired cognition in schizophrenia. The use of schizophrenia-associated biomarkers both as endpoints and for segmentation of homogeneous populations for early detection of cognitive enhancing agents has been advanced to enhance the drug discovery process.

Methods: In this study, the mismatch negativity (MMN) event-related brain potential (ERP), considered one of the few fully developed biomarkers in schizophrenia, was employed: a) to stratify 24 healthy volunteers into subgroups exhibiting low, medium, or high auditory sensory discrimination based on pre-attentive detection of deviant auditory features, and b) to assess their acute response to a low (500 mg) and moderate dose (1000 mg) of CDP-choline, a dietary supplement with selective agonist actions at α7 nAChRs.

Results: No significant whole group effects were observed with CDP-choline, and MMN changes were observed only with analysis of subgroups. The effects of CDP-choline interacted both with deviant type and auditory deviance detection level, with individuals exhibiting low MMNs showing enhanced amplitudes, while those with high MMNs evidenced reduced amplitudes with acute dosing of CDP-choline.

Conclusions: These preliminary findings of improved auditory deviance detection with CDP-choline in our biomarker-defined healthy surrogate group supports the contention that α7 nicotinic cholinergic agonism be studied as a potential pro-cognitive mechanism in patients with schizophrenia.

Keywords: Alpha 7 nicotinic acetylcholine receptor, α7 nAChR, Nicotine, CDP-choline, Event-related potential, ERP, Deviance detection, Mismatch negativity, MMN, Schizophrenia

Background

Nicotinic acetylcholine receptors (nAChR) have been implicated in cognitive functioning and preclinical studies have strongly supported attentional enhancing effects of agonists acting at α7 and α4β2 nAChR subunits in the hippocampus and prefrontal cortex (Bentley et al. 2011; dos Santos and Granon 2012; Levin et al. 2006; Mansvelder et al. 2006; Sarter et al. 2009; Wallace and Bertrand 2013a, b). The prototypical nAChR

agonist nicotine, which is the main psychoactive agent in tobacco, has been shown to reverse withdrawal-induced task performance impairments in smokers (Heishman et al. 1994) and has exerted positive effects in multiple cognitive domains, including motor abilities, attention and memory, when administered in single "smoking doses" to non-smokers (Heishman et al. 2010).

Smoking prevalence in schizophrenia (SZ), a disorder in which cognitive disturbances are core features and are relatively nonresponsive to available antipsychotic treatments (Gold 2004; Marder and Fenton 2004), ranges from 45 to 88%, compared to < 20% in the general population (Dickerson et al. 2013; Morisano et al. 2013). Observed in animal models of SZ and in SZ patients, transient improvements in sensory, attentional, mnemonic and executive functions with acute nicotine/nAChR agonist treatment (D'Souza and Markou 2012; Kucinski et al. 2011; Leiser et al. 2009; Olincy and Freedman 2012; Radek et al. 2010) have collectively promoted the hypothesis of smoking in SZ as self-medication for cognitive deficits mediated via nAChR pathophysiology (Kumari and Postma 2005; Wing et al. 2012; Winterer 2010).

Converging lines of research have prioritized the α7 nAChR as one of the most promising targets in the development of cognitive pharmacotherapies for patients with SZ (Buchanan et al. 2007; Green 2007). Found both in SZ patients and their biological relatives, a sensory gating deficit (inability to inhibit responses to redundant, irrelevant stimuli) indexed by suppression of the auditory P50 event-related potential (ERP) has shown genetic linkage to the locus on chromosome 15q13-14, which codes (i.e., CHRNA7) for the α7 nAChR subunit (Freedman et al. 1997; Raux et al. 2002). Possibly reflecting single nucleotide changes within promoter regions of CHRNA7 (Leonard et al. 2002), diminished numbers of apparently structurally intact α7 nAChRs have been shown in the hippocampus (Freedman et al. 1995), frontal cortex (Guan et al. 1999) and the nucleus reticularis thalami (Court et al. 1999) of SZ postmortem brains. Results from clinical trials of novel α7 molecules in SZ patients have been mixed (Young and Geyer 2013). DMXB-A (a.k.a. GTS-21), the first α7 partial agonist to be developed, evidenced pro-gating and pro-cognitive properties in an acute dosing paradigm (Olincy et al. 2006) but failed to impact cognitive performance with chronic (4-weeks) treatment (Freedman et al. 2008) and similar null effects were recently observed in an 8-week study with the α7 nAChR partial agonist, RG3487 (Umbricht et al. 2014). This contrasts with proof-of-concept trials with partial α7 agonists EVP-6124 (Hilt et al. 2011) and TC-5619 (Lieberman et al. 2013), both showing improved cognition in SZ patients at week 12. Reviews of these and other α7 molecules under various stages of clinical development have tentatively underscored the potential of α7 modulators as add-on therapy to antipsychotics, but point to the need for a better understanding of brain functions regulated by this receptor system (Bencherif et al. 2012; Geerts 2012; Hurst et al. 2012; Wallace and Bertrand 2013a; Young and Geyer 2013).

Choline, an amine that is a precursor for the synthesis of acetylcholine, is an essential nutrient that has many biological functions, and in addition to being a lipid component involved in cell membrane protection and repair (Blusztajn 1998; Zeisel and Blusztujn 1994; Zeisel 2000) is a selective full agonist at the α7 nAChR (Albuquerque et al. 1998; Alkondon et al. 1999; Fayuk and Yakel 2004). As gestational choline supplementation enhances gating and cognition in adult offspring mice (Meck and Williams 2003; Stevens et al. 2008, 2014) and increases rates of efficient sensory inhibition (P50 suppression) in

human infants whose mothers' diets during pregnancy were supplemented with choline (Ross et al. 2013), dietary choline supplementation has been promoted as a possible preventive intervention for cognitive deficits in individuals considered to be "at risk" for SZ (Corriveau and Glenn 2012; Freedman 2014).

Choline's potential to address cognitive impairment associated with SZ has received only minimal attention. 5'-citidine diphosphocholine or CDP-choline (citicoline) is a dietary supplement which acts as a key intermediate in the biosynthesis of phosphatidylcholine from choline (Secades et al. 1995). CDP-choline has been shown to improve impaired cognition associated with chronic ischaemia, head trauma, dementia and normal aging (Alvarez-Sabin and Roman 2011; Conant and Schauss 2004; Davalos et al. 2012; Fioravanti and Buckley 2006; Garcia-Cobos et al. 2010; Secades 2012). In a 16-week trial combining CDP-choline with the positive allosteric modulator (PAM) of the α7 and α4/β2 nAChRs, galantamine, clinical symptoms of SZ patients were unaffected but overall functional level of patients was increased, as was performance on a test of free verbal recall (Deutsch et al. 2013). CDP-choline in this study was administered in the clinically recommended maximum dose range (2000 mg/day) but nAChR agonist effects often display an inverted U-shaped dose response curve, with maximal effects being observed at low and ultralow doses (Castner et al. 2011; Hahn et al. 2002; Werkheiser et al. 2011).

The primary objective of this present study is to investigate the acute group-wise effects of low-to-moderate doses (500 mg, 1000 mg) of CDP-choline in a sample of healthy volunteers. Prior to the implementation of costly and time consuming CDP-choline clinical trials in patients, this study will employ a rationale strategy advocated for the early identification of pro-cognitive drug actions, which involves the use of a within-subject challenge dose design (placebo vs. active) in biomarker-identified subgroups (surrogate populations) that have only a limited symptom profile but without the confounds (e.g. medication, disease chronicity, symptom variability) associated with the disorder (Chou et al. 2012; Koychev et al. 2012). Cortical cholinergic input is required for normal auditory sensory and perceptual processing (Leach et al. 2013), deficits of which are highly frequent in SZ and are indexed by ERP biomarkers (Javitt 2009). The mismatch negativity (MMN) ERP, which can probe dysfunction in basic perceptual processes isolated to primary sensory regions and can be modeled in preclinical studies, fulfills criteria for use as an endophenotypic marker (Gottesman and Gould 2003) of the SZ disease (Belger et al. 2012; Takahashi et al. 2013), and is considered one of the few fully developed, "already mature" electrophysiologic biomarkers (Butler et al. 2012; Green et al. 2009), allowing for unique opportunities for use as a translational biomarker in SZ drug discovery (Javitt et al. 2008). An essential feature of this mature biomarker is its substantial test-retest reliability, which exceeds 0.8 in healthy volunteers and patients and is of particular importance in clinical trials with repeated measures designs (Light et al. 2012).

Auditory MMN, requiring no behavioural response or attention, is elicited as a frontocentral maximum negative peak on the scalp (at ~ 120–250 ms) when a sequence of repetitive stimuli is interrupted infrequently by deviant stimuli differing in any physical or abstract manner. It is the earliest neural sign of acoustic change detection, and although there are different explanations for the MMN (Fishman 2013; May and Tiitinin 2010), the "sensory memory" hypothesis proposes that it is an automatic, pre-attentive

process that results from the comparison of standard and deviant memory traces of stimulus features in brief (lasting up to 30 sec) auditory ("echoic") sensory memory (Näätänen et al. 2011). Greater discrepancies between deviant and standard memory traces (i.e., increasing deviance) are associated with larger MMN amplitudes and shorter latencies, both measures being correlated with behavioural discrimination of sounds (Näätänen et al. 2012). Frequently found in SZ (vs. bipolar disorder), deficits in MMN generation are also observed in unaffected family members and first-episode patients (Sumiyoshi et al. 2013; Nagai et al. 2013a, 2013b; Näätänen et al. 2014), and are exhibited in patients in response to a variety of auditory deviants, although duration deviant MMNs are viewed as being more trait specific for this disorder, while pitch and intensity deviant MMNs have shown different temporal changes over the course of the illness (Näätänen and Kahkonen 2008; Todd et al. 2008). Impaired MMN generation in SZ is linked to structural (Rasser et al. 2011; Salisbury et al. 2007) and functional (Javitt 2000; Light and Braff 2005) impairments in the auditory sensory cortex and correlates with negative symptoms and poor executive functioning (Kiang et al. 2007; Näätänen et al. 2004; Turetsky et al. 2009; Umbricht et al. 2006) as well as deficits in social/occupational functioning (Lee et al. 2014; Light and Braff 2005), while in healthy volunteers, the greater the MMN amplitude, the stronger the functional status of the individual (Light et al. 2007).

MMN is relatively unaffected by antipsychotics, although we have shown it to correlate with clozapine dose (Horton et al. 2011) which, among its other actions, indirectly increases acetylcholine synaptic transmission (Ichikawa et al. 2002) and cortical glutamate (Tanahashi et al. 2012). Strongly dependent on glutamatergic signaling, MMN is attenuated in rats, monkeys and healthy adults with high-affinity NMDA (N-methyl-D-aspartate)-type glutamate receptor antagonists (Javitt et al., 1996; Tikhonravov et al. 2008; Umbricht et al. 2000) such as ketamine which, when combined with nicotine, fails to disrupt MMN in some (Knott et al. 2012) but not all investigations (Mathalon et al. 2014). Most frequently investigated in healthy participants with frequency deviants, nicotinic stimulation has resulted in negative (Knott et al. 2006, 2011), diminishing (Knott et al. 2009) and enhancing effects on MMN amplitude (Dunbar et al. 2007), with the latter positive outcome also being shown with pattern (Baldeweg et al. 2006), temporal (Martin et al. 2009) and visual deviants (Fisher et al. 2010). Such response variability is also seen in the relatively few studies in SZ, with nicotine not affecting frequency deviant MMN (Dulude et al. 2010; Inami et al. 2007), shortening latency of intensity-deviant MMN (Fisher et al. 2012) and in our work, "normalizing" duration-deviant MMN by increasing the diminished MMN in patients to a level comparable to that seen in healthy volunteers (Dulude et al. 2010).

Contributing to variability in MMN are individual difference in age (Ruzzoli et al. 2012), intelligence (Bazana and Stelmack 2002), gender and personality (Matsubayashi et al. 2008). These factors, as well as genetic influences, and inter-subject differences in smoker vs. nonsmoker status, pre-drug state, and functional level are also significant sources of individual variability in nicotine response (Gilbert and Gilbert 1995; Kupferschmidt et al. 2010; Li et al. 2009; Perkins 1995; Perkins 2009; Poltavski and Petros 2005). Frequently shown in animal models and in human studies, baseline-dependent differences have influenced behavioural, cognitive, and subjective mood responses to nicotine (Perkins 1999). More recently, baseline-dependent neural responses to nicotine have been evidenced with two widely used biomarkers of SZ, namely, P50-indexed auditory sensory gating

(Knott et al. 2010, 2013) and MMN-indexed auditory sensory discrimination (Knott et al. 2014), with both biomarkers being enhanced by acute nicotine, but only in individuals with relatively diminished, SZ-like P50 gating and MMN baseline responses. In individuals with high baseline gating and discriminability, P50 suppression and MMN amplitude were either not affected, or were attenuated by single dose nicotine treatment. Only two reports have examined the effects of α7 nAChR medications on MMN, both being conducted in SZ patients. While JNJ-39393406, an α7 PAM, failed to alter MMN (Winterer et al. 2013), the α7 partial agonist EVP-6124 increased the frequency deviant MMN in a dose-dependent manner (Preskorn et al. 2014).

Taking advantage of demonstrated, biomarker-defined inter-individual heterogenecity in sensory response to nicotinic receptor stimulation, this study will carry out an exploratory analysis on the possible relationship between endogenous choline and response to CDP-choline by examining how individuals stratified on the basis of MMN amplitude compare in their response to an acute low and moderate dose of CDP-choline. In line with previous suggestions of an inverted U-shaped response characterizing cognitive effects of nicotinic stimulation (Newhouse et al. 2004), and based on our recent study with the prototypical nAChR agonist, nicotine, which enhanced auditory deviance detection in individuals with small amplitude MMNs and attenuated deviance detection in those with higher amplitude MMNs (Knott et al. 2014), we hypothesized that both doses of CDP-choline (vs. placebo) would increase deviance detection (MMN) in individuals exhibiting relatively diminished detection ability (i.e. low baseline MMN amplitudes) and exert negative or diminishing effects in those with relatively moderate, optimal, or above optimal detection ability (i.e., medium or high baseline MMN amplitudes). As the lower dose is likely to be associated with less α7 receptor desensitization, MMN enhancement is expected to be greater with 500 mg (vs. 1000 mg) of CDP-choline. The study limited sample recruitment to healthy, young, male adults with a non-smoking history in order to reduce other sources of inter-individual variability.

Methods

The study protocol was approved by the Research Ethics Boards of the Royal Ottawa Health Care Group and the University of Ottawa and was carried out in accordance with the Canadian Tri-Council Policy Statement for Ethical Conduct for Research Involving Humans. All volunteers provided written consent prior to participation and were compensated $200 CAD for their time and effort.

Participants

Recruited by advertisements, the study sample consisted of 24 healthy, right handed males between 18–40 years of age. Volunteers were initially screened by telephone and then by personal interview. Based on history and physical exam, all participants were medically and neurologically normal and, as screened with the SCID-NP (Structured Clinical Interview – Non-Patient version for DSM-IV: Williams et al. 1992) and FIGS (Family Interview for Genetic Studies: Maxwell, 1992), had no personal or immediate (first degree biological relatives) family history of psychiatric disorders. Participants were nonsmokers, having smoked less than 100 cigarettes in their lifetime and none in

the past year, and exhibited an expired air carbon monoxide level < 3 ppm, which is consistent with a nonsmoker status (Cropsey et al. 2006). None of the participants reported any use of smokeless tobacco products (e.g. nicotine gum or patch).

Design

Participants were assessed in three separate sessions (placebo and two doses of CDP-choline) within a randomized, double-blind, crossover design. Session order was counterbalanced with respect to the total sample (not within each subgroup, which were designated at study completion), so that the 6 possible randomization orders were repeated four times across 24 participants. Approximately 8–12 days separated the sessions in order to allow for CDP-choline elimination.

Procedure

Test sessions were conducted between 9:00 a.m. – 1:00 p.m., each following overnight abstinence from smoking/nicotine, caffeine, alcohol, drugs/medication and food. Three hours after treatment administration, the time of maximal drug absorption, ERPs were recorded following which, adverse events and vital signs were evaluated for safety purposes.

CDP-choline

Participants were administered CDP-choline orally in two active doses, 500 mg (2 × 250 mg capsules) and 1000 mg (4 × 250 mg capsules). In study trials, clinically effective CDP-choline has been administered orally and by injection with doses ranging from 500 – 4000 mg/day, although generally efficacy has not substantially improved beyond 2000 mg/day. When administered orally, it is absorbed almost completely, with bioavailability being 92 – 94% and approximately the same as when administered intravenously (Agut et al. 1983). Single oral doses dose-dependently raise plasma levels and increase brain choline levels, with peripheral levels rising slowly and peaking at 3 – 5 hr, and with elimination half-life extending up to 56 hr (Wurtman et al. 2000). In studies with CDP-choline administered up to 12 months, it showed excellent tolerability and safety, with a few transient (never severe) adverse effects (e.g. stomach pain, diarrhea) (Conant et al. 2004; Fioravanti et al. 2006; Saver 2008). A "double dummy" procedure was used with participants being administered 4 capsules in each session so that the dose remained blind (e.g. 2 placebo capsules and 2 × 250 mg capsules comprised the 500 mg CDP-choline condition). The placebo capsules (containing cellulose) physically matched the active capsules.

Paradigm

During the MMN paradigm participants viewed a silent video (The Blue Planet by BBC, 2001). In the optimal MMN paradigm (Näätänen et al. 2004), auditory tonal stimuli of 70 dB sound pressure level (SPL) were presented binaurally through headphones and consisted of standard (p = 0.5) stimuli (composed of 500, 1000, and 1500 Hz pure tones of 75 ms duration) that were randomly intermixed with deviant (p = 0.5) stimuli. Stimulus onset asynchrony (SOA) was fixed at 500 ms. The deviant tones differed from the standard tones in terms of frequency, duration, intensity, perceived location of sound origin, or contained a silent gap in the middle of the tone (i.e. gap deviants). The

duration deviant was only 25 ms in duration (instead of 75 ms). Half of the frequency deviants were 10% lower (composed of 450, 900, and 1350 Hz partials) and the other half were 10% higher (composed of 550, 1100, and 1650 Hz partials). Half of the intensity variants were at 80 dB and the other half at 60 dB. A change in perceived location was created by creating an 800 μs time difference between the channels, leading to a change in location of approximately 90°. Half of the deviants had a 800 μs delay in the right channel while the other half was in the left channel. In the gap deviants 7 ms (including a 1 ms rise and fall) were removed from the middle of the standard stimulus. Three blocks of these stimulus sequences were presented for a total of 15 min (5535 stimuli). Each sequence started with a 15 standard tones, followed by a sequence in which every second tone was a standard ($p = 0.5$) and every other tone was one of the five deviants ($p = 0.1$ each). One deviant of each category was presented once every five deviants. No two deviants were presented consecutively.

Recordings

ERPs were recorded with a cap embedded with $Ag^{+}/Ag^{+}Cl^{-}$ electrodes (EasyCap, Herrching-Brieibrunn, Germany) positioned on 8 scalp locations, including left, right, and middle frontal (F_3, F_4, F_Z); left, right, and middle central (C_3, C_4, C_Z) and both middle parietal (P_Z) and occipital (O_Z) sites, according to the 10–10 system. An electrode on the nose served as reference and a ground electrode was positioned above the F_Z site. Electrodes were placed above and below the right eye to record vertical electrooculographic (VEOG) activity and at the external canthus of both eyes to measure horizontal electrooculographic (HEOG) activity. Electrical recordings were carried out using a Brain Vision V-8 Amp® (Brain Products GmbH, Munich, Germany) amplifier and Brain Vision Recorder® (Brain Products GmbH, Munich, Germany) software. Electrical activity was sampled at 500 Hz, with amplifier bandpass filters set at 0.1-100.0 Hz. Electrode impedances were kept below 5 kΩ. Off-line analysis was performed with Brain Vision Analyzer® software (Brain Products, GmbH, Munich, DE). For each stimulus, electrical epochs of 500 ms duration (beginning 100 ms prior to stimulus onset) were digitally filtered (0.1-20 Hz) (Sabri & Campbell 2002), ocular (Gratton et al. 1983) and baseline corrected (relative to the pre-stimulus segment), and only epochs with EEG voltages below 75 μV were used for final ERP averages, which were constructed separately for the standard and each deviant stimulus type at each electrode site. Waveforms for the low and high frequency deviants, those for the low and high intensity deviants, and those for the right and left location, were averaged together. MMNs were analyzed with difference waveforms, which were derived by digital point-by-point subtraction of the standard stimulus values from those elicited by each of the deviant stimuli. Based on visual inspection of the grand average waveforms (i.e., averaged across all participants), MMN amplitude was measured as the most negative peak between 120–250 ms. MMN amplitude and latency (time to reach peak MMN) were measured at the midline frontal site (F_Z), within the region exhibiting maximal MMN amplitude. Amplitude of the N1 component (peak negativity between 90–120 ms) elicited by the standard stimulus was also measured (from F_Z) to determine whether or not MMN modulation by CDP-choline was associated with alterations in sensory registration.

Symptoms

Adverse events were evaluated by having participants complete a 5-point Likert scale (0 = none, 4 = severe) on common symptoms (e.g., jitteriness, headache, nausea, vomiting) associated with nicotinic stimulation (adapted from Harkrider and Hedrick 2005).

Vitals

Heart rate (HR) (beats per minute [bpm]), systolic (SBP) and diastolic (DBP) blood pressure (milliliters per milligram of mercury [ml/mgHg]) were measured before and after gum chewing, with the participants in a sitting position. These measures were only used for safety purposes.

Analysis

Statistical analysis was carried out with the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL). In order to reduce Type I statistical errors, analyses was limited to MMNs derived from frontal electrodes, where amplitude is maximal. In the primary group-wise analyses with the entire sample (N = 24), the five deviant MMNs were analyzed in separate repeated measures analysis of variance (ANOVA) with treatment (3 levels: placebo, 500 mg, 1000 mg) and site (F_3, F_Z, F_4) as within-subject factors. In the secondary, exploratory analyses, separate mixed ANOVAs were carried out with the 5 deviant MMNs, with treatment and site as within-subject factors and group (3 levels: low, medium and high amplitude MMN participants) as a between-subject factor. Using placebo session data, groups were derived with respect to each of the 5 MMN deviant types by ranking midline frontal (F_Z) baseline (placebo) amplitudes of participants from the smallest to largest and designating the two groups of 8 individuals with the extreme low and high amplitudes as the "low" and "high" groups, respectively. The remaining 8 participants were designated as the "medium" group. This same stratification procedure has been used in our previous work on nicotine and sensory gating (Knott et al. 2013). The ANOVAs also included an examination of order effects, but these were not evident with any of the study findings. Greenhouse-Geisser correction was applied to within-subject factors with more than 2 levels and, regardless of whether significance (p >0.05) was observed with main or interaction effects, follow-up comparisons (Bonferroni-corrected) were conducted to test *a priori* hypotheses. Of primary interest in the exploratory analyses were the effects of treatment and group interaction effects, testing significance of CDP-choline (vs. placebo) effects within each group. If site was not involved in the interactions, comparisons were carried out with MMN values at the frontal midline (F_Z) site. Additional *post-hoc* analyses were also carried out to further clarify the source of interaction effects. Adverse events and vital signs were analyzed with similar mixed ANOVAs but without the site factor.

The use of placebo MMN scores in the exploratory analyses both for representing the best point estimate of a given individuals 'usual' MMN (for subgrouping) and for inclusion in the mixed ANOVA model possibly introduced a regression toward the mean bias (Barnett et al. 2005) in the findings (e.g. an individual who exhibits a smaller MMN in the low baseline group would be more likely to show a higher amplitude score in the next session, even if no drug was administered in the session). Since regression to the mean effects would be expected regardless of whether we segmented participants

into subgroups with either placebo or CDP-choline session MMN scores, we ran two additional sets of mixed ANOVAs using the 500 mg and 1000 mg session data to subgroup our participants.

Results

Grand averaged raw midline (F_Z, C_Z, P_Z) waveforms elicited by the 5 deviant and standard stimuli are shown in Figure 1, and grand average difference waveforms (deviant waveform minus standard waveform) for each deviant are displayed in Figure 2, along with the topographic distribution maps of peak MMN activity associated with each deviant type. Robust MMN components were elicited by all deviants, with maximum amplitude being shown at frontal electrodes.

Figure 3 displays the grand averaged MMNs for each deviant in the 3 segmented groups. In order to establish the presence of an MMN in the low baseline amplitude group, amplitudes at F_Z to all deviants in the placebo condition were compared to zero using a *t*-test. Amplitudes and 2-tailed *t*-test statistics are summarized in Table 1. Except for the MMN elicited by the gap deviant, MMN amplitudes for all deviants in the low baseline group were significantly different from zero.

Duration MMN

In the primary group-wise analysis, treatment effects were not significant but a site effect emerged [F, (2, 40) = 13.80, $p < 0.001$], with amplitudes at Fz > F4 > F3 ($p < 0.05$).

Analysis yielded significant group [F, (2, 21) = 11.01, $p < 0.01$] and group x treatment interaction effects [F (4, 36) = 4.81, $p < 0.005$] for amplitude. Grand-average midfrontal (F_Z) difference waveforms for each deviant and treatment, in each group are shown in

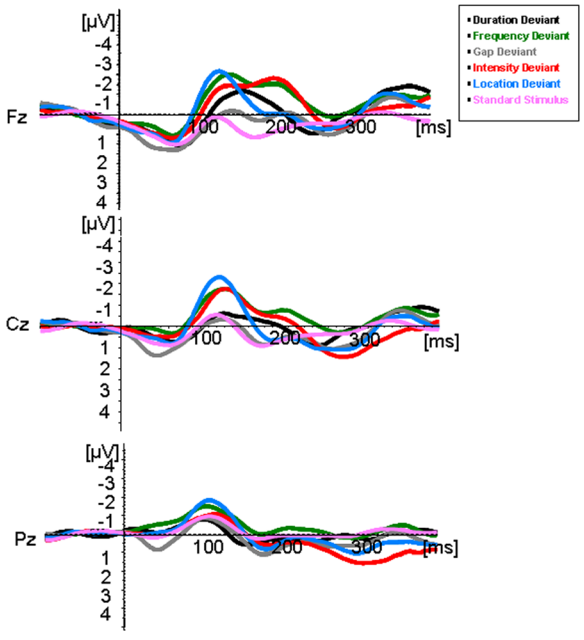

Figure 1 Grand averaged unsubtracted waveforms for all participants for the standard and each deviant stimulus during placebo treatment.

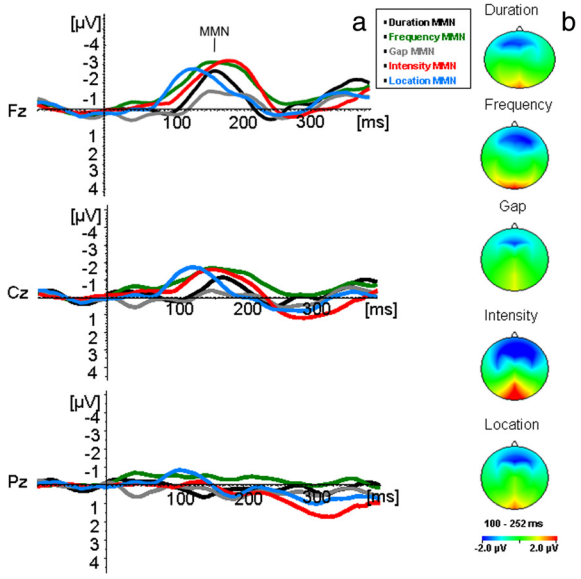

Figure 2 Grand averaged waveforms (a) and their scalp voltage distributions (b) for all participants for each deviant in the placebo session.

Figure 4. Treatment comparisons within the low baseline amplitude group found significantly larger MMNs with the 500 mg ($p < 0.01$) and 1000 mg dose of CDP-choline ($p < 0.05$) compared to placebo. No significant treatment differences were observed in the medium baseline amplitude group, but in the high baseline amplitude group both 500 mg ($p < 0.05$) and 1000 mg CDP-choline doses ($p < 0.01$) produced significantly smaller MMNs compared to placebo.

Post-hoc comparisons showed all groups differed from each other in the placebo session ($p < 0.01$), and while only medium and high baseline amplitude groups were significantly different in the 500 mg dose session ($p < 0.05$), none of the groups differed from each other in the 1000 mg dose session.

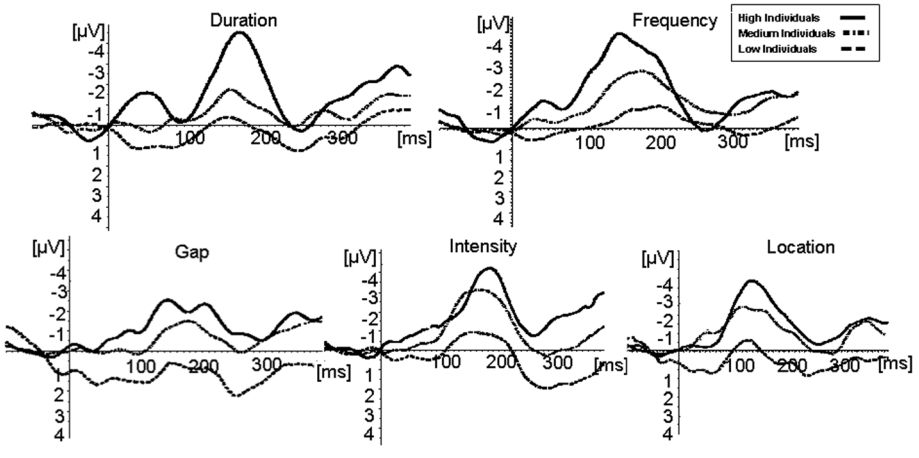

Figure 3 Grand averaged subtracted MMN waveforms (at Fz) of low, medium and high amplitude groups for each deviant during placebo treatment.

Table 1 Mean MMN amplitudes (±SE) at F_Z plus *t*-statistic and significance values resulting from 2-tailed comparison of means against zero for all placebo derived deviants in the low amplitude group

Deviant	Mean amplitude (±SE)	*t* value	Significance
Duration	−0.67 μV (0.54)	−3.53	$p = .010$
Frequency	−1.18 μV (1.09)	−3.05	$p = .019$
Gap	0.95 μV (0.78)	0.35	$p = .740$
Intensity	−1.48 μV (1.15)	−3.64	$p = .008$
Location	−1.01 μV (0.91)	−3.14	$p = .016$

No significant main or interaction effects were observed for MMN latency.

Frequency MMN

Group-wise analysis yielded no treatment effects, but site was significant [F (2, 42) = 5.04, $p < 0.02$], with amplitudes at Fz > F4 > F3 ($p < 0.05$).

Amplitude analysis resulted in a significant group [F (2.21) = 8.28 ($p < 0.003$] effect and a non-significant trend for a group x treatment interaction [F = (4, 36) = 2.39, $p < 0.08$]. As shown in Figure 4, treatment comparisons failed to show any CDP-choline effects in either low or medium baseline amplitude groups, but MMNs were significantly reduced in the high baseline amplitude group with the 500 mg dose compared to placebo ($p < 0.05$).

Groups were significantly different from each other in the placebo session ($p < 0.01$) but not during the two active treatment sessions.

No significant effects were observed for MMN latency.

Gap MMN

Group-wise analysis did not show a treatment effect but site was significant [F (2, 42) = 12.57, $p < 0.001$], with amplitudes at Fz > F4 > F3 ($p < 0.05$).

MMN elicited by the gap deviants was affected by group [F (2,21) = 23.89, $p < .001$] and a group x treatment interaction [F (4, 36) = 3.02, $p < 0.05$]. Shown in Figure 4, treatment comparisons within each group showed a trend for the 500 mg dose to increase MMN in the low baseline amplitude group ($p < 0.08$), while in the high baseline amplitude group MMN reduction was seen with the 500 mg dose ($p < 0.05$) and approached significance with the 1000 mg dose ($p < 0.06$).

All groups were significantly different from each other in the placebo ($p < 0.05$) and 1000 mg dose session ($p < 0.05$) but while amplitudes of the low baseline group were significantly smaller than those of the medium and high baseline groups during the 500 mg dose session ($p < 0.05$), they were similar in the medium and high baseline groups. No group, treatment or interaction effects were observed for MMN latency.

Intensity MMN

Group-wise analysis showed no treatment effect but site was significant [F (2, 42) = 12.48, $p < 0.001$], with amplitudes at Fz > F4 > F3 ($p < 0.05$).

Group [F (2,21) = 4.47, p ¸0.03] and group x treatment interaction effects [F (4, 36) = 4.92, $p < 0.04$] were found for intensity MMN. As displayed in Figure 4, treatment

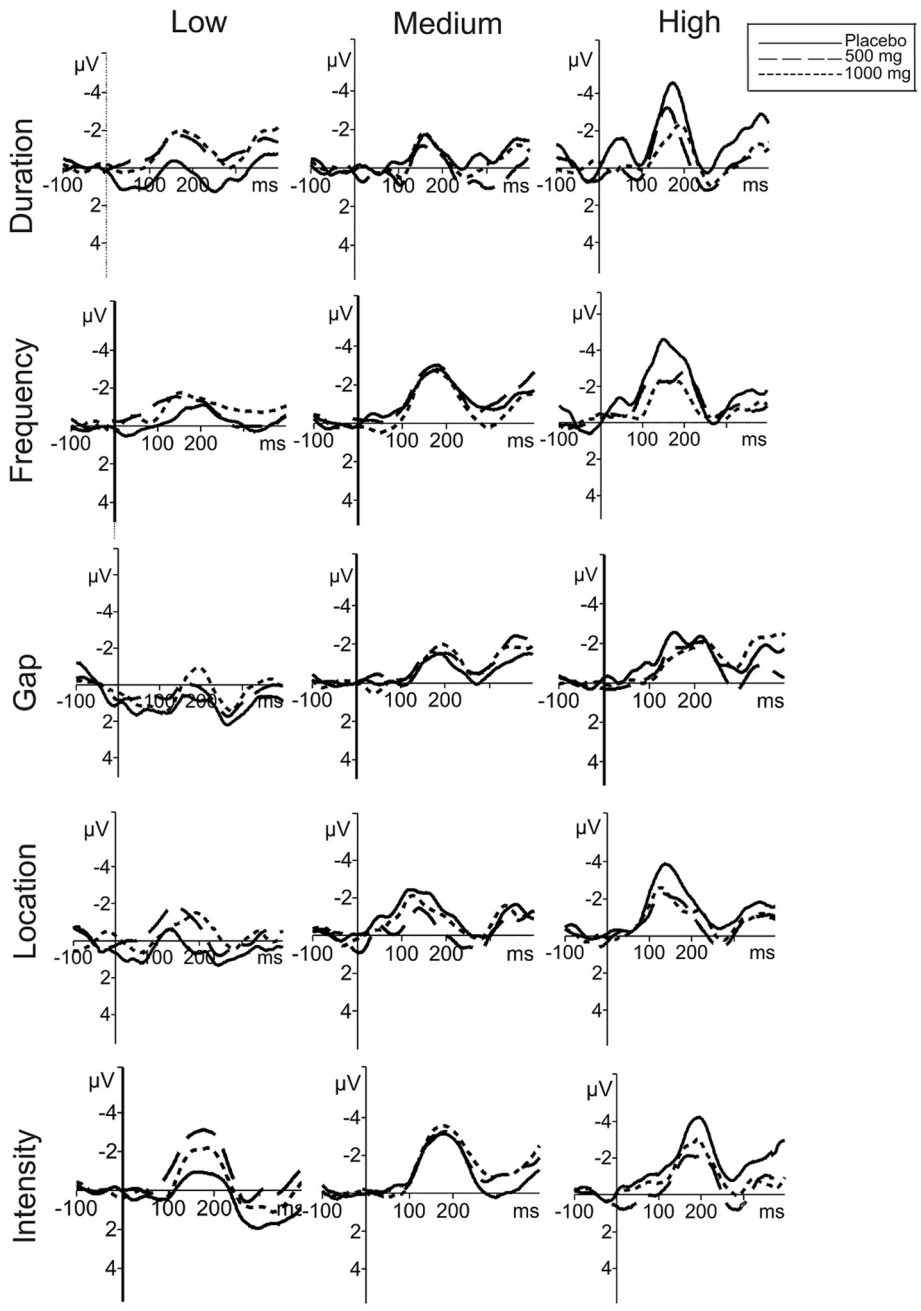

Figure 4 Grand averaged MMN waveforms (at Fz) displaying treatment differences by deviant and by baseline (placebo) grouping.

comparisons in the low baseline amplitude group showed the 500 mg dose produced significantly larger MMNs than placebo ($p < 0.01$) and a similar, non-significant trend ($p < 0.06$) was shown with the 1000 mg dose compared to placebo. The medium baseline group failed to exhibit any significant treatment effects but in the high baseline amplitude group MMN was attenuated (vs. placebo) with both 500 mg ($p < 0.01$) and 1000 mg doses ($p < 0.006$).

Post-hoc comparisons showed groups to be significantly different from each other during placebo ($p < 0.01$) but not during the 500 mg or 1000 mg treatment sessions.

MMN latency was not affected by treatment.

Location MMN

No treatment effect was found with group-wise analysis but a significant site effect was shown [F (2, 42) = 9.95, $p < 0.001$], with amplitudes at Fz > F4 > F3 ($p < 0.05$).

The location MMN amplitudes were significantly altered by group [F (2,21) = 7.60, $p < 0.01$] and group x treatment interaction effects [F (4, 36) = 4.56, $p < 0.05$]. As observed in the low baseline amplitude group (Figure 4), treatment comparisons showed significant (vs. placebo) MMN amplitude increases with the 500 mg dose ($p < 0.05$) and a similar but non-significant trend for MMN amplitude increases with the 1000 mg dose ($p < 0.08$). CDP-choline exerted opposite effects in the medium and high baseline amplitude groups, with the 500 mg reducing MMN compared to placebo ($p < 0.05$).

Group amplitudes were significantly different from each other during placebo treatment ($p < 0.05$) but not during CDP-choline treatment.

MMN latency analysis did not yield any significant main or interaction effects.

Standard N1

CDP-choline did not exert any significant effects on NI amplitude or latency.

Additional analyses

For the mixed ANOVAs conducted with subgroups formed with the 500 mg session data and the 1000 mg session data, significant group differences, as shown in the primary analysis, were observed for the different deviants but no significant treatment or group x treatment interactions were found.

Adverse symptoms

There were no serious adverse events associated with CDP-choline and no adverse events led to discontinuation by any of the participants. Analysis did not yield any significant treatment differences in self-reported adverse reactions.

Vitals

No significant differences were observed between placebo and CDP-choline doses with respect to heart rate or blood pressure measures.

Discussion

There were no significant whole group effects with CDP-choline but exploratory analysis showed individual differences in MMN response to the acute choline agonist challenge. Our findings with CDP-choline underscore previous reports of individual variability in sensory and cognitive response to nicotine and they extend these observations to the modulating effects of a choline supplement on auditory deviance detection, a pre-attentive sensory process which is commonly impaired in SZ. Depending on treatment dose, initial amplitude, and deviant type, deviance detection was shown to be enhanced, suppressed or insensitive to modulations of choline, which among its other properties, exerts agonist actions at α7 receptors. These findings add some support to the use of a "test dose" design in healthy surrogates, aided by specific biomarkers predicting and assessing

an individual's drug sensitivity, for early detection of pro-cognitive effects of nicotinic agents for SZ cognition (Chou et al. 2012; Koychev et al. 2012).

Improvement in acoustic change detection with CDP-choline, in the absence of changes in obligatory sensory registration indexed by the NI ERP, was shown in individuals with relatively diminished neural response (MMN) to auditory deviants, while in those with optimal or supraoptimal responses, a reduction in change detection was evidenced with this acute α7 agonist treatment. In general, the findings parallel our earlier report of the dual actions of the broad spectrum nAChR agonist, nicotine, on MMN in groups of healthy surrogates exhibiting relatively compromised and efficient deviance detection (Knott et al. 2014). Increases in auditory change detection in individuals with diminished MMNs are of particular importance for SZ. Additionally, as these effects were shown in nonsmokers, the gains with CDP-choline reflect a true enhancement of a suboptimal sensory level process and are not simply reflecting a "normalization" or "remediation" of a sensory deficiency that may accompany the more general disturbance of cognitive neural networks seen during smoking/nicotine withdrawal in chronic smokers (Beaver et al. 2011; Cole et al. 2010).

The observation that both the augmenting and suppressing effects of CDP-choline on auditory change detection in the biomarker-defined subgroups were deviant dependent generally mirrors the baseline-dependent effects of nicotine reported in neuropsychiatric disorders, with those exhibiting the most impaired cognition in select domains evidencing the greatest improvement with nicotine (Morisano et al. 2013; Newhouse et al. 2004; Perkins 1999). Although non-significant dose-related trend effects were observed with some deviants (gap, intensity), CDP-choline in general was able to both increase (in low amplitude individuals) and decrease MMN (in high amplitude individuals) elicited by duration, intensity and location deviants. The MMN elicited by the frequency deviant was only attenuated, and not increased by CDP-choline, and this was shown in the high amplitude group. Gap-deviant MMN was not affected by the choline supplement, an effect which may in part be related to measurement variability as the MMN in the low amplitude group was relatively undetectable in the placebo and drug conditions.

The number, location, and roles of cortical MMN generators remains unresolved (Tata and Ward 2005) but neuroimaging evidence to date has implicated a temporofrontal network, with MMN and functional magnetic resonance imaging (fMRI) BOLD responses elicited by changes in regularity of different elemental auditory features being generated in separate loci of the superior temporal gyrus (Alho et al. 2013; Näätänen et al. 2011). The two distinct processes thought to be involved in auditory change detection, including a "sensory" mechanism (detects a deviant sound on the basis of differential refractoriness of neural populations sensitive to the standard and deviant sounds) and a "cognitive" mechanism (reveals deviance by comparing incoming auditory information with a template derived by previous input), also seem to be anatomically separate, with the former involving primary auditory areas, while the latter involves secondary auditory areas (Szycik et al. 2013). Differential sensitivity of auditory deviants to CDP-choline may reflect the variable distribution of neuronal α7 nAChRs, which are heavily expressed in the primary auditory cortex and are integral to its structural and functional development (Ji and Suga 2008; Soto et al. 2006). In similar stratified subgroups, the deviance-dependent nicotine effects on MMN were shown to be slightly

different in that the dual nicotine responses of MMN amplitude enhancement and suppression were not apparent with the same deviant type (i.e., nicotine either increased or decreased detection of specific auditory deviants), possibly reflecting regional differences in the number of non-α7 nicotinic receptors.

Although directly enhancing signal processing in primary sensory regions (Sarter and Bruno 1997), the diffuse cholinergic input system extends to the frontal cortex where it can trigger complex patterns of recruitment of cholinergic modules that project to sensory and sensory-associated cortical regions to enhance the detection and processing of stimuli of a particular modality (Gatmayo et al. 2003; Nelson et al. 2005). Nicotinic receptor stimulation modulates the release of multiple neurotransmitters, and enhances tone-evoked physiological responsivity in the auditory cortex via activation of NMDA receptor-mediated glutamatergic neurotransmission (Flores-Hernandez et al. 2009; Konradsson-Geuken et al. 2009; Levy and Aoki 2002; Liang et al. 2008; Metherate and Hsieh 2003; Metherate 2004; Yang et al. 2013). nAChRs are abundantly expressed in the prefrontal cortex (PFC) and play a key role in the regulation of complex cognitive processes (Wallace and Bertrand 2013b). Studies of MMN source localization point to a role for the frontal cortex, where α7 subunit receptors are found to be highly prominent in the postsynaptic density of glutamatergic synapses and are thought to provide the depolarization necessary for NMDA receptor neurotransmission (Yang et al. 2013). The ability of CDP-choline to modulate MMN in a manner that varies between individuals and deviant types may result from the coordinated interplay of α7 nAChR modulated NMDA sensory and higher cortical circuits, with each region varying inter-individually both in its participation in feature specific auditory change detection and its regulation by α7-nicotinic and glutamatergic signaling.

Dose differences emerged with CDP-choline, with MMN being affected most often with the lower (500 mg) dose. Depending on the feature change, significant alterations in MMN seen with 500 mg were sometimes observed with the 1000 mg dose (duration- and intensity-deviant MMN), with the direction and degree of MMN change being similar across doses. Depending on the individual's amplitude, the same dose was able to increase and decrease neural responses to auditory deviants, CDP-choline generally acting to increase MMN in the low amplitude group while decreasing MMN in the higher amplitude group. Observed across the neuroimaging literature, the pattern of neural response induced by cholinergic modulation often resembles an inverted U-shaped function that depends upon the level of regional activation *prior* to drug challenge (Bentley et al. 2011). Hence, enhanced regional activity is most readily observed with pro-cholinergic drugs when such activity is relatively low under placebo, but decreased activity is seen when regional activation is high to begin with (e.g. Thiel et al. 2005). A similar type of inverted-U response is seen when comparing subject types, with pro-cholinergic drugs normalizing task/stimulus-evoked activations in individuals who, because of aging-, disease- or genetic-related factors, exhibit abnormally low or high activation, while in individuals with normal activation patterns studies show either no modulation or a *reverse* pattern of modulation in the same region and with the same task/stimulus paradigm (Bentley et al. 2011).

MMN increases with CDP-choline were most frequently observed with the low dose. Pro-cognitive effects of low and ultra-low doses of α7 agonists have been reported in

numerous preclinical studies. Although the underlying neural mechanisms are still unclear, these low concentration agonists are described as 'co-agonists' as they have been shown to facilitate receptor activation and enhance the acetylcholine-evoked current without provoking receptor desensitization (Castner et al. 2011; Prickaerts et al. 2012; Wallace and Bertrand 2013a). As microdialysis studies have shown that α7 receptor agonists can directly increase glutamate (Gioanni et al. 1999) and dopamine levels in the prefrontal cortex (Livingstone et al. 2009; Sydserff et al. 2009), improved deviance detection indexed by frontal MMN increases with low dose CDP-choline may be achieved through multiple mechanisms.

Possibly related to individual differences in the number and sensitivity of α7 nAChRs, diminished auditory change detection characterizing the low baseline amplitude group may be due to a relatively hypo-cholinergic state within sensory (auditory) cortex, while efficient detection of auditory change may reflect an optimal cholinergic tone. Consequently, the lower tonic cholinergic activity and decreased stimulus discriminability in the low baseline group allows for a greater dynamic range of response secondary to pro-cholinergic stimulation with CDP-choline, resulting in increased MMNs. By contrast, α7 agonist stimulation with CDP-choline in the high amplitude group may have pushed these participants towards a hyper-cholinergic state relative to what they are accustomed to, and while this enhances sensory cortex activation, concomitantly it results in reductions in selectivity to stimulus features and attributes (Bentley et al. 2011; Kuo et al. 2009; Zinke et al. 2006). Meta-analyses of imaging studies using magnetic resonance spectroscopy to quantify neurometabolites have shown reduced hippocampal choline (expressed as choline/creatine ratio) levels in SZ (Kraguljac et al. 2012) and it is possible that variability in endogenous brain choline may underly individual differences in normal deviance processing. Also of potential relevance to these findings of individual differences in response to CDP-choline is the choline uptake transporter (CHT), which imports choline from extracellular space to presynaptic terminals for use in normal acetylcholine synthesis/cholinergic transmission (Sarter and Parikh 2005). As CHT capacity has been associated with variability in cognitive functioning (Sarter and Parikh 2009), and as human CHT gene polymorphisms have been associated with individual differences in cortico-limbic activation (Neumann et al. 2006) and attentional processing (Berry et al. 2014), genetic differences in CHT capacity may underly some of the inter-individual variability in acoustic change detection response to CDP-choline.

Limitations

Our findings are preliminary and are in need of replication with larger samples. These data can be considered an incremental advancement in the current state of knowledge on choline agonism - sensory processing relationships with caveats of: 1) lack of real plasma-based biomarkers of endogenous choline availability; 2) no effort to control for covariates affecting choline activity or MMN, and 3) obviously, no SZ patients were studied. Although the recruitment of healthy volunteers can be considered a strength in that it reduced the potential confounding effects associated with clinical trials in patients (e.g. medication, disease chronicity), acute CDP-choline test-dose challenge studies are required in medicated patients prior to full phase II trials. Nonsmokers were targeted to ensure that any benefits gained with CDP-choline could not be attributed simply to a

reversal of withdrawal-reduced cognitive impairment, which may play a role in smokers tested with nicotinic agents. Although nonsmoking patients are frequently used in early phase trials (e.g. Koike et al. 2005; Olincy et al. 2006), SZ smokers and nonsmokers have differed in their response to nicotine and α7 agonists (Lieberman et al. 2013) and comparison of their acute response to CDP-choline would inform future investigations. The dose levels were limited and may have included lower (250 mg) and higher (2000 mg) doses for a more complete dose–response profile, and future studies might repeat dosing in closely spaced sessions to examine issues related to receptor desensitization. Collection of choline plasma levels would also be useful in data interpretation. Our subgroups were based on placebo data, which was also included in the statistical analyses. It is possible that a 'regression to the mean' effect (arising from the fact that [low] deviance detection could only improve, and ceiling [high] deviance detection only deteriorate) may have contributed to the study findings, but the extent of this contribution is unclear and several factors do not convincingly support a strong role in that: a) with counterbalancing (see Analysis section), placebo was relatively equally distributed across the three sessions, thus substantially attenuating a regression to the mean effect; b) regression to the mean effects would be expected to be consistently shown with all deviant types and both doses but this was not the case and c) our additional set of mixed ANOVAs using the low or moderate dose session data to segment our groups did not result in any group x treatment interactions. From this analysis we can tentatively conclude that CDP-choline effects in our placebo-based MMN subgroups do not reflect a significant regression to the mean influence. However, reducing regression to the mean influences in future studies can be accomplished by selecting MMN subgroups from a larger sample, or study participants could undergo an additional 'pre-selective' session, the data from which would be used to stratify participants into subgroups but not for statistical analysis. MMN recordings were not taken from mastoid sites, which would have allowed for a more specific interpretation of CDP-choline effects on sensory processing at sites more proximal to the auditory cortex. Given the contribution of sensory level processing to higher order mental operations (Javitt 2000), neuropsychological testing accompanying the ERPs would help us to understand the cognitive implications of choline modulated sensory processing. Moreover, additional studies are required to assess whether sensory and/or cognitive mechanisms of auditory deviance detection are impacted by cholinergic stimulation. As nAChRs are found throughout midbrain and brainstem tracts of the auditory pathway (Habbicht and Vater 1996; Happe and Morley 1998; Happe and Morley 2004; Morley 2005), both regions being shown to display deviance detection properties (Escera et al. 2013), the use of early latency ERPs components (<100 ms) may be important in mapping the extent to which α7 receptor modulation affects deviance processing along the auditory hierarchy.

Conclusion

Sensory and cognitive impairments are core features of SZ involving α7 nAChRs, which are considered potential therapeutic targets for new treatments. Using the MMN, one of the few biomarkers which can be reliably applied in translational research and drug development studies (Todd et al. 2013), acute α7 agonist treatment with the dietary supplement CDP-choline did not show any significant effects in our sample as a whole, but was shown to positively influence deviance detection in a surrogate subgroup

displaying diminished deviance detection, while exerting detrimental effects in individuals exhibiting optimal deviance detection. Although these preliminary findings need replication and extension to other surrogate populations (e.g. schizotypal personality), the modulating low dose effects of CDP-choline on auditory change detection indexed with the translational biomarker MMN support further study of α7 receptor agonism as a potential sensory enhancing mechanism in patients with schizophrenia.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
Each of the authors participated in this research by contributing to the conception and design of the project (VK), performance of the experiment (VI, JC, DS, SD, SS, MS, EB), event-related potential analysis (DI), and interpretation, writing and editing (VK, DI, VI, AL). No technical writers, language editors, and/or writing agencies were employed in preparing the manuscript. All authors read and approved the final manuscript.

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