Influence of a Nicotinic Treatment on Auditory Sensory Processing in Schizophrenia

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I would like to dedicate this work to the patients with schizophrenia and their families who have given their time to participate in this research. I strongly believe that by working together we will make a difference and achieve a scientific breakthrough in the understanding and treatment of schizophrenia.

Abstract

Schizophrenia (SCZ) is a neurodevelopmental disorder with prominent and intrusive experiences of positive (e.g., hallucinations) and negative symptoms (e.g., social withdrawal) in addition to widespread psychosocial, cognitive and sensory processing dysfunctions, which are generally experienced before the onset of the first psychotic episode. At the sensory level, early auditory information processing deficits, characterized at the neural level with event-related potentials (ERPs), are considered possible candidate biomarkers (endophenotypes) for SCZ and potential valid targets for understanding the neurobiology of SCZ and for developing novel therapeutic interventions. Traditional dopamine-targeting pharmacological treatments ameliorate mainly positive symptoms but show little impact on negative symptoms or cognitive/sensory impairments, which persist following medication stabilization. Nicotine, a non-selective nicotinic acetylcholinergic receptor (nAChR) agonist and the main psychoactive compound in tobacco smoking, is consumed by 60-80% of individuals with SCZ and shown with acute dosing to improve cognitive performance and early auditory information processing. The α7 nAChR is explicitly associated with neural and sensory/cognitive processing anomalies in SCZ, but novel α7 nAChR targeting treatments have shown mixed effects, which have been attributed in part to the substantial clinical/cognitive/neurophysiologic heterogeneity in SCZ. One alternative strategy for identifying efficacious novel nicotinic agents in future clinical trials is to use biomarkers to target more homogeneous sub-groups of SCZ patients.

The primary objective of this thesis was to conduct separate investigations in stratified sub-groups of healthy volunteers and patients with SCZ, assessing ERP measures of auditory sensory processing in response to the acute effects of a cholinergic treatment combining a dietary

supplement, CDP-choline, with selective α7 nAChR agonist properties and galantamine, a nAChR positive allosteric modulator (PAM), which was posited to augment α7 nAChR signalling.

Auditory sensory processing was examined with ERP paradigms assessing two functions commonly impaired in SCZ; (a) the ability to inhibit intrinsic neural responses to redundant stimuli, as measured by suppression of the P50 auditory ERP and (b) the ability to facilitate responses to infrequent but salient (deviant) stimuli, as measured by the mismatch negativity (MMN) ERP. Acknowledging the baseline-dependent effects of nicotine, each of the four investigations assessed the role of inter-individual differences in response to the cholinergic treatment by adopting a baseline median-split approach to stratify participants into low, medium, and high P50 baseline suppressors and low and high baseline deviance detectors. A novel ERP design element of this research was to replace the conventional tone/click stimuli typically used to elicit P50/MMN with speech stimuli, thus allowing for more meaningful interpretations of findings in relation to hallucinations and speech processing deficits in SCZ.

In investigations with both healthy volunteers and patients with SCZ, the combination treatment exerted similar group-dependent modulatory actions on sensory processing. In contrast to individuals exhibiting high P50 suppression ability and who evidenced reduced sensory gating with active (vs. placebo) treatment, individuals with low P50 suppression showed improved gating following CDP-choline/galantamine administration. Similarly, the combined treatment diminished auditory deviance detection in individuals with high MMN amplitudes but also enhanced deviance detection in individuals with low MMN amplitudes.

Findings from these acute drug challenge studies suggest that a PAM-enhanced nicotinic treatment strategy may have pro-sensory properties in SCZ, and they support further

investigation with a longer treatment course of this combined CDP-choline/galantamine intervention using dosage challenges to find optimal combinations. Adopting a baseline stratification approach in these trials and utilizing a range of assessment tools would help to individualize treatment and determine if improvements in early auditory information processing with this combination of nicotinic cholinergic treatment impact cognitive and psychosocial functioning.

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List of Abbreviations

α7	alpha 7
^{1}H-MRS	proton magnetic resonance spectroscopy
5-HT	serotonin
Ach	acetylcholine
AChE-I	acetylcholinesterase inhibitor
ANOVA	analyses of variance
AVH	auditory verbal hallucinations
BMI	body mass index
CB	cannabinoid
CDP-choline	citidine dyphosphocholine
CHR	clinical high risk
CHR-	clinical high risk who did not develop psychosis
CHR+	clinical high risk who later developed psychosis
CIHR	Canadian Institutes of Health Research
CO	carbon monoxide
COMT	catechol-o-methyltransferase
CONS	consonant change deviant
CPZ	chlorpromazine
D2	dopamine D2 receptor
DA	dopamine
dB	decibel
DBA/2	dilute brown, non-agouti; H-2^{d} haplotype mouse
dP50	P50 amplitude difference
DSM-IV	diagnostics and statistical manual of mental disorders - IV
EAIP	early auditory information processing
EEG	electroencephalograph
ERP	event related potentials
F	female
FET	Fisher's exact test
FIGS	family interview for genetic studies
FRE	frequency deviant
GABA	gamma-aminobutyric acid
GWAS	genome-wide association studies
HEOG	horizontal electro-oculographic

HG	high group
hr	hour
Hz	Hertz
INT	intensity deviant
kΩ	kiloohms
LG	low group
M	mean
M	male
mAChR	muscarinic acetylcholine receptors
MATRICS	measurement and treatment research to improve cognition in schizophrenia
MCCB	consensus cognitive battery
MEG	magnetoencephalographic
Met	methionine
mg	milligram
MG	medium group
min	minute
MMN	mismatch negativity
mRNA	messenger ribonucleic acid
ms	milliseconds
nACh	nicotinic acetylcholine
nAChR	nicotinic acetylcholine receptors
NIMH	National Institute of Mental Health
NMDA	N-methyl-D-aspartate
NMDAR	N-methyl-D-aspartate receptor
NS	non-smokers
p	probability
PAM	positive allosteric modulator
PANSS	Positive and Negative Symptom Scale
PET	positron emission tomography
Pla	placebo
PPI	prepulse inhibition
PSPs	post-synaptic potentials
PSYRATS	Psychotic Symptom Rating Scales
RO	recent-onset
rP50	P50 amplitude ratio
S	smokers

S_1	conditioning stimulus
S_2	testing stimulus
SCID-NP	Structured Clinical Interview, Non-Patient Version
SCZ	schizophrenia
SD	standard deviation
SE	standard error
SG	sensory gating
SPECT	single photon emission computer tomography
SPL	sound pressure level
SPSS	statistical package for social sciences
t1/2	half-life
Tx	treatment (CDP-choline/galantamine)
UMRF	University of Ottawa Medical Research Fund
Val	valine
VEOG	vertical electro-oculographic
VOW	vowel change deviant
VOWDUR	vowel duration deviant
µM	micromolar
µV	microvolt

Preface

The presentation of this dissertation focusing on drug challenge studies exploring the modulatory effect of a dietary supplement with α7 nicotinic acetylcholinergic receptor (α7 nAChR) agonist properties in combination with a positive allosteric modulator (PAM) on auditory sensory processing in healthy individuals and persons with schizophrenia (SCZ), follows the standard guidelines for a manuscript-based dissertation. In Chapter 1, a general Introduction presents an overview of the essential background leading to the rationale. It includes brief review sections describing the etiology and clinical/cognitive manifestations of SCZ, auditory sensory processing deficits in SCZ and their measurement with electroencephalographic (EEG) derived event-related potential (ERP) measures, α7 nAChR deficits and cholinergic impairments in SCZ, and the effects of nicotine and nicotinic modulators on auditory sensory processing. Four randomized trials examining the acute effects of the combined cholinergic treatment on auditory sensory gating and auditory deviance detection are presented in Chapters 2/3 and 4/5, respectively. Finally, general discussion points and conclusions are presented in Chapters 6 and 7.
Author contributions are presented in every paper/chapter.

Chapter 1

General Introduction

1.1 Overview

This research aimed to examine the modulating effect of Citidine dyphosphocholine (CDP-choline) with galantamine on neurophysiologic markers of auditory sensory processing in healthy individuals and those with schizophrenia (SCZ). Following a brief introduction to SCZ and associated cognitive dysfunction and ERP endophenotypes of early auditory information processing in SCZ, the nicotinic cholinergic system, although not the primary neurotransmitter system implicated in SCZ, is reviewed as a known modulator of cognitive/sensory processes, with emphasis on the effects of nicotine and the α7 nicotinic acetylcholine receptor (α7 nAChR) on ERP measures of two sensory processes commonly shown to be impaired in SCZ – auditory sensory gating (SG) and auditory deviance detection. In light of past failures by nicotinic agonists to normalize these deficient sensory functions in SCZ, an alternative strategy of using a pro-choline dietary supplement with α7 nAChR agonist properties (CDP-choline) and a positive allosteric modulator (PAM) of the nAChR (galantamine) is presented and couched within the main thesis objective that aims to investigate this combined treatment on auditory gating, measured with the P50 ERP, and deviance detection, as measured with the mismatch negativity (MMN) ERP, in both healthy volunteers and patients with SCZ.

Finally, considering the substantial clinical/cognitive/neurobiological heterogeneity in SCZ, which may have contributed to mixed findings with previous nicotinic agents, the thesis objective was framed within the attempt to address marked frequent response heterogeneity in SCZ by assessing the baseline-dependency effects of the combination treatment in order to provide a meaningful subtyping approach that could help to identify homogeneous target groups within SCZ.

1.2 Schizophrenia: etiology, symptoms, and treatments

Schizophrenia (SCZ) is a debilitating mental illness with a worldwide prevalence of ~ 1%, that onsets during adolescence to early adulthood and has significant social (e.g., poor interpersonal relationships) and economic (unemployment) implications. During the past 70+ years of research, multiple theories have been put forth regarding the origin of SCZ, but contemporary knowledge suggests that the etiopathogenesis of SCZ is multifactorial, with the majority of evidence supporting a neurodevelopmental theory (Fatemi and Folsom, 2009; Owen et al., 2016; Rybakowski, 2021; Walker et al., 2004). This theory postulates that aberrant neuromaturational processes, secondary to interactions between genetic predisposition and environmental (including pregnancy) factors, trigger the behavioural expression of SCZ when impacted by stressful events. Although genome-wide association studies (GWAS) have identified hundreds of molecular-genetic processes increasing a predisposition to SCZ, they have yet to find any specific genetic mechanism as a causal or therapeutic target.

Individuals with SCZ experience vastly varying degrees of positive (hallucinations and delusions), negative (apathy, social withdrawal) and cognitive (decision-making, attention, memory, speech, and learning difficulties) symptoms. The prodrome phase may present with sensory-cognitive impairments and negative symptoms before the onset of the first psychotic episode (Lieberman et al., 2002; Light and Braff, 1999). Positive symptoms may stabilize or decrease over the course of the illness; however, individuals with chronic SCZ continue to demonstrate a waxing and waning of positive/negative symptoms and debilitating sensory-cognitive impairments with potentially severe implications on social functioning (Javitt and Freedman, 2015; Javitt and Sweet, 2015). The current understanding of the pathogenic mechanisms underlying symptoms and symptom progression in the course of the SCZ illness (from the prodrome to the first episode to chronic SCZ) is constituted in the dopamine hypothesis, which

posits that alterations of dopamine (DA) neurotransmission (excessive presynaptic DA synthesis and release, resulting in D2 receptor overactivation) in the mesolimbic system are implicated in the pathogenesis of SCZ and responsible for positive symptoms. In contrast, diminished DA neurotransmission in the mesocortical pathway (resulting in D2 receptor hypostimulation) underly negative/cognitive symptoms (Lau et al., 2013). This is complemented by the glutamatergic hypothesis, which considers alterations in glutamate neurotransmission at the N-methyl-D-aspartate (NMDA) receptor in prefrontal brain regions to be associated with both negative and sensory/cognitive symptoms (Davis et al., 1991; Howes et al., 2015; Javitt, 2010; Kantrowitz & Javitt, 2010).

As abnormalities in neurotransmission are one of the key findings in SCZ pathology, pharmacotherapies are the cornerstones of the management of this disorder (Lähteenvuo and Tiihonen, 2021). More than 60 years have passed following the initial application of the antipsychotic chlorpromazine, a first-generation dopamine D2 antagonist, to reduce positive clinical symptoms. And still, approximately 20-40% of individuals do not respond to pharmacological treatments and those that do only experience a 30% reduction in symptoms (Lally et al., 2016; Sonnenschein and Grace, 2021). The dopamine D2 receptor is a drug target for all first-generation drugs against SCZ currently present on the market, and many second and third-generation antipsychotics, antagonists of D2-like (D2, D3, D4) receptor subtypes and other aminergic receptors, also attempt to correct chemical imbalances in the brain to successfully alleviate positive symptoms with better tolerance and less extrapyramidal effects (Stępnicki et al., 2018). The longitudinal course of SCZ evidences a high level of heterogeneity in individual and symptom outcomes, and the putative failure of these single-target (“magic bullet”) drugs to address negative symptoms and cognitive deficits has left many patients with debilitating

residual symptoms, social dysfunction, difficulties with adherence and adverse drug-related effects (Maroney, 2020). Accumulating evidence has shown SCZ to be a multi-faceted, polygenic disease with complex pathomechanisms (Kondej et al., 2018) involving many neurotransmitter systems beyond DA and including glutamate, gamma-aminobutyric acid (GABA), serotonin and acetylcholine (ACh) (Yang and Tsai, 2017). There is a growing consensus that drugs selectively targeting one neurotransmitter pathway are unlikely to meet all the therapeutic needs of this heterogeneous disorder (Li et al., 2016). Polypharmacology is now considered an increasingly important aspect in drug discovery with current efforts in drug development, gradually shifting from a one drug-one target concept to multi-target drugs ("magic shotguns") for several molecular pathways (Kondej et al., 2018; Miyamoto et al., 2012) to treat positive and negative symptoms and cognitive deficits.

1.3 Cognitive functions in schizophrenia

Cognitive impairments are experienced by 80% of individuals with SCZ (Keefe and Fenton, 2007; Palmer et al., 1997; Reichenberg et al., 2009) and, in comparison to clinical symptoms like hallucinations, investigations into interventions targeting cognitive deficits were only initiated in the past three decades when it became clear that, despite their ability to alleviate positive symptoms, antipsychotics failed to improve cognitive functioning (and worsened depending on dose, polypharmacy, and anti-cholinergic load of antipsychotic drugs) (Hori et al., 2006; Sakurai et al., 2013). These impairments in cognition have been shown to be one of the strongest determinants of daily social and occupational functional outcomes in these patients (Fett et al., 2010; Green, 1996, 2016; Green et al., 2000, 2004) and have serious consequences for functional recovery in this clinical population.

Deficits in varying cognitive domains have been reported in patients with SCZ (Mesholam-Gately et al., 2009; Rajji et al., 2009; Schaefer et al., 2013) and to help improve

treatment research and understanding of the wide range and variability of cognitive impairments, the National Institute of Mental Health (NIMH) introduced the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative, tasked to implement a consensus on the methods to measure and evaluate cognition and to identify treatments targeting specific cognitive domains for SCZ. Individuals with SCZ have since been shown to express significant (1.0 to 1.7 SD in comparison to healthy individuals) impairments in processing speed, attention, working memory, verbal learning, visual learning, reasoning, and problem-solving, and social cognition, all seven cognitive domains now assessed by the MATRICS Consensus Cognitive Battery (MCCB) (Kern et al., 2011).

Cognitive impairments are considered to be a core feature of SCZ and are not shown to be associated with or moderated by the illness duration or burden of positive symptoms. However, the examination of individuals with recent-onset (RO; within the first year) psychosis revealed that cognitive impairments were present at the onset of the psychotic illness (Mesholam-Gately et al., 2009), with observed cognitive domains in antipsychotic-naïve RO patients (Fatouros-Bergman et al., 2014) being shown to be similar to those with chronic SCZ (Fioravanti et al., 2005, 2012; Heinrichs and Zakzanis, 1998; Schaefer et al., 2013). Individuals at genetic and clinical (CHR) high prodromal risk of developing SCZ moderately express cognitive impairments in comparison to RO and chronic SCZ (Fusar-Poli et al., 2012; Snitz et al., 2006). And longitudinal studies revealed that individuals at clinical high risk who later developed psychotic symptoms (CHR+) exhibited greater cognitive impairments in comparison to those individuals (CHR-) who did not develop the illness (de Herdt et al., 2013; Fusar-Poli et al., 2012). Although the severity of baseline cognitive impairment has been linked with later conversion to psychosis (Lam et al., 2018), it is similar in CHR+ individuals and chronic SCZ

participants, and conversion to psychosis does not in itself trigger a progression or worsening of cognition. The majority of patients with chronic SCZ do not show a significant progressive cognitive decline, although antipsychotics have been questioned for their role in the progression of cognitive deficits in association with high antipsychotic dosage, high D2 receptor occupancy, polypharmacy, and concomitant use of anti-cholinergic medications (Hori et al., 2006; Sakurai et al., 2013).

Recent GWAS studies in SCZ have found overlapping genomic influences to underly cognitive impairments and SCZ, but these genomic variations were not unique to SCZ as they also were shown to underly cognition in the general population and in individuals with bipolar disorder (Harvey et al., 2020; Jones and Harvey, 2020). Furthermore, cognitive impairments are now recognized as primary treatment targets for SCZ, and the latest genomic findings suggest that treatment interventions do not need to be specific to SCZ with regards to the underlying genomic influences and that novel treatments ameliorating cognitive functioning in healthy individuals would be expected to also show a similar effect in patients with SCZ (Jones and Harvey, 2020). The preclinical testing on healthy individuals offers a translational opportunity for screening therapeutics, allowing for the identification of potential efficacious interventions that can progress through to clinical testing in SCZ patients.

Several drug targets and add-on/adjunctive pharmacological interventions for cognitive improvement have been proposed since the implementation of the MATRICS initiative. Yet, the search continues with intrinsic challenges complicating the identification of proper drug targets and limiting a significant breakthrough, including an incomplete understanding of the etiology and pathophysiology of the SCZ disease, limited translational success from animal models used in drug discovery research, clinical trials with complex and high variability phenotypes (for

cognitive, positive and negative symptoms) amongst individuals with SCZ, in addition to targeting single neural receptors in a disease that proves to be complex and involves multiple brain regions and neural receptor systems.

In helping to address the unmet need to treat cognitive impairment as a core feature of SCZ, research over the past few decades has increasingly used objective, brain-based biomarkers, which can aid in the identification of molecular pathways underlying the disease (i.e., endophenotypes; which possess characteristics that reflect actions of genes predisposing an individual to a disorder, and/or act as predictive biomarkers to see if an intervention will improve cognition) (Kim et al., 2020). With criteria emphasizing their association with a functional outcome (e.g., improvement in attention or employment status) and/or pharmacological response (e.g., change in a relevant pharmacodynamic index) (Green et al., 2004), predictive biomarkers probing brain processes underlying persistent cognitive deficits in SCZ have consisted of various non-invasive techniques including structural and functional neuroimaging, and neurophysiological measures such as electroencephalography (EEG) and event-related potentials (ERPs). Apart from their high tolerability and practicality (relatively low cost and ease of implementation) and their direct indexing of neuronal activity underlying cognitive functions, neurophysiological measures are well suited for use as biomarkers in cognitive development studies as many can be recorded in passive paradigms requiring no attention, task engagement or behavioural response, and their high temporal resolution uniquely allows for tracking the flow of information in the brain from sensory through to association cortices and hence can efficiently parse abnormalities in automatic/pre-attentive and controlled/attention-dependent components of cognition (Rissling et al., 2010). Assessable only with neurophysiologic procedures and not with conventional neuropsychological testing, abnormalities in early sensory processes (occurring

milliseconds following the reception of a stimulus) have been a consistent finding in SCZ that correlates well with cognitive deficits and global functional outcome (Javitt et al., 2008). And they have garnered considerable interest as candidate endophenotypes for helping to elucidate pathomechanisms underlying cognition and as potential predictive biomarkers in the treatment of cognition in SCZ (Kim et al., 2020).

1.4 Sensory processing in schizophrenia

A person's ability to understand and interact effectively with their surrounding world ultimately depends on their underlying sensory experiences of it. It has been suggested that a breakdown in processes that regulate the inflow of sensory information is fundamental, and impairments are thought to lead to failure in one's ability to interact with the environment, contributing to delusional beliefs, social withdrawal, impaired cognition and decline in functioning (Javitt, 2009a; Leitman et al., 2010; Thomas et al., 2017; Venables, 1964; Vinogradov and Nagarajan, 2017). The cognitive dysfunction of SCZ encompasses profound disturbances in sensory processing, as first documented by Kraepelin and Bleuler's descriptions of perceptual abnormalities in SCZ patients (Javitt, 2009b). Patients are often disturbed by their sensory distortions in auditory and visual domains (e.g., light and colours may seem more intense and fragmented, and sounds too loud and intrusive) and, unaffected by anti-dopaminergic antipsychotic drugs, many aspects of sensory dysfunction persist chronically (Javitt and Freedman, 2015).

Considered intermediaries between molecular and cellular mechanisms and clinical symptoms of SCZ, the nature and consequences of sensory processing deficits have been re-characterized over recent decades in the light of a modern understanding of the involved molecular and neurological brain mechanisms (Javitt and Freedman, 2015). Also, corroborated

by both behavioural and neuroimaging-based measures, sensory deficits, frequently examined with respect to audition, have been most effectively demonstrated using neurophysiological measures such as ERPs, which within milliseconds following the reception of a stimulus, are able to trace the flow of information from sense organs, through brainstem/subcortical regions and into the sensory cortex and then higher cortical brain regions (Rissling et al., 2010). Elementary sensations such as auditory detection thresholds in response to isolated stimuli were generally found normal in patients (Javitt, 2009b), suggesting peripheral and brainstem auditory processing is preserved. However, significant impairment has been observed in early auditory sensory processing in the comparative response to and discrimination of physical sound characteristics (e.g., intensity, duration and pitch) of successive auditory stimuli, which are critically dependent on the primary auditory cortex (Javitt and Sweet, 2015) and have been most extensively studied with the P50 and mismatch negativity (MMN) ERPs (Kim et al., 2020).

1.4.1 ERPs

EEG-based ERP measures, recorded from an electrode array sampling electric fields across the scalp, consist of voltage fluctuations time-locked to stimuli or responses that become evident after signal averaging (time-domain analyses) over repeated trials, separating stimulus related activity from background EEG (Luck, 2005). Voltage deflections in the averaged ERP waveform have been characterized as particular components, which are typically defined by latency (in milliseconds), polarity (P for positive, N for negative), scalp topography and variation with experimental variations. Primarily sensitive to transient changes in neural activity over periods of tens or hundreds of milliseconds, ERPs may be broadly sub-divided into early, exogenous sensory-evoked components, which emerge within the first 100 milliseconds or so after stimulus onset and basically reflect automatic detection of physical features of stimuli, while later

endogenous, or cognitive-related components index stimulus context (Figure 1.1). The amplitude and latency of the respective components are often interpreted as estimating the strength and time course of allocated neural resources. ERPs instantaneously detected at the scalp originate from the summation of post-synaptic potentials (PSPs) occurring in many thousands of similarly oriented cortical pyramidal cells. Although identification of the neural sources of these ERP components is incomplete and hindered by the blurring of voltage fields by scalp/skull tissues and the relatively low spatial resolution of the ERP technique, converging use of source localization techniques (to de-blur scalp ERP signals), neuroimaging and other methodologies (e.g., independent component analysis) will allow for more precise elucidation of the neuroanatomical loci of these components and related processes.

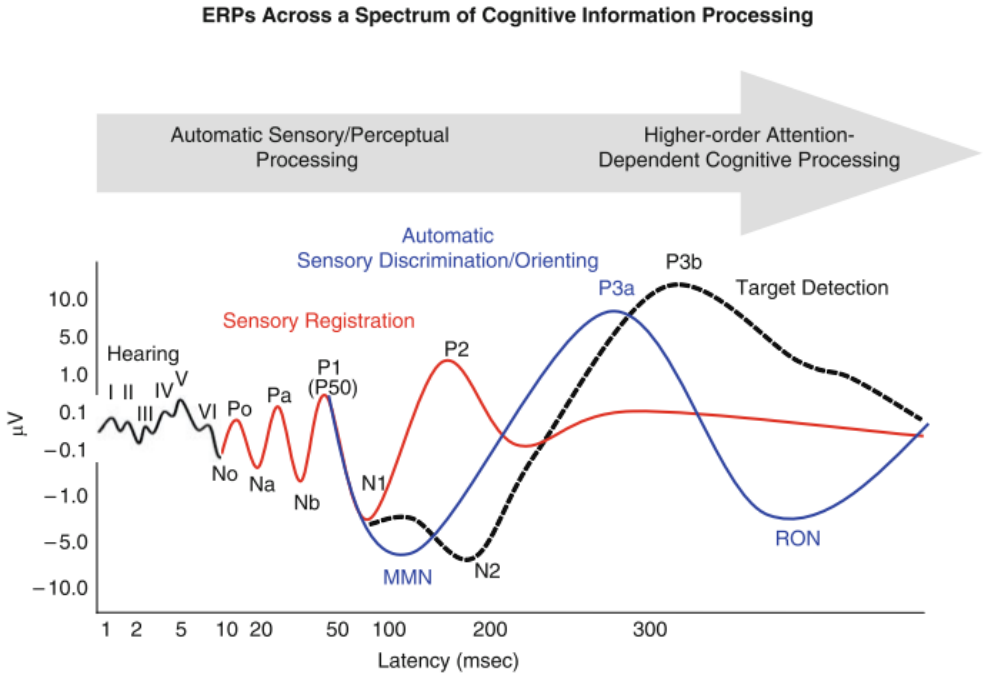

Figure 1.1 An 'ideal' schematic representation of ERP waveforms from automatic sensory registration to higher-order processing of sound stimuli. Copied with permission from Behavioral neurobiology of schizophrenia and its treatment, Chapter "*Neurophysiological Measures of Sensory Registration, Stimulus Discrimination, and Selection in Schizophrenia Patients*", Figure 2 (Swerdlow, 2010).

1.4.2 Sensory gating – The P50 ERP

It has been suggested that patients with SCZ have deficits in the ability to filter (gate out) extraneous/redundant sensory information predisposing them to misperceive environmental stimuli and inappropriate assessment of stimulus salience (Evans et al., 2007). Auditory SG is one of the first pre-attentive auditory sensory mechanisms to be neurophysiologically examined in SCZ and has been found to be impaired across the SCZ spectrum as observed in meta-analytic studies showing auditory gating deficits in acutely ill and stable chronic SCZ patients (Bramon, Rabe-Hesketh, Sham, Robin M. Murray, et al., 2004; Patterson et al., 2008), and by findings of similar gating deficits in individuals at high risk for SCZ (Bodatsch et al., 2015; Brockhaus-Dumke et al., 2008), and in healthy biological relatives of SCZ patients (Turetsky et al., 2007). ERP measures of SG are most frequently indexed with the positive P50 peak generated during the presentation of a dual-click, conditioning-testing, auditory paradigm (Nagamoto et al., 1989). P50, the largest initial cortical response to an auditory stimulus, is a central-maximum positive scalp component occurring at ~ 50 ms following an initial (conditioning) auditory stimulus (S_1), which is then followed by a second identical (testing) stimulus (S_2), typically presented 500 ms following S_1. In healthy persons, the response to S_2 is suppressed or 'gated out', resulting in an attenuated S_2P50 amplitude – an example of inhibitory SG (Figure 1.2). The amplitude ratio (S_2P50/S_1P50: rP50) and amplitude difference (S_1P50 – S_2P50: dP50) scores are gating indices that reflect the degree of healthy/impaired SG, with meta-analyses consistently showing, with high effect sizes, P50 suppression to be robust at > 55% (e.g. rP50 < 0.45) in non-patients and relatively weak at < 20% (e.g. rP50 > 0.80) in patients with SCZ (Bramon et al., 2004; de Wilde et al., 2007; Patterson et al., 2008), with rP50 as the main measure of SG ranging from 0.93 to 1.56 (Atagun et al., 2020). Possibly confounded by their psychopathology, deficits in P50 inhibition have not been associated with patient self-reports of sensory disturbances (Light and

Braff, 2000), but perceptual anomalies are associated with P50 deficiencies in schizotypal adults (Croft et al., 2001). Associations between P50 gating deficiency and positive/negative symptoms have been inconsistent, but the P50 deficit has been present in both predominantly positive symptom and negative symptom patients (Adler et al., 1990). Similarly, some studies have found that rP50 varies with the intensity, frequency, and severity of hallucinations (Smith et al., 2013), but other studies have reported opposite findings (Zhu et al., 2017). P50 response suppression processes are thought to engage an entire network of bottom-up and top-down brain events, implicating a number of cortical/subcortical brain regions (including the brainstem and auditory/temporal and frontal cortices (Grunwald et al., 2003; Mayer et al., 2009)) neurotransmitters but are mostly dependent on glutamate and inhibitory GABAergic neurotransmission and cholinergic signalling (Boutros et al., 1999, 2013; Potter et al., 2006). At the preclinical level, the neurobiological mechanisms underlying P50 inhibition have been examined in the rat with the P20-N40 peaks, the rodent equivalent of the human P50 (Freedman et al., 2000), which has its origin in the hippocampal pyramidal neurons (Bickford-Wimer et al., 1990; Miller and Freedman, 1995). Accordingly, while the initial auditory stimulus (S_1) activates pyramidal neurons, the successive auditory stimulus (S_2) results in P50 inhibition as a result of the activation of presynaptic $GABA_B$ receptors on glutamatergic afferents (Freedman et al., 2000). Specifically, excitatory PSPs that give rise to the initial P50 peak (S_1P50) also simultaneously co-activate $GABA_B$ receptors, a process that involves activation of alpha-7-nicotinic acetyl cholinergic receptors ($\alpha 7$ nAChRs: cholinergic receptors from the reticular-septal pathway) (Hershman et al., 1995) on GABA interneurons, which inhibits the firing of pyramidal neurons. Since glutamate release is inhibited by presynaptic $GABA_B$ receptors following the first stimulus (S_1), the subsequent second stimulus (S_2) is only able to produce a

modest excitation of the pyramidal cell – hence S_2P50 amplitude is diminished (Daskalakis et al., 2007).

The majority of studies examining relationships between P50 gating and cognition found P50 deficits were associated with and predicted poor attention and working memory, consistent with the role of inhibitory SG in protecting the brain from being responsive to extraneous stimulation so that it can be ready to respond to more meaningful sensory (task-related) stimuli (Braff & Light, 2004; Jones et al., 2016; Kim et al., 2020b; Potter et al., 2006; Smith et al., 2010; Vlcek et al., 2014). Auditory P50 SG deficits in infants have even been shown to predict cognitive and mood disorders at age 3 (Hutchison et al., 2017), and further, in individuals with SCZ, impaired auditory P50 SG may contribute to functional impairment as it has been associated with community outcome and quality of life scores (Santos et al., 2010). Current neuroleptics have not been shown to significantly improve auditory SG (Su et al., 2012); however, nicotine (a ubiquitous nAChR modulator) (Adler et al., 1992; Knott et al., 2010, 2013) and α7 nAChR agonists (Freedman, 2014) were shown to improve gating measures in individuals with SCZ and in healthy participants (this is further discussed in section 1.5, and Chapters 2 and 3).

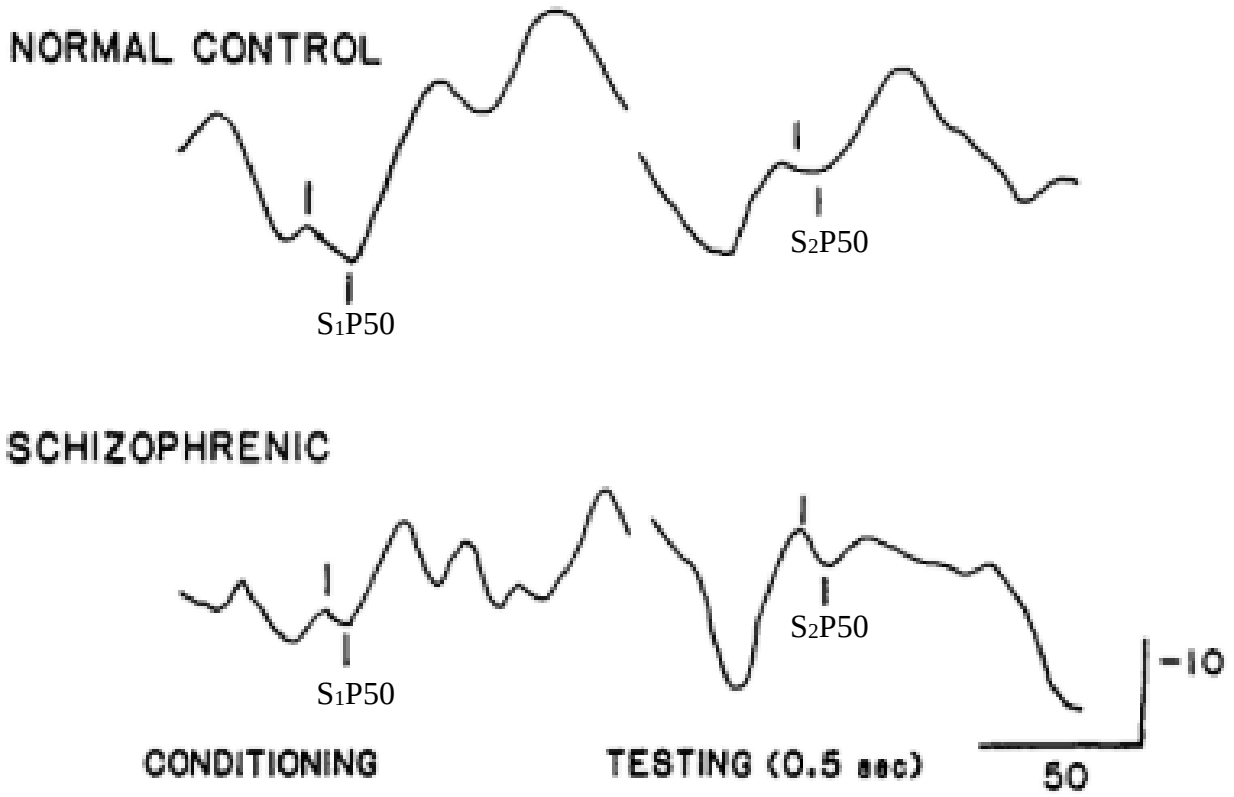

Figure 1.2 Mean S_1P50 and S_2P50 amplitudes in healthy controls (top) and patients with schizophrenia (bottom). Copied with permission from (Freedman et al., 1987).

1.4.3 Deviance detection – The mismatch negativity (MMN) ERP

Adaptation requires that the organism detects and responds to rare, sudden information changes in the environment (e.g., fire alarms, car horns) that potentially carry information relevant to our survival. The human sensory systems possess several mechanisms of change detection, and in the auditory domain, acoustic changes can be processed pre-attentively, allowing us to safely focus on task-relevant parts of our environment (Volosin et al., 2021). Auditory change detection processes have been studied with two ERPs: the N1 (a negative component peaking at ~ 100ms) elicited by acoustic transients (e.g., on- and off-sets), and MMN – the first cortical response that discriminates between stimuli in the absence of conscious attention (Näätänen et al., 1989). The auditory MMN ERP has been extensively studied for several decades in an "Oddball" paradigm

(Figure 1.3), where it is elicited by intermittent discriminable 'deviant' sounds (e.g., changes in sound intensity [loudness], duration [length of tone presentation], frequency [pitch] and location [left or right vs. both ears]) (Näätänen et al., 2016; Pakarinen et al., 2009; Tamminen et al., 2015). This change detection is indexed as a negative component, maximum at the frontocentral scalp site, beginning within ~ 50 ms after the presentation of the deviant sound and peaking at ~ 150 ms post-stimulus onset (Light and Braff, 2005). Using multiple techniques, including EEG, neuroimaging and intracranial recordings in both humans and monkeys, the MMN has been shown to be mainly generated within the primary and secondary auditory cortices, with contributions from the frontal cortex (El Karoui et al., 2015; Javitt, 1996, 2000; Rosburg et al., 2005). Although the exact meaning and mechanisms of the MMN are still unresolved, three dominant explanations for the MMN have been proposed. The 'neural adaptation' hypothesis proposes that while the repeated presentation of standard sounds results in attenuated (adapted) responses of feature-selective neurons in the auditory cortex, the presentation of rare deviant sounds activates less adapted neurons (vs. those activated by frequent standard sounds) and thus elicit a larger obligatory response resulting in the MMN as shown following the subtraction procedure (Fitzgerald & Todd, 2020; Todd et al., 2012). This contrasts with the 'sensory memory' hypothesis, which proposes that the MMN is a 'non-obligatory' (novel) response reflecting the degree of deviation between properties of an incoming sound and those of a neural 'memory trace' established by preceding standard sounds (Fishman, 2014). The 'predictive error' account of the MMN proposes that the auditory system acquires an internal model of sound input regularities and uses that information to predict and anticipate what should happen next. If these predictions differ from the actual stimulus, it results in a mismatch signal (Rao &

Ballard, 1999). This predictive coding account of MMN and its dysregulation in SCZ have been increasingly linked to NMDAR neurotransmission (Wacongne, 2016; Wacongne et al., 2012).

Deficient MMN in SCZ has been well documented for multiple types of deviants by a large body of studies and meta-analyses, with the degree of deficit in MMN generation being as large as it is in other well-validated neurocognitive tests and with the mean effect size of the SCZ deficit being about 1.0 SD (Näätänen & Kähkönen, 2009; Umbricht & Krljesb, 2005). Although not consistently evident at first psychosis, diminished MMN is a stable finding across the course of the illness (Erickson et al., 2016), with MMN reductions correlating with illness duration (Umbricht and Krljesb, 2005) and progressive amplitude reduction over time being associated with volume loss in regions of the auditory cortex, which, along with frontal cortex, is the main MMN generator (Curtis et al., 2021; Rasser et al., 2011; Salisbury et al., 2007, 2020). There is a trend for reduced MMN in unaffected family members (Earls et al., 2016; Erickson et al., 2016), and in some but not all studies, MMN has been shown to be reduced in individuals at high clinical risk for psychosis and to predict who will progress to SCZ (Hamilton et al., 2020).

Some studies have found MMN to vary with the presence and severity of clinical (positive and negative) symptoms (Näätänen & Kähkönen, 2009; Umbricht & Krljesb, 2005), and deficits in MMN generation in SCZ have been associated with poor performance in auditory discrimination (Javitt and Freedman, 2015) and neurocognitive tasks (attention, working memory, executive function) (Baldeweg et al., 2004; Light et al., 2007; Näätänen et al., 2011) and with measures of psychosocial functioning (e.g. independent living, occupational status) (Light and Braff, 2005).

Structural equation modelling of measures of early auditory sensory processing (in 1415 SCZ patients), particularly MMN, showed a direct (mediating) effect on cognition, which in turn

had a direct mediating effect on negative symptoms, and that both cognition and negative symptoms were shown to have direct effects on the functional outcome of patients (Thomas et al., 2017). Of therapeutic interest is the model's prediction that a 1 μV change in early auditory sensory processing (including MMN) would result in improvements of approximately d = 0.78 for cognition and d = 0.28 for psychosocial functioning. These latter findings suggest that interventions that reliably enhance measures of early auditory sensory processing in SCZ would be rational targets for therapeutic development (Swerdlow et al., 2018).

Targeting glutamatergic mechanisms, particularly involving N-methyl-D-aspartate-type receptors (NMDAR), has been suggested as one strategy for enhancing auditory system neuroplasticity to address cognitive deficits in SCZ. The investigation of NMDAR modulators stems in part from the well-characterized role of brain NMDAR function in SCZ pathophysiology (Kantrowitz & Javitt, 2010) and associated MMN deficits, which are reproduced in healthy humans with the administration of the NMDAR antagonist ketamine (Schwertner et al., 2018). The use of direct and indirect NMDAR-modulating drugs to date has produced mixed results and has not yet been translated into clinical practice (Kantrowitz, Epstein, et al., 2018; Kantrowitz, Swerdlow, et al., 2018). Although MMN is highly dependent on NMDAR function, evidence suggests a potential role for α7 nAChRs (Bali et al., 2017; Ehrlichman et al., 2008; Javitt, 1996; Javitt et al., 2012; Rosburg and Kreitschmann-Andermahr, 2016; Umbricht and Krljesb, 2005) as activation of these receptors can indirectly modulate the glutamate system (Broide and Leslie, 1999). α7 nAChR activation allows for the release of GABA, which activates presynaptic $GABA_B$ receptors on the excitatory inputs to NMDAR receptors on pyramidal cells.

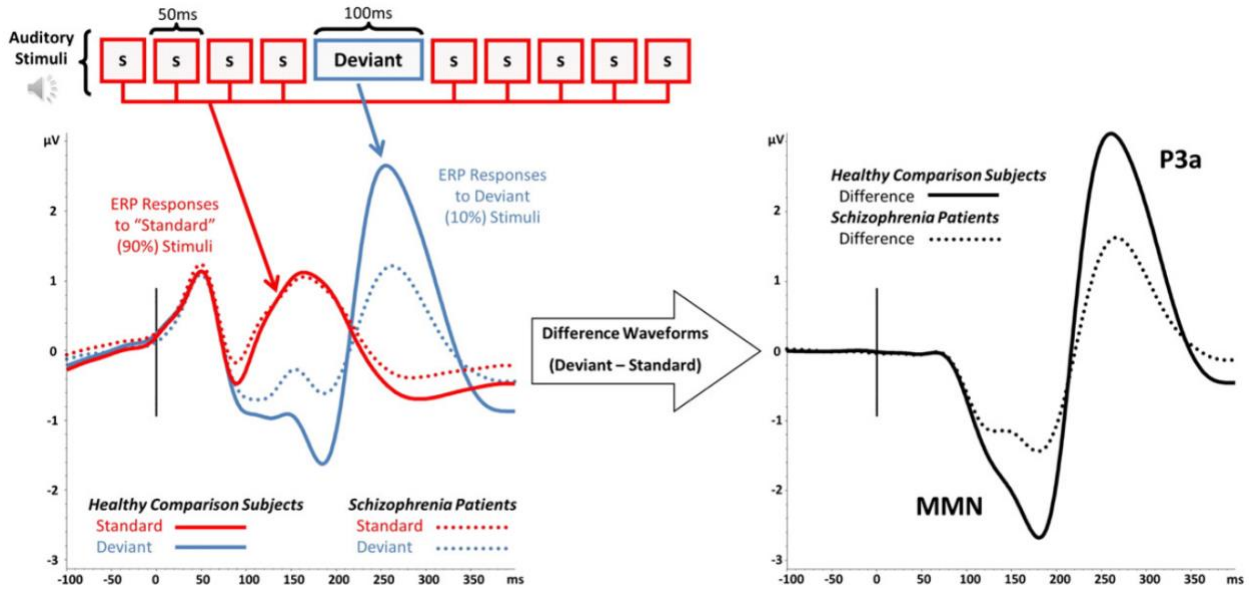

Figure 1.3 Grand averaged difference waveforms (deviant minus standard) in healthy controls and patients with SCZ elicited during the presentation of the duration deviant in the oddball paradigm. Copied with permission from (Light et al., 2015).

1.5 Nicotinic modulation of early auditory information processing

Acute administration of nicotine, either smoked or orally (gum) or transdermally (patch) administered, has been shown to improve domains of cognition, specifically attention, working memory, processing speed and verbal learning and memory in non-smoking SCZ patients and in animal models (Adler et al., 1993; Ahlers et al., 2014; Beck et al., 2015; Boggs et al., 2014; George et al., 2002; Gupta and Mittal, 2014; Harris et al., 2004; Lucatch et al., 2018; Reed et al., 2016; Sacco et al., 2005). This specific nicotine-induced pro-cognitive effect is believed to contribute to high smoking rates of 60-80% observed in the SCZ population, which is compared to 10-15% in healthy populations (Cather et al., 2017); however, cigarette smoking in SCZ contributes for a significantly shorter life span (~ 28 years) in these individuals due to smoking-related diseases (Olfson et al., 2015). Reports on the smoking behaviours of patients with SCZ evidenced higher rates, deeper puffs, heavier nicotine extraction, and preference for cigarettes

with higher nicotine concentration in comparison to the general public (Masterson and O'Shea, 1984). While smoking rates decreased since the 1970s (recent rates in: Canada 17%; UK 20%; and US 19%) (Guignard et al., 2015; Pasquereau et al., 2021), reports from populations that live with mental health challenges did not show the same reductions in SCZ specifically, also indicating greater dependence (de Leon and Diaz, 2005; Li et al., 2019; Prochaska et al., 2017; Taylor et al., 2021). Initial reports suggested a role for smoking in alleviating the severity of negative and cognitive symptoms and in reducing the extrapyramidal effects experienced with first-generation neuroleptics. The initial set of research findings supporting the 'self-medication' hypothesis (Masterson and O'Shea, 1984) was then followed by fields of research attempting to better understand the involvement of smoking, nicotine, nicotinic receptors, the cholinergic system and potential pharmacological treatments to replace cigarette smoking in SCZ.

Studies examining genetic associations outlined that smoking increases the risk of developing SCZ (Niemelä et al., 2016), emphasizing maternal smoking where genes implicated in neurodevelopment were shown to be impacted in the ventral tegmental area (Sagud et al., 2019)). Higher smoking rates are also observed in healthy first-degree relatives of people with schizophrenia (Ferchiou et al., 2012) hence arguing against a causality interaction between smoking and SCZ. These findings emphasize that common genetic/vulnerability mechanisms underly cigarette smoking, nicotine dependence, and schizophrenia (Sagud et al., 2019).

1.5.1 Nicotine in the brain

Nicotine that is inhaled following cigarette smoking is primarily absorbed through the alveoli in the lungs and reaches the brain in approximately 10 seconds following the first puff (Benowitz et al., 2009; McKinney and Vansickel, 2016). Following the first puff, nicotine was shown to reach the brain in 5 seconds and to reach 80% of maximal brain concentration in 15-20 seconds

(Berridge et al., 2010) and is followed by an elimination half-life (t1/2) ranging on average between 100 – 150 min (Rose et al., 2010). Factors such as age, sex, ethnicity, genetic variations, diet/food intake, time of day, hormones, medications, and smoking status influence nicotine metabolism and elimination (Benowitz et al., 2009).

In the brain, nicotine binds and activates nicotinic acetylcholine receptors (nAChRs), which are ligand-gated cross-membrane pores composed of five subunits (Changeux et al., 1998; le Novère et al., 2002; Unwin, 2003). There are currently 16 encoding genes identified for α1 - α10 (where α8 was only identified in chicken), β1 – β4, γ, σ, ε subunits which can combine to form homomeric and heteromeric ligand-gated ion channels (Nees, 2015). The conformation and stoichiometry of the subunits composing the nAChR channel greatly affect its affinity to ligands and its functionality. The binding of nicotine to nAChRs occurs in a ubiquitous manner where nicotine is found to exert high affinity to receptors comprised of α2 - α5 subunits combined with β subunits (most commonly β2 in the mammalian brain), while α7 - α9 nAChRs without the β subunit express low affinity to nicotine and are recognized as fast activating-deactivating receptors (Deneris et al., 1991; Leonard et al., 1996).

The widespread distribution of nAChRs elucidates the importance of their role in essential brain functions. Results from in situ hybridization studies indicated that α4β2 and α7 nAChRs are one of the most important subunits in the human brain as their mRNA is distributed across key regions such as the striatum, hippocampus, basal ganglia, brainstem, and the cerebellum (Gotti and Clementi, 2004). Further characterization of nAChRs has shown that these receptors are found on neuronal dendrites, somas, and at perisynaptic and synaptic sites therefore, indicating these receptors' involvement in signal transduction, fast pre-/post-synaptic

neuronal communications, and in the regulation of cellular functions via the modulation of calcium influx (Gotti and Clementi, 2004).

The activation of nAChRs induces the activation and inhibition of neuronal processes based on their location in the brain and within neurons (Dani and Bertrand, 2007). In the hippocampus specifically, α7 nAChRs are most prominent and are evidenced to interact with GABAergic interneurons and pyramidal cells in the mediation of important learning and memory mechanisms (Bertrand and Wallace, 2020). In the midbrain, the firing mode and frequency of dopaminergic neurons are modulated in part by interactions between excitatory presynaptic α7 nAChRs, inhibitory β2 nAChRs on GABAergic interneurons, and post-synaptic nAChRs which are believed to also be implicated in the mechanisms underlying the addictive property of nicotine and associated cognitive processes (Dani and Bertrand, 2007).

Genetic polymorphisms in coding and non-coding regions of the CHRNA7 gene, which codes for the α7 nAChR, were shown to be associated with SCZ and with impairments in auditory SG indexed by the P50 (Freedman et al., 2003; Leonard et al., 2002). Findings from postmortem α7 nAChR binding studies reported decreased binding levels in several brain regions, notably the prefrontal cortex, the CA3 hippocampal region (Freedman et al., 1995; Leonard et al., 1996), and the cingulate cortex of smokers with SCZ, while increased levels were observed in temporal cortical areas (Gibbons and Dean, 2016). Additionally, a chromosome 15q13.3 deletion, which includes the CHRNA7 gene, was found to have a high penetrance for SCZ (Bassett et al., 2008; Stefansson et al., 2008). While this genetic association is not mendelian or causative of the disease or symptom-specific, it does contribute to the search of an endophenotypic factor which was initially suggested by Meehl in the 1960s (Meehl, 1962) as a

valuable strategy to achieve better therapeutic and etiology understanding of this neuropsychiatric disease.

1.5.2 Nicotine & P50

Auditory SG has been shown to be sensitive to different neurotransmitters; however, incongruent findings continue to highlight not only the neuropathophysiological complexity of SCZ but also the intricate mechanisms that modulating agents may express, highlighting that their effect can not be translated by a simple linear function. Meta-analyses are still diverging on the impact of antipsychotics on SG with the latest expressing that medicated patients with SCZ show better SG measures than unmedicated patients (Atagun et al., 2020). Furthermore, older studies have reported improved SG with a number of second-generation antipsychotic medications (Adler et al., 2004; Csomor et al., 2014; de Wilde et al., 2007; Holstein et al., 2011; Oranje et al., 2013), which in addition to inhibitory effects on DA receptors have been evidenced to block 5-HT_3 serotonergic receptors and consequently increase the cortical release of ACh (Adler et al., 2004; Barnes et al., 1989; Light et al., 2000; Nagamoto et al., 1996). Clozapine, the 'gold standard' for treatment-refractory SCZ (Siskind et al., 2016), normalizes the P50 ratio coincident with improvement in clinical symptoms (Becker et al., 2004; Nagamoto et al., 1999). In animal models, the neurobiological effects of clozapine, which releases ACh in the hippocampus (Shirazi-Southall et al., 2002), include activation of α7 nAChRs. Normalization of the gating deficits in DBA/2 mice is blocked by selective α7 receptor antagonists but not by α4ß2 receptor antagonist treatment, thus implicating the involvement of low-affinity nicotinic receptor in clozapine's effects (Simosky et al., 2003). Conversely, others found no effect of first- and second-generation antipsychotics on P50 SG (Bramon et al., 2004; Sanchez-Morla et al., 2009; Su et al., 2012). Interestingly, studies showed that P50 SG improvement was only evident

in healthy individuals who expressed lower P50 suppression levels (Csomor et al., 2008; Ucar et al., 2012) and similarly in rats who expressed lower suppression levels at baseline (Adler et al., 1986). Analogously, nicotine's effect on P50 SG has long been examined and evidence has shown improved P50 SG in the DBA/2 mouse strain (a dilute brown, non-agouti; H-2^d haplotype mouse; an inbred mouse model of SCZ expressing low levels of hippocampal α7 nAChRs and SG impairments) (Adler et al., 1998; Light and Braff, 1999; Olincy et al., 2006; Stevens and Wear, 1997), as well as in patients with SCZ, their healthy biological relatives, and healthy individuals who express relatively lower SG scores (Adler et al., 1992; de La Salle et al., 2013; Knott et al., 2010, 2013; Millar et al., 2011).

In healthy individuals, nicotine has been shown to improve P50 SG where low baseline suppressors (i.e., individuals with reduced SG) exhibited lower S_2P50 amplitudes following nicotine administration, indicating that nicotine ameliorated the gating-out of redundant stimuli while the opposite effect was shown in high baseline suppressors (i.e., individuals with efficient SG) and hence diminished P50 gating scores (de La Salle et al., 2013; Knott et al., 2010, 2013).

Nicotine was shown to improve P50 SG in healthy relatives of patients with SCZ who demonstrate impaired P50 gating, typically observed in 50% of relatives to individuals with SCZ (Adler et al., 1992), and the nicotine effect was shown to be mediated by reduced response to the testing (S_2) stimulus, manifested as lower S_2P50 amplitudes. This nicotinic effect was also observed in individuals with SCZ (Adler et al., 1993) where P50 ratios (S_2/S_1) were diminished in patients following acute nicotine consumption. P50 abnormalities have been shown to be less pronounced among SCZ patients who are current smokers than those who are non-smokers, suggesting a positive effect on chronic cigarette smoking on ameliorating this inhibitory deficit (Chen et al., 2011).

1.5.3 Nicotine & MMN

In contrast to the mixed findings on the effects of antipsychotics on P50 SG, the evidence suggests that these agents do not exert an impact on MMN (Light et al., 2015). In contrast to the extensive research conducted on measures of deviance detection and its modulation via the glutamatergic system (Greenwood et al., 2018; Javitt, 1996; Kantrowitz, Epstein, et al., 2018; Kantrowitz et al., 2016; Swerdlow et al., 2016; Tikhonravov et al., 2008), less is known about its alteration with nicotine and nicotinic modulators. In healthy individuals, acute administration of nicotine was shown to enhance MMN amplitudes (Baldeweg et al., 2006) and latencies (Inami et al., 2008), evidenced to be related to an increased response to the standard tone (Baldeweg et al., 2006) and shown to be blocked while simultaneously administering ketamine, a selective NMDAR antagonist (Hamilton, D'Souza, et al., 2018). In contrast, healthy participants with a predisposition to auditory hallucinations expressed nicotine-mediated MMN amplitude increases when under intravenous ketamine conditions (Knott et al., 2012). Furthermore, this nicotine-induced MMN enhancement was observed in both smokers and non-smokers (Harkrider and Hedrick, 2005; Martin et al., 2009). The effects of nicotine on change detection in SCZ patients may be deviant-dependent as nicotine gum was found to increase and normalize (vs. healthy controls) MMN elicited by changes in tone duration but not changes in tone pitch (Dulude et al., 2010). Interestingly, enhanced MMN amplitudes were evidenced following a combined nicotine and nabilone (a cannabinoid, CB1, receptor agonist) co-administration in healthy participants, while no effect was observed when these treatments were administered alone (de La Salle et al., 2019a). Healthy tobacco-naïve cannabis users also showed larger MMN amplitudes following acute nicotine administration (Impey et al., 2015). Furthermore, just as with P50 SG, nicotine effects on MMN were also found to be baseline dependent with nicotine-mediated MMN amplitude increases reported in healthy low groups (Knott et al., 2014; Smith et al., 2015). In

contrast, in patients with SCZ, nicotine was only shown to shorten the MMN latency in patients with persistent auditory verbal hallucinations (Fisher, Grant, et al., 2012) and in smokers (no effect in non-smokers) (Inami and Kirino, 2019). These findings (Baldeweg et al., 2006; Dunbar et al., 2007; Featherstone and Siegel, 2015; Hamilton, D'Souza, et al., 2018; Harkrider and Hedrick, 2005; Inami and Kirino, 2019; Martin et al., 2009) led to greater interest in examining the impact of nAChR modulation targeting specifically the α7 receptors as recent findings suggest an association and interplay between the brain's α7 nAChRs and the glutamatergic system in the hippocampal CA1 region (Bali et al., 2017, 2019).

1.6 The cholinergic system in schizophrenia

The differential effects of nicotine in healthy individuals and patients with SCZ on cognition and early auditory sensory processing (the auditory P50 SG and deviance detection mismatch negativity [MMN] ERPs) may be attributed to varying technical, environmental, and physiological factors including the testing environment, task administration, recording, data processing, analytical procedure, participant's performance at baseline, sex, type of food intake, physiological elements that impact nicotine absorption (weight, body composition, activity level), smoking status and plasma levels of nicotine and other commonly used substances (i.e., caffeine, alcohol) that might interact with nicotine, in addition to genetic influences on the expression of neuronal receptors in the brain mediating the psychoactive effects of nicotine (i.e., nAChR expression) (Ettinger et al., 2009). Moreover, the availability/occupancy, conformational ratios, and stoichiometry of nAChRs impact the response to nicotine (Lindstrom, 1997).

In contrast to acute/chronic nicotine exposure as an exogenous nAChR modulator, ACh is the endogenous neurotransmitter released by the basal forebrain cholinergic system comprised of the medial septal nucleus, the vertical and horizontal limbs of the diagonal band of Broca, the

substantia innominiata, the nucleus basalis of Meynert, the magnocellular preoptic nucleus, and the ventral pallidum (Ballinger et al., 2016; Eickhoff et al., 2022; Woolf, 1991). In response to specific neurophysiological functions, ACh can be released in a tonic and phasic manner, projecting to the frontal cortex, the hippocampus, the amygdala and thalamus, where ACh non-selectively binds to and activates nAChRs and muscarinic acetylcholine receptors (mAChRs) (Eickhoff et al., 2022). In concert with the glutamatergic, dopaminergic, and GABAergic neurotransmitter systems, Ach has been shown to be implicated in several neurological functions, including cognition, where preclinical and clinical studies have shown that ACh may play a key role in modulating/facilitating processes underlying planning, decision making, attention, memory, as well as fear and stress response (Amalric et al., 2021; Ballinger et al., 2016; Eickhoff et al., 2022; Lindstrom, 1997). This association of ACh is further supported by the observations of correlations between cognitive impairments/declines and the cholinergic burden instigated by the anticholinergic effect of current antipsychotics in patients with SCZ (Eum et al., 2017; Joshi et al., 2021; Rehse et al., 2016). This antipsychotic-associated anticholinergic burden was observed in more than 50% of patients regardless of the type of antipsychotic (i.e., typical vs. atypical, or both) and regimen (i.e., mono- vs. polypharmacy) and the mediated cognitive impairments were observed across all cognitive domains (Joshi et al., 2021) and have been shown to impact the response to cognitive treatment (Vinogradov et al., 2009).

1.6.1 Nicotinic impairments in schizophrenia

With respect to choline, a precursor and metabolite of Ach which selectively binds to α7-nAChRs (Papke et al., 1996), proton magnetic resonance spectroscopy (^{1}H-MRS) studies in SCZ (vs. healthy controls) have reported inconsistent findings with respect to brain choline levels and

a recent review and meta-analysis found no major differences between patients and healthy controls in levels of absolute choline in all regions of the brain although lower levels of choline/creatinine (creatinine is known to be implicated in regulating cellular energy metabolism) ratios in the hippocampus were significant (Kraguljac et al., 2012). Varying decreases and increases of levels of choline in the basal ganglia, hippocampus, dorsolateral prefrontal cortex, and temporal lobe have been reported; however, there was not enough data to reach a significant conclusion with such inconsistencies. It is important to clarify that choline levels measured by ^{1}H-MRS studies is a composite number which includes levels of choline, phosphocholine, glycerophosphocholine, ACh, and cytidine diphosphate choline, where phosphatidylcholine (the most prominent form of choline in the brain) is not detectable by ^{1}H-MRS; thus, ^{1}H-MRS choline levels are indicative of neuronal membrane integrity and biochemistry (Cecil et al., 1999). Systematic reviews and meta-analyses have not yet found an effect of treatment or illness chronicity on brain choline levels in SCZ (Iwata et al., 2018; Kubota et al., 2020).

Conversely, post-mortem studies in SCZ have shown marked decreases in the levels of nAChRs in the brain, particularly decreases in the availability of α7 nAChRs in the hippocampus and cingulate cortex (Court et al., 1999; Martin-Ruiz et al., 2003). Also, choline acetyltransferase levels were decreased in the nucleus accumbens (Karson et al., 1993, 1996) in comparison to the levels observed in healthy controls. In parallel, molecular imaging studies using single photon emission computer tomography (SPECT) revealed decreases in ß2-nAChRs, which was speculated to indicate a malfunction in the desensitization or turnover of nicotine and was shown to be correlated with the severity of negative symptoms (D'Souza et al., 2012). Furthermore, α7 nAChRs were shown via positron emission tomography (PET) studies to be reduced in recent

onset psychosis in the hippocampus and the cingulate and frontal cortices (Coughlin et al., 2018; Wong et al., 2018). In addition, using structural magnetic resonance imaging, gray matter volume of the basal forebrain cholinergic nuclei was shown to be decreased in patients with SCZ and associated with deficits in attentional processing (Avram et al., 2021). These marked cholinergic system differences observed in SCZ in comparison to healthy individuals, in addition to the α7 nAChR deficits presented in Section 1.5.1, indicate significant α7 nicotinic perturbations which, although not found to be causative of the disease or its pathological phenotype, may have important causal and treatment implications for cognitive and early auditory sensory processing impairments in SCZ.

1.6.2 Nicotinic trials for cognitive/sensory deficits

Paralleling nicotine's enhancing effects on cognitive and auditory sensory processing in healthy individuals and patients with SCZ, several nAChR-targeting compounds are under consideration for their potential benefits in alleviating cognitive/sensory impairments that may impact the social and daily functioning of patients with SCZ. In preclinical models of SCZ, partial agonists (i.e., DMXB-A, BMS-933043, A582941, SSR 180711) and positive allosteric modulators (i.e., JNJ-39393406, CCMI, PNU120596, AVL-3288) of the α7 nAChRs have shown improvements in cognitive/sensory deficits, but these findings have generally not shown a successful translation in human studies (Bristow et al., 2016; Frazier et al., 1998; Kohlhaas et al., 2015; Miller and Freedman, 1995; Potasiewicz et al., 2017; Winterer et al., 2013). A good number of these preclinical and clinical trials have used P50 suppression as a translational biomarker (Hashimoto, 2015). For example, in rodents, inhibition of the P20-N40 ERP gating response (analogous to the human P50 ERP), shown to be reduced in mouse strains (DBA/2) expressing lower hippocampal α7 nAChRs (Stevens et al., 1996), was found to be improved by an α7 nAChR partial agonist,

DMXB-A, and dependent on α7 nAChR signalling in the hippocampus as receptor blockade using α-bungarotoxin prevented the initial improvement in inhibition (Simosky et al., 2001). Similar positive effects have been observed in early pilot and phase-I clinical trials, with SCZ patients demonstrating normalization of P50 deficits and cognitive improvement with the α7 agonist DMXB-A in a relatively small phase-I trial (Olincy et al., 2006) but no clinical or cognitive improvements were observed in a larger phase-II trial using a sustained release DMXB-A system (Kem et al., 2018; Tregellas and Wylie, 2019). The translation of positive preclinical findings with novel nicotinic agonists to human larger phase-III studies has also not shown the same success, with inconsistent improvements observed in cognitive, SG, and deviance detection measures alike (Dunbar et al., 2007; Featherstone & Siegel, 2015; Gee et al., 2017; Kantrowitz, Swerdlow, et al., 2018; Kohlhaas et al., 2015). A recent systematic review and meta-analysis reported that the quality of the evidence is too weak to support α7 agonists as an add-on treatment for cognitive deficits in SCZ as variations in analysis methods, outcomes and results amongst studies prevent an accurate summation of evidence and conclusion on cognitive effects (Recio-Barbero et al., 2021).

1.6.3 Choline and brain functioning

1.6.3.1 Choline in the brain

While pharmacological approaches have dominated the exploration of nicotinic agonists as potential therapeutics for SCZ, the increasing awareness of the influence of dietary patterns on biological pathways underlying general health and specifically on brain functions involved in cognition has led to the identification of diet as a modifiable risk factor and nutritional approaches as potential opportunities for intervention in mental health disorders including SCZ (Dauncey, 2012; Marx et al., 2017). Observational evidence shows a connection between the

presence of SCZ spectrum disorders and poorer quality dietary patterns (Aucoin et al., 2020). Diet clearly influences neurotransmission and even subtle changes in diets may moderate levels of essential nutrients such as tryptophan and tyrosine, precursors for the neuronal synthesis of serotonin and dopamine, respectively (Zeisel, 1986). Choline is an essential nutrient largely obtained through appropriate dietary intake (~ 400-600 mg/day) of a wide variety of foods (e.g., eggs and meats) and is complimented by endogenous synthesis in the liver and to a much smaller degree in the brain (McCann et al., 2006; Sanders and Zeisel, 2007). Choline is essential for the normal function of all cells and has many diverse roles. Apart from maintaining the structural integrity and signalling functions of cell and neuronal membranes via the synthesis of phospholipids and contributing to epigenetic changes via methyl metabolism to betaine and homocysteine reduction (Derbyshire and Obeid, 2020), choline is a precursor of ACh and a selective full agonist for presynaptic and postsynaptic α7 nAChRs (Albuquerque et al., 1998; Alkondon et al., 1997; Papke et al., 1996).

Extracellular synaptic levels of choline in the brain, in the range of 3-5 μM (Alkondon and Albuquerque, 2006), are thought to be sufficient to control the activity of α7 nAChRs (Alkondon et al., 1999). Findings of brain choline levels in SCZ assessed with MRS have been inconsistent, but generally lower levels of hippocampal choline have been observed (Kraguljac et al., 2012), and while choline concentration in the thalamus was lower (vs. healthy controls) in individuals at high genetic risk (family members of SCZ) (Yoo et al., 2009), anterior cingulate choline concentrations were higher in clinical high risk individuals who converted (vs. non-converters) to SCZ (Jessen et al., 2006). Exogenous *in vitro* application of choline to rat brain slices has resulted in nAChR upregulation (Gahring et al., 2010) and dose-dependent increases in ACh and lipid-bound (phosphatidylcholine) choline (Ulus et al., 1989). Intracerebral injection of

choline has similarly increased brain choline, which was rapidly transformed into lipid (phosphocholine and then CDP-choline) forms (Ansell and Spanner, 1968), while oral) (Millington and Wurtman, 1982) and intraperitoneal administration of choline in rats produced sequential increases in brain choline and ACh levels (Cohen and Wurtman, 1976). Rodent studies have also found dietary choline supplementation (vs. control diets) to result in nAChR upregulation (Coutcher et al., 1992), increases in plasma of free and phosphorylated (phosphorylcholine, CDP-choline) choline (Haubrich et al., 1976) as well as choline and ACh elevations in the brain and cerebral spinal fluid (Cohen and Wurtman, 1976; Klein et al., 1991).

In human studies, orally administered choline increases plasma and brain choline concentrations (Babb et al., 2004) and in a dose-dependent manner (Stoll et al., 1995), with increases in brain choline levels being greater in younger compared to older adults (Cohen et al., 1995), possibly related to reduced choline transport across the blood-brain barrier evidenced in the aging brain (Mooradian, 1988). Plasma choline levels are related to the amount of choline in the diet and increase substantially after high-choline meals, and although not significantly lowered with a short (2-day) low-choline diet (Hirsch et al., 1978), levels are markedly reduced during 72-hr fasting (Ding et al., 2018). Although having no effect on choline and ACh in the brain, consumption of a choline-free diet in rats lowered levels of choline and phosphorylcholine in plasma (Millington and Wurtman, 1982). Plasma choline, along with metabolic processes, plays a key role in maintaining homeostasis of brain choline, with extracellular choline concentration in the brain closely paralleling fluctuations in the plasma level of choline (Klein et al., 1990). Net choline release and uptake in the brain are dependent on plasma choline level (Klein et al., 1992) and consequently directly influenced by nutritional choline intake (Klein et al., 1991; Wecker and Trommer, 1984).

1.6.3.2 Choline and cognition

Although these pro-cognitive effects of choline administration or status have not been consistently observed in earlier studies (Lippelt et al., 2016; Wallace, 2018). The importance of dietary choline in cognition is highlighted by large population studies reporting higher total choline and phosphatidylcholine intakes in younger and older adults to be associated with better cognitive performance on tests assessing frontal and temporal lobe functions and a lower risk of incident dementia (Liu et al., 2021; Poly et al., 2011; Ylilauri et al., 2019). Higher choline intake has also been associated with more efficient attentional and executive functions in adults (Edwards et al., 2021, 2022). Reviews of human and animal observational and intervention studies focusing on the effects of choline availability on brain health across the lifespan have, overall, provided compelling support for the relevance of dietary choline in cognition (Bekdash, 2019; Gámiz and Gallo, 2021; Leermakers et al., 2015).

Particular interest has been focused on early development when demands for choline increase during gestation and lactation. Although less consistently shown in human randomized trials and observational studies, which are markedly lacking in dose-response assessments, both human and animal research reviewed supports a possible causal relationship between maternal choline intake/supplementations, enhanced cognitive performance in offspring, and changes in brain function pointing mainly to the hippocampus and the cholinergic system (Derbyshire and Obeid, 2020; McCann et al., 2006). Perhaps reflecting their cortical developmental functions, including the timely development of cerebral inhibitory neurons required for normal SG, α7 nAChRs are expressed at 10-fold higher levels in the fetal hippocampus than in adults (Court et al., 1997), and the first two trimesters are not activated by cholinergic axons but by choline concentrations in the amniotic fluid, which are largely maintained by dietary intake (Papke et al.,

2005). As several maternal risk factors for SCZ are associated with decreased choline availability for the fetus (Zeisel, 2006), several investigations using the P50 biomarker have examined the effects of perinatal choline supplementation as a potential safe approach for early prevention of inhibitory deficits associated with SCZ (Freedman and Ross, 2015; Ross et al., 2010). In one study, dietary supplementation of maternal choline from conception through weaning in the inbred mouse strain DBA/2 (associated with diminished expression of hippocampal α7 receptors) significantly increased P50 gating (solely by a reduction in S_2 amplitude) in the hippocampus of adult offspring (vs. mice gestated on a normal choline diet) and produced a concurrent increase in hippocampal α7 nAChRs (Stevens et al., 2008). Further, gating improvements in adult offspring were only observed in the wildtype DBA/2 mice and not in mice heterozygotic or null-mutant for the α7 nAChR promoter gene (CHRNA7), thus indicating that gestational choline supplementation acted through α7 receptors to improve inhibition (Stevens et al., 2014). In a recent pilot study in humans, infants of mothers who received a choline-supplemented diet during gestation exhibited better SG (during 5^{th} postnatal week, but not 13^{th} week) than infants whose mothers were treated with placebo (Ross et al., 2013). The CHRNA7 genotype diminished P50 inhibition in the placebo-treated infants but not in the choline-treated infants.

1.6.3.3 CDP-choline and cognition

Cytidine-5'-diphosphocholine (citicoline, CDP-choline) is an alternative compound that contains choline and is an endogenous intermediate in the biosynthesis of choline phospholipids used in cell and neuronal membranes (Kennedy and Weiss, 1956) and a drug used to treat neurological (stroke, brain injury) disorders (Saver, 2008), and is a widely consumed dietary supplement

(Wignall and Brown, 2014). Exogenous CDP-choline is rapidly metabolized to yield choline and cytidine, which enter the circulation separately and cross the blood-brain barrier into brain cells where they are converted in part to ACh and resynthesized to form CDP-choline, the precursor of the key membrane phospholipids, phosphocholine, phosphatidylcholine, and sphingomyelin (Weiss et al., 1958). Administered orally or parenterally, CDP-choline is metabolized quickly within minutes (Galletti et al., 1985) and results in pronounced increases of plasma cytidine and choline in rats (López-Coviella et al., 1995) and in humans, plasma choline and uridine (a metabolite of cytidine) following oral administration peak at ~ 2-3 hrs (Wurtman et al., 2000) and also evidence a much smaller, delayed peak at ~ 24 hrs (Sarkar et al., 2012). Although the uptake of CDP-choline by the brain is considered to be relatively low (Galletti et al., 1991), MRS measurement of choline resonance in the brain after single oral doses (500 mg, 2000 mg, 4000 mg) showed, on average, a significant 18% increase (vs. placebo), which was limited to younger (vs. older) adults (Babb et al., 1996).

The pro-cognitive effects of CDP-choline have been demonstrated in healthy adult volunteers who showed improved attention and motor speed with repeated dosing (250 mg, 500 mg) over 28 days (McGlade et al., 2012, 2019). As with the cognitive enhancing effects of choline, which can vary with an individual's performance level (Sitaram et al., 1978), the acute cognitive effects of CDP-choline have been shown to be baseline-dependent and followed an inverted-U curve, improving processing speed working memory, verbal learning/memory and executive functions at 500 mg and 1000 mg doses (vs. placebo) in low baseline performers, while exerting no effects in medium baseline performers, and diminishing cognition in high baseline performers (Knott, de La Salle, et al., 2015). Similar baseline-dependent effects on SG have been found, with only healthy volunteers exhibiting low baseline P50 suppression showing

increased gating and P50 inhibition with CDP-choline (500 mg, 1000 mg), concurrent with improvements in executive function (Knott, Smith, et al., 2014). MMN-indexed auditory deviance detection has also been found to be increased with CDP-choline (500 mg, 1000 mg) but only in individuals with reduced baseline MMN amplitudes (Knott, Impey, et al., 2015).

CDP-choline has exerted significant neuroprotective and cognitive ameliorating properties in various preclinical models of neurodegenerative diseases (Secades, 2019), and although early clinical trials added support to these benefits (Fioravanti and Yanagi, 2005), more recent and well-controlled trials have shown no benefit from CDP-choline in acute ischemic stroke or traumatic brain injury, but it may be a suitable treatment for mild brain vascular-related disorders and cognitive impairment (Grieb, 2014; Secades, 2019). Relatively few studies have examined its effects in SCZ, but in one study, CDP-choline add-on therapy (2,500 mg/day for 8 weeks) to risperidone significantly improved negative symptoms and general psychopathology in chronic patients (Ghajar et al., 2018). As was shown in healthy volunteers, acute CDP-choline administration in SCZ patients increased SG at a low dose (500 mg vs. 1000 mg and 2000 mg) but only in patients exhibiting lower SG levels at baseline (Aidelbaum et al., 2018). Depending on the deviant feature, improved auditory deviance detection (MMN) with low (500 mg) and higher (1000 mg) CDP-choline doses was observed in patients with SCZ who exhibited smaller MMN amplitudes at baseline (Aidelbaum et al., 2022).

1.6.4 Nicotine response variability

An intriguing finding from previous research is that behavioural response to nicotine is subject to considerable inter-individual variability (Ettinger et al., 2009). With respect to CDP-choline, the pro-cognitive/sensory effects are observed in the low baseline groups and the opposite effect (i.e., worsening, impairing responses) was reported in these studies in high baseline groups for

cognitive, P50 and MMN measures. The precise reasons for this variability are unclear but are likely to be manifold, including genotype factors, receptor availability, gender, drug absorption, smoker/non-smoker status, and performance, as well as neural activation levels at baseline or under placebo (Ettinger et al., 2009). Individual differences are one of the major challenges of psychiatry drug development (Zhu, 2021), and this is particularly so with SCZ, a highly heterogeneous disorder with remarkable intersubject variability in clinical and cognitive presentations (Sun et al., 2021). Possibly evident with low-level sensory functions, SCZ has been shown to include a number of cognitive subgroups, including severe impairment, good functioning, and one or more selective or modest impairment clusters (Bora, 2016). One of the reasons that SCZ, and psychiatric diseases in general, have shown the lowest probability of success in clinical drug development has been the failure of clinical design features to take into consideration the potential effect of symptom heterogeneity (Zhu, 2021). Few clinical trials to date have reported stratifying patients according to the presence or degree of cognitive (or sensory) impairment. This suggests that the vast majority of these trials in SCZ may have been underpowered due to their inclusion of cognitively (or sensory) "normal" patients. During phase 1 clinical development with single dose challenges, patient stratification may be one useful strategy for the early identification of a pharmacological effect in subgroups, which can support decision-making for future stage larger trials pursuing precision treatment in SCZ subgroups.

In addition to the role of heterogeneity, another theme that often emerges in the failure of clinical trials of α7 agonists is that of drug dosing. Presynaptically located on neuronal terminals, α7 nAChRs enable low concentrations of a drug to act specifically on the receptor, while higher doses may block nAChRs (Adler et al., 1993; Brunzell and McIntosh, 2011; Young and Geyer, 2013). These observations support the putative U-shaped dose-response function of α7 nAChR

treatments and highlight the need to test lower doses. In animal models, the greatest response to a nAChR agonist is often observed with a low drug dose. As an example, low exposure to the α7 nAChR partial agonists AZD0328 and SSR180711 improved recognition and short-term memory performance, while higher doses did not improve cognition (Werkheiser et al., 2011). In a non-human primate study where, a low dose of an α7 nAChR agonist (PHA543613) increased neuronal activity in the prefrontal cortex and improved spatial working memory performance, whereas higher doses were not effective (Yang et al., 2013). A number of α7 clinical trials have found greater efficacy at lower doses, as shown with DMXB-A (Olincy et al., 2006), encenicline (Keefe et al., 2015), and in early trials with TC-5619 (Walling et al., 2016). Lower doses of CDP-choline have also been shown to yield similar (vs. higher doses) improvement in cognitive measures in low-performing healthy volunteers (Knott, de La Salle, et al., 2015) and depending on the gating index, produced greater improvements in P50 suppression (Aidelbaum et al., 2018; Knott, Smith, et al., 2014) and deviance detection (Aidelbaum et al., 2022; Knott, Impey, et al., 2015) in both low-functioning healthy normal participants and SCZ patients displaying reduced baseline suppression/detection responses. If confirmed, these results suggest that the inverted-U shaped response curve for α7 agonists, including CDP-choline, may peak at a very low dose, and beyond this peak, higher doses will likely result in minimal or no improvement in sensory or cognitive functions (Tregellas and Wylie, 2019).

1.6.5 Allosteric modulation of nAChRs

Related to drug dosing, the state of nAChR (active vs. desensitized) and the time spent in the desensitized state are essential moderating factors of nicotinic agonist effects, especially in the light of evidence suggesting cognitive improvements following nAChR antagonist administration (Levin, 2013). All neuronal nAChRs become temporarily inactive after prolonged

exposure to an agonist (Quick and Lester, 2002). Receptor desensitization occurs following exposure to agonists (i.e., act as functional antagonists) and depends on the quantity, duration, and type of agonist as well as the receptor affinity to the compound (Deutsch and Burket, 2020). The α7 nAChRs, in particular, rapidly become desensitized in response to ligand binding (López-Hernández et al., 2009; Peng et al., 1994), and as a result, low concentrations of a nAChR agonist may be more effective than higher concentration, as the latter will maintain receptors in a desensitized and unresponsive state. Choline, in comparison to Ach, has been shown to leave the receptor in a less stable desensitized state (Albuquerque et al., 2009). One approach to limit the effects of desensitization is to develop shorter half-life drugs that can produce a large transient stimulation of the receptor and produce a greater pro-cognitive/sensory effect relative to a drug producing a more constant elevation in receptor stimulation (Kem et al., 2018).

Another approach for increasing α7-related neurotransmission is through the use of positive allosteric modulators (PAMs). In contrast to the actions of agonists, which activate receptors directly by binding at the primary (orthosteric) ligand site, PAMs affect receptor function by interacting at secondary (allosteric) binding sites, where they facilitate the effects of the endogenous neurotransmitters. Importantly for nAChRs, PAMs are expected to cause less side effects (Uteshev, 2014) than nicotinic agonists and are less likely to cause desensitization (Williams et al., 2011). Pre-clinical α7 PAM trials have shown pro-cognitive effects, with the first α7 PAM, PNU-120596, improving auditory gating deficits in rats (Hurst et al., 2013) but not all clinical trials with α7 PAMs have proved successful, including JNJ-39393406, which failed to show any effects on P50 in SCZ (Winterer et al., 2013), several α7 PAMs such as AVL-3288 have shown positive P50 gating effects in early phase clinical testing in humans (Gee et al.,

2017) and clinical trials in SCZ are underway. Although there are controversial reports in the literature regarding its PAM activity (Kowal et al., 2018), galantamine is generally considered to be an α7 PAM and an acetylcholinesterase inhibitor (AChE-I) (Albuquerque et al., 1997). Galantamine is a type-I PAM which has been shown to increase the receptor's sensitivity to agonists, current magnitudes, and empirical Hill coefficients without impacting binding onset and decay kinetics (Williams et al., 2011).

Galantamine is known to enhance ACh's effect on GABA and glutamate release in rat and human hippocampal slices and to increase currents in part by NMDA receptors. These findings were resistant to AChE-I administration but interacted with methylcaconitine, an α7 nAChR antagonist, indicating that galantamine's effect is mediated via its positive allosteric modulatory impact rather than its AChE-I effect (Woodruff-Pak et al., 2002). Galantamine was shown to improve learning and memory performance and exerts protective features against amyloid ß toxicity in Alzheimer's Disease, therefore has been a recognized treatment for this neurodegenerative disease (Woodruff-Pak et al., 2002). In case reports of patients with SCZ, galantamine as an add-on therapy to antipsychotic treatment improved negative symptoms (Arnold et al., 2004; Ochoa and Clark, 2006). As for positive and cognitive symptoms, galantamine has produced mixed effects in numerous clinical trials (Metz and Pavlov, 2021). Galantamine selectively enhanced processing speed and verbal memory (Buchanan et al., 2008) in addition to significantly improving attention and delayed memory subscale scores by 1 SD (Schubert et al., 2006). Furthermore, in a meta-analysis of 6 randomized trials, galantamine significantly improved cognitive deficits (vs. placebo) and, at a trend level, improved positive and negative symptoms (Koola et al., 2020). Combination treatment of the α7 agonist CDP-choline with the nAChR PAM galantamine, which was aimed at preventing choline from

becoming a functional antagonist and improving the efficiency of coupling the binding of choline to channel opening, was found to exhibit different behavioural effects than CDP-choline alone in an animal model of NMDA receptor hypofunction relevant to SCZ (Deutsch et al., 2008a) thus confirming the allosteric modulatory influence of galantamine. In a subsequent small (N = 6) open-label pilot trial involving the first administration (12 weeks) of CDP-choline (2 g/day) and galantamine (24 mg/day) in patients with SCZ, this α7 nicotinic agonist strategy was found to reduce overall symptom severity and both positive and negative symptoms (Deutsch et al., 2008b). In a larger (N = 43) 16-week placebo-controlled trial, the combination treatment failed to alter positive negative or overall cognitive symptoms but significantly improved memory (auditory verbal recall) and overall functioning. Although non-significant, changes in clinical symptoms were in the direction of effects mirrored with the cognitive measure and overall functioning (Deutsch et al., 2013). Given the superior safety profile of CDP-choline compared to choline and diphosphatidylcholine (Synoradzki and Grieb, 2019), these findings support further investigation of the combination of CDP-choline and nAChR PAMs as an α7 nAChR agonist intervention for cognitive impairments in SCZ. A precedent for this approach is evidenced in the allosteric potentiation of nicotine effects on rodents (Hahn, Reneski, et al., 2020) and human cognitive performance (Hahn, Shrieves, et al., 2020). Previous studies in dementia have also shown improved outcomes when combining CDP-choline and AChE-Is (Castagna et al., 2016; Gareri et al., 2017).

1.7 Summary, objectives and hypotheses

In light of the current review and following over 60 years since the administration of the first drug observed to have an alleviating effect on positive symptoms, 60-80% of individuals with SCZ today continue to experience the debilitating impact that this illness exerts, especially on

cognitive abilities and sensory processes which, more than clinical symptoms are directly associated with social and occupational outcomes. Following over 30 years of drug research targeting cognitive/sensory functioning in SCZ, and despite a better understanding of some mechanistic features and expanding hypotheses into the underlying causes of SCZ, dopaminergic medications used in the treatment of SCZ have limited cognitive efficacy, and the issue of cognitive enhancement still remains a clinically unsolved challenge. While pre-clinical animal models in drug discovery have shed light on specific targets and neural mechanisms, the success rate of these translational studies is very low due in part to the complex phenotypes and high variability robustly observed in clinical trials. Hence, targeting a single neural receptor system, the dopaminergic system, has been useful in ameliorating positive symptoms, but it has not been fruitful in SCZ/cognitive drug discovery of cognitive/sensory enhancers as complex pathomechanisms underlying these deficits in SCZ are shown to involve multiple interactive neurocircuitries and pharmacological pathways, including the nAChR system.

Higher smoking rates in the SCZ population sparked an interest in the nicotine agonist as its activation of the α7 subtype of the nAChR was hypothesized to help alleviate cognitive/sensory symptoms. The development of efficacious nicotinic agents for SCZ has been hampered in part by the unique properties of the α7 nAChR, including the low probability of channel opening and also rapid desensitization with even brief exposure to agonists. Selecting the proper dose of administration of an α7 nAChR ligand is of critical importance in clinical trial design and there is convincing evidence that a low-dose nicotinic agonist may actually produce a pro-cognitive effect not seen with higher doses.

Choline is an endogenous agonist of α7 nAChRs and, when increased non-pharmaceutically (i.e., diet) or by supplements, is associated with pro-cognitive actions. The

dietary supplement CDP-choline may be a promising α7 candidate treatment for SCZ as preliminary findings have shown acute low and intermediate doses to improve early auditory information processing (EAIP) impairments indexed by P50 and MMN biomarkers. One possible strategy for increasing the effect size ceiling of CDP-choline may be to co-administer the exogenous α7 agonist with an α7 PAM, as the α7 PAM would potentially enhance the selective α7 activation/efficacy/potency of choline. The nAChR PAM galantamine has demonstrated the ability to modulate the cognitive enhancing effects of nicotinic (nicotine) stimulation and, when co-administered with low dose CDP-choline, may be a useful approach for augmenting α7 nAChR activity and biomarker responsivity.

Also confounding the outcome of drug trials of nicotinic agonists for SCZ cognition are clinical design features, including the failure to take into consideration the high complexity and marked inter-individual variability of cognitive phenotypes and the degree of impairment at baseline of cognitive/sensory processes of patients. This may have led to a 'concealing' effect of the impact that a potential drug may have on cognitive/sensory deficits in those patients who express relatively greater cognitive and sensory challenges compared to patients whose cognitive/sensory processes are more comparable to healthy controls and thus, may not benefit from pro-cognitive agents. The resulting heterogeneity in drug response supports the contention that α7 nAChR-based pro-cognitive/sensory strategies should identify and target subgroups of individuals who exhibit lower levels of cognitive/sensory functioning in order to increase power and likelihood of unveiling pro-cognitive effects.

Impaired EAIP is a consistent finding in SCZ that is well characterized by P50 and MMN biomarkers. Present in patients and their family members, neurophysiological endophenotypes like P50 and MMN form the causal links between genetic influences and overt phenotypic

expression and are, therefore, key in the understanding of the underlying biological mechanisms of disease risk and expression. Moreover, these neurophysiological markers are sensitive to the involvement of specific underlying neurochemical systems, including nicotinic neurotransmission, and can be modelled in pre-clinical studies, offering a unique opportunity for use as translational biomarkers in SCZ drug discovery and as proof-of-concept or proof-of-mechanism measures. Auditory verbal hallucinations (AVH) are a hallmark symptom experienced by 75% (Blom, 2015; Slade and Bentall, 1988) of individuals with SCZ and implicate structural and functional deficits in the primary auditory cortex and parahippocampal cortices (Allen et al., 2008; de Leede-Smith and Barkus, 2013). These underlie auditory sensory processing and linguistic impairments in SCZ (Allen et al., 2008, 2012; de Leede-Smith and Barkus, 2013). Relationships between auditory gating and deviance detection deficits and AVHs have largely been based on paradigms using simple, non-verbal stimuli (i.e., clicks, tones), and although similar sensory deficits have been observed with speech stimuli (Hirano et al., 2010; Pakarinen et al., 2009), these speech-related gating and deviance detection deficits have not been examined in relation to nicotinic stimulation.

Taking into consideration concerns with nicotinic dose and response heterogeneity, and with the general objective of furthering research on CDP-choline and optimizing its activity with conjunctive administration with an allosteric modulator, this thesis aims to examine the effect of a low-dose, selective α7 nAChR agonist CDP-choline in combination with a moderate dose nAChR PAM, galantamine, on early auditory sensory processing of speech stimuli indexed by P50 and MMN ERPs, and to assess differential responsivity in healthy volunteers and patients with SCZ stratified by baseline (placebo) P50 and MMN markers.

1.7.1 Primary objectives

Research objective 1: To examine the effect of combined CDP-choline and galantamine administration on auditory SG, indexed by P50 suppression, in healthy participants stratified into low and high baseline gating groups. (Chapter 2)

Hypothesis: Compared to placebo, the combined CDP-choline/galantamine treatment was hypothesized to enhance auditory gating (increase P50 suppression) in low gating individuals while exerting no effect or decreasing auditory gating in high baseline gating individuals.

Research objective 2: To examine the effect of combined CDP-choline and galantamine administration on auditory SG, indexed by P50 suppression, in patients with SCZ stratified into low and high baseline gating groups. (Chapter 3)

Hypothesis: Compared to patients exhibiting more normal baseline auditory gating, it was hypothesized that patients with low baseline gating would exhibit greater gating improvements (i.e., increased P50 suppression) following the acute dose of CDP-choline/galantamine in comparison to placebo.

Research objective 3: To examine the effect of combined CDP-choline and galantamine administration on auditory deviance detection, indexed by the MMN ERP, in healthy participants stratified into low, medium, and high baseline amplitude groups. (Chapter 4)

Hypothesis: In low amplitude baseline groups, it was hypothesized that CDP-choline/galantamine would increase MMN amplitudes in comparison to placebo. Moderate-high baseline groups were expected to show no changes or reductions of MMN amplitudes following the CDP-choline/galantamine vs. placebo treatment.

Research objective 4: To examine the effect of combined CDP-choline and galantamine administration on auditory deviance detection, indexed by the MMN ERP, in patients with SCZ stratified into low, medium, and high baseline amplitude groups. (Chapter 5)

Hypothesis: The combined CDP-choline/galantamine treatment was hypothesized to result in increased deviance detection (higher MMN amplitudes) in patients who demonstrated low baseline MMN amplitudes. Conversely, individuals with high baseline MMN amplitudes were expected to show no changes or lower MMN amplitudes following CDP-choline/galantamine in comparison to placebo.

1.7.2 Secondary objective

Given the involvement of auditory cortex dysfunction in AVH, and auditory sensory processing deficits in SCZ, with the latter being putatively linked with impaired nicotinic neurotransmission, a secondary, exploratory objective will examine the relationship between AVH ratings in patients with their auditory sensory response (P50, MMN) to CDP-choline/galantamine treatment.

Chapter 2

Effects of CDP-Choline and Galantamine on P50 Sensory Gating in Healthy Volunteers

2.1 Preface

Overview

The objective of this manuscript was to assess the effect of a single moderate dose of CDP-choline and galantamine on P50 ERPs and sensory gating indices (rP50 and dP50) to speech sounds in thirty healthy volunteers stratified into low and high gaters based on their baseline gating performance.

Statement of author contribution

This study was designed by Dr. Verner Knott, with contributing input from Joelle Choueiry. The study setup was done by Joelle Choueiry and Dhrasti Shah. Paradigm programming with auditory speech stimuli was done by Joelle Choueiry, Derek Fisher, and Dylan Smith. Participant recruitment and screening were done by Joelle Choueiry and Crystal Blais. Recruited participants were clinically interviewed by Dr. Vadim Illivitsky. Administration of study tasks and ERP recording were done by Joelle Choueiry and Crystal Blais. ERP processing and analyses, statistical analyses, tables and figures and manuscript writing were done by Joelle Choueiry. The final manuscript was reviewed by all authors.

2.2 Title page

Combining CDP-choline and galantamine: Effects of a selective α7 nicotinic acetylcholine receptor agonist strategy on P50 sensory gating of speech sounds in healthy volunteers

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2.3 Abstract

Schizophrenia (SCZ) patients and relatives have deficits in early cortical sensory gating (SG) typically measured by suppression of electroencephalography-derived P50 event-related potentials (ERPs) in a conditioning-testing (S_1-S_2) paradigm. Associated with alpha 7 nicotinic acetylcholine receptor (α7 nAChR) dysfunction and shown to be improved with nicotine and α7 nAChR agonists, SG has recently been shown to be improved in low P50 suppressing SCZ patients following acute CDP-choline treatment.

This pilot study in healthy humans assessed the SG effects of an α7 nAChR strategy combining CDP-choline with galantamine, a positive allosteric modulator (PAM) of nAChRs, aimed at increasing and prolonging nicotinic receptor activity.

The combined effect of CDP-choline (500 mg) and galantamine (16 mg) on speech P50 gating indices rP50 (S_2/S_1) and dP50 ($S_1 – S_2$) was examined in thirty healthy participants stratified into low and high baseline P50 suppressors in a randomized, double-blinded, placebo-controlled and counterbalanced design.

In low suppressors, CDP-choline/galantamine (vs. placebo) improved rP50 and dP50 gating, and reduced S_2P50 amplitudes. No P50 gating effects were observed in high suppressors; however, CDP-choline/galantamine (vs. placebo) increased their S_2P50 amplitudes.

Findings from this pilot study with CDP-choline/galantamine in a healthy, SCZ-like surrogate sample are consistent with the association of α7 nAChR mechanisms in SG impairment in SCZ and support further research trials with CDP-choline and galantamine targeting sensory processes.

2.4 Introduction

The cholinergic system is now recognized for its associations with substance abuse and dependence (i.e. nicotine and cocaine), dementia, Parkinson's disease, Alzheimer's disease and schizophrenia (SCZ) (Grasing, 2016; Nees, 2015). The strikingly high tobacco smoking rate, 60-80%, in SCZ populations (compared to 10-15% of healthy individuals) prompted in part the examination of the cholinergic system (Cather et al., 2017). Nicotine, the psychoactive compound in tobacco, is a ubiquitous agonist that binds to high and low affinity nicotinic acetylcholine receptors (nAChRs; α2-6β2-4 and α7-9 respectively), and mediates its effects in the brain via the cholinergic system's interactions with dopaminergic, glutamatergic, and GABAergic neural pathways (Koukouli & Maskos, 2015). Tobacco smoking was hypothesized to be a form of self-medication as individuals with SCZ sought relief of cognitive dysfunction by smoking (Kumari & Postma, 2005). Cognitive impairments are a core feature of the illness associated with the affected individual's functional outcome (Hashimoto, 2015; Smucny et al., 2013). Pharmacological interventions and therapies today are efficient at controlling and alleviating positive symptoms, however, there is still no recognized neurocognitive treatment or cognitive interventions for SCZ despite the National Institute of Mental Health's Measure and Treatment Research To Improve Cognition in Schizophrenia (MATRICS) initiatives and the extensive research conducted according to its guidelines (Bertrand & Terry, 2018).

Following reports of lower α7 nAChR expression in post-mortem brains of SCZ patients (compared to matching healthy controls) (Court et al., 1999; Freedman et al., 1995; Guan et al., 2000), and associations of multiple single nucleotide polymorphisms in the promoter region of the CHRNA7 gene (responsible for the α7 subunit expression) with SCZ (Leonard et al., 2002); The MATRICS identified the α7 nAChR, as a major molecular and neuropharmacological target associated with learning, memory, attentional mechanisms and an essential modulator of sensory

gating (SG) (Azzopardi et al., 2013; Braff, 2011; Jones et al., 2016; Mackowick et al., 2014). SG mechanisms are responsible for filtering/gating out redundant and irrelevant information and have been associated with an individual's functional outcome and cognitive proficiency (Braff, 1990; Cullum et al., 1993; Erwin et al., 1998; Geyer, 2006; Potter et al., 2006; Smith et al., 2010; Smucny et al., 2013). Animal models and human studies further examining the role of different nicotinic receptors implicated in SG outlined a mediating role for the α7 nAChR specifically (Hashimoto, 2015; Leonard et al., 1996; Smucny et al., 2015).

SG is indexed by an auditory P50 paradigm in brain electrophysiological studies employing electroencephalography (EEG)-derived event-related potentials (ERP), a non-invasive technique boasting high temporal resolution, that measure neural electrical correlates of information processing at the scalp level. P50 ERPs are elicited following the presentation of a pair of identical auditory stimuli (S_1-S_2) in a conditioning-testing paradigm. Healthy SG mechanisms block the neural response to the testing S_2 stimulus, resulting in diminished/suppressed S_2P50 amplitudes (in comparison to S_1P50). P50 amplitude ratio scores (rP50, S_2/S_1) and amplitude difference scores (dP50, $S_1 – S_2$) are typically calculated and used as indices of SG efficiency. Following over two decades of investigations, SG is now suggested to be a multistage process of response suppression (Boutros et al., 1999, 2013) implicating the temporal neocortex, prefrontal cortex and hippocampus as the main three regions of the human "nuclear auditory repetition suppression apparatus" (Boutros et al., 2013).

Reduced gating and suppression scores have been observed across the SCZ spectrum disorder identifying P50 SG as an important SCZ biomarker and endophenotype (Braff et al., 2007; Braff & Freedman, 2002; Brockhaus-Dumke et al., 2008; Cadenhead et al., 2000; Giakoumaki, 2012; Oranje et al., 2013; Patterson et al., 2008; Turetsky et al., 2007). Individuals with chronic SCZ reliably reported lower suppression scores of ≤ 20% (compared to healthy controls ≥ 55%)

(Bramon et al., 2004; Patterson et al., 2008; Su et al., 2012), a phenomena also observed in their unaffected relatives (Clementz et al., 1998). Also, 40% of healthy individuals express rP50 scores within 1 SD of mean ratios measured in SCZ patients (Patterson et al., 2008). Therefore, healthy volunteers with lower rP50 scores are ideal candidates as they facilitate treatment examination without the confounding factors inherent to the SCZ population (i.e. symptomatology and medications). Hence, multiple studies from our laboratory (de La Salle et al., 2013; Knott et al., 2013; Knott, Smith, et al., 2014) and other laboratories (Csomor et al., 2008, 2014; Holstein et al., 2011) have used placebo rP50 scores to segment groups into high-low suppressors.

Contrary to reports of positive treatment effects (Adler et al., 2004; Oranje et al., 2013), a meta-analysis concluded that current psychosis treatments offer no significant impact on P50 SG (Su et al., 2012). However, P50 gating improvements following nicotine administration have been consistently shown and replicated in patients with SCZ, their unaffected relatives and in healthy individuals who show relatively reduced SG (Adler et al., 1992; de La Salle et al., 2013; Knott et al., 2010; Millar et al., 2011) further supporting evidence for the self medication hypothesis (Mackowick et al., 2014). Unfortunately, cigarette smoking is the culprit behind diseases that lead to a shorter lifespan (by ~28 years) in smokers with SCZ (Olfson et al., 2015) and recent clinical trials have reported opposing findings to the nicotine self-medication hypothesis (Boggs et al., 2014, 2018). Also, nicotine offers poor potential as a long-term treatment as it is highly addictive and health consequences for long-term exposure are unknown.

Over three decades of neuropharmacological experiments targeting the cholinergic system to alleviate cognitive impairments have yet to yield an efficient compound. The significant heterogeneity of the SCZ symptomatology was highlighted as an important

confounding factor in a recent review suggesting that smaller size research experiments with precise inclusion/exclusion patient criteria might show a better outcome (Bertrand & Terry, 2018).

Cytidine diphosphocholine (CDP-choline) has been the subject of extensive research for several decades as it exerted cognitive benefits potentially associated with its capacity to increase choline metabolism, a selective α7 agonist that has also been shown to increase GABA neurotransmission in the hippocampus (Albuquerque et al., 1998; Secades, 2011). Our laboratory examined CDP-choline's effect on impaired SG and provided evidence of improved P50 SG and suppression following acute CDP-choline administration in healthy volunteers (Knott, Smith, et al., 2014) and SCZ patients (Aidelbaum et al., 2018) expressing reduced P50 gating indices at baseline. Analogously, perinatal (during gestation and lactation) cholinergic supplementation was shown to be beneficial for neurodevelopmental P50 inhibition (associated to higher risk of attentional problems and SCZ symptoms) following reports of improved sensory inhibition in adult offsprings of DBA/2 mice (a SCZ-like model of aberrant sensory gating) expressing the wild-type α7 nAChR gene (Chrna7) (Stevens et al., 2014), and reports of cerebral inhibition in 76% of newborn infants (vs. 43% in the placebo group) (Ross et al., 2013).

α7 nAChR's characteristic rapid desensitization rate prompted the examination of α7 nAChR positive allosteric modulators (PAMs) that enhance the receptor's functioning by either increasing its sensitivity to the agonist (Type-I) or by slowing its desensitization rate in addition to increasing agonist affinity (Type-II) (Wallace & Bertrand, 2015). According to two recent reviews, only a few PAMs have been shown to enhance the P50 SG analogue P20-N40 in DBA/2 mice (Hashimoto, 2015; Smucny et al., 2015). Galantamine, a selective nAChR PAM evidenced to improve prepulse inhibition deficits in rats (Hohnadel et al., 2007; Shao et al., 2014), has also been shown to improve cognition in patients suffering from Alzheimer's disease

in addition to delaying the progression of the illness (Scott & Goa, 2000). In SCZ patients, galantamine facilitated aspects of processing speed and verbal memory (Buchanan et al., 2008). Galantamine exerts its pro-cognitive effect on the cholinergic system through a dual mechanism where in addition to its allosteric modulation of nAChRs it inhibits acetylcholinesterase enzymes responsible for the elimination of acetylcholine from synapses (Jann et al., 2002; Scott & Goa, 2000). Lower levels of acetylcholine have been consistently reported in individuals suffering from psychiatric or neurological illnesses characterized by cognitive impairments (i.e. SCZ and Alzheimer's disease). Consequently, PAMs may not exert their full potential unless a nAChR agonist is also available for receptor binding at synapses.

Administering a combined treatment consisting of an α7 nAChR agonist and a PAM may be a promising complementary strategy when considering galantamine's dual action benefits and the α7 nAChR's fast desensitization rate. Only two studies have attempted to examine this strategy in different SCZ and non-clinical populations to date, yielding mixed findings ranging from no clinical improvement to minor cognitive improvements on auditory verbal memory tasks (Deutsch et al., 2013; Deutsch et al., 2008a,b). Varying baseline cognitive impairments and different exploratory treatment doses may in part account for inconsistent findings considering CDP-choline's dose-related differential effect. nAChR agonist effects in general, take the shape of an inverted U-shaped dose-response curve with maximal effects being observed at low doses (Castner et al., 2011; Hahn et al., 2002; Prickaerts et al., 2012; Werkheiser et al., 2011). Dose-related SG improvements were also observed following extensive CDP-choline examinations in our laboratory (Knott et al., 2014). This complimentary treatment strategy of administering a relatively low dose of a nAChR agonist and PAM has not yet been examined in a P50 SG experiment. With respect to the acute doses, lower to moderate acute CDP-choline doses (500

mg, 1000 mg) have been shown to be most optimal in recent single dose studies that examined its acute effects on a battery measuring multiple cognitive domains (Knott, de La Salle, et al., 2015), on P50 gating (Aidelbaum et al., 2018; Knott, Smith, et al., 2014) and on other brain electrical measures indexing different levels of attentional and memory processing (Hyde et al., 2016; Knott, de La Salle, et al., 2015; Knott, Impey, et al., 2015).

In a tentative model explaining the emergence of positive (i.e. hallucinations and delusions) clinical symptoms, SG was proposed as one of the main underlying components (Javanbakht, 2006). Furthermore, neural regions implicated in SG have also been associated with the occurrence of AVHs in SCZ patients (Boutros et al., 2013; de Leede-Smith & Barkus, 2013). The P50 paradigm employing click/tone stimuli has been extensively examined in healthy individuals and SCZ (Adler et al., 1998; Boutros et al., 2004; Clementz et al., 1998; Freedman et al., 1991; Nagamoto et al., 1991; Patterson et al., 2008), hence presenting speech (instead of click/tone) stimuli while maintaining the typically tested and recommended presenting, recording and processing parameters might provide more insight into the previously reported associations between P50 SG and the occurrence and severity of AVHs (Faugere et al., 2016; Hirano et al., 2010; Javanbakht, 2006; Smith et al., 2013; Smucny et al., 2013; Thoma et al., 2017). P50m (the magnetoencephalographic [MEG] measure of P50) gating of human voices was examined by replacing the click stimuli with verbal phonemes (Hirano et al., 2010), and reported lower P50 gating scores in SCZ (vs. healthy controls). Also, greater gating impairments were associated with a higher propensity for AVH scores.

Therefore, the primary objective of this pilot study was to assess the acute effect of this combined cholinergic treatment, consisting of a lower (500 mg) dose of CDP-choline and a moderate (16 mg) dose of galantamine (Deutsch et al., 2013), on speech P50 SG indices (rP50

and dP50) in healthy volunteers stratified into low and high suppressor groups. Relative to placebo, this cholinergic treatment was expected to modulate P50 gating in relation to gating efficiency at baseline, where low suppressors were expected to show SG improvements while high suppressors show no changes or worsened SG scores.

2.5 Materials and methods

2.5.1 Individuals

Thirty healthy male (N=24) and female volunteers (mean age of 39.73; SE ± 2.18) were recruited based on a medical and psychiatric interview and received $75 upon study completion. A psychiatric screening was conducted on eligible volunteers using the Structured Clinical Interview, non-patient version (SCID-NP; (Williams et al., 1992)), for DSM-IV assessing for illicit substance abuse/dependency and assessing for personal psychiatric history. Included participants also reported no history of psychiatric illnesses in their first-degree relatives based on the Family Interview for Genetic Studies (FIGS; (Maxwell, 1992)). Study participants had normal laboratory and drug screen tests, normal weight, normal hearing, no significant medical/neurological illness (including head trauma/seizure), no past or current DSM-IV disorders, were not taking any prescription medications, any herbal medicines/supplements or any over-the-counter medications. Study procedures and recruitment of healthy volunteers for this study were undertaken in compliance with the Research Ethics Boards of The Royal Ottawa Mental Health Care Group and the University of Ottawa.

2.5.2 Experimental design

Volunteers were assessed in a randomized, double-blind, placebo-controlled and counterbalanced design including a placebo session and an active treatment (CDP-choline + galantamine) session. The number of participants assigned to begin with the placebo session was maintained equal to the number of participants that were assigned to begin with the active

treatment session. Testing sessions were at least seven days apart to allow for CDP-choline washout.

2.5.3 Treatment administration

Participants were orally administered 500 mg (2 x 250 mg capsules) of CDP-choline and 16 mg of galantamine (250 mg capsule filled with 234 mg of cellulose). All capsules were identical in shape, size and colour and matched the non-active placebo capsules (250 mg of cellulose).

CDP-choline and galantamine have no reports of serious adverse events at the clinical doses administered during this study. (See supplementary material for more information in Annexe 1).

2.5.4 Experimental procedures

Participants attended a screening session and two testing sessions. A day before the scheduled testing session, participants received a phone call reminding and instructing them to abstain from food, drugs, alcohol, caffeine, and cigarettes from midnight until their arrival to the laboratory (between 8:00 a.m. and 11:30 a.m.). Before placebo or CDP-choline administration (at time 0 minutes), exhaled carbon monoxide (CO) was measured to verify smoking abstinence (< 3 p.p.m. for non-smokers and less than the exhaled CO level at the screening session for smokers). Participants were seated in a dimly lit, sound-attenuated chamber and watched an emotionally neutral movie during the treatment absorption period. Placebo or galantamine was administered an hour after placebo/CDP-choline and participants continued to watch their movie for another half-hour. The P50 paradigm (duration: 16 minutes) and ERP recordings began at peak CDP-choline/galantamine absorption time (at ~ 90 minutes). Participants were instructed to remain seated and relaxed, to visually fixate on the center of a turned off computer screen in front of them, and to ignore the P50 stimuli sounds they heard through headphones.

2.5.5 P50 paradigm

The auditory P50 ERP to speech paradigm involved the presentation of 120 consonant-vowel pairs te-te (/te:/; F = 101 Hz; 170 ms duration; (Pakarinen et al., 2009)), a modification of the original P50 paradigm that typically employs clicks/tones. Consonant-vowel pairs were presented according to the parameters typically employed in the literature and our laboratory, binaurally at a sound pressure level of 80 dB with a 500 ms inter-pair interval, as SCZ patients show deficits specifically at 500 ms (vs. 100 ms), and a 10 s inter-pair interval (Nagamoto et al., 1991).

2.5.6 ERP Recording and processing

Brain Vision Quickamp® (Brain Products, Gmbh, Munich, Germany) amplifier and Brain Vision Recorder® software were used for EEG recordings with amplifier bandpass filters set at 0.1 to 70 Hz and continuous digitization at 500 Hz. Thirty Ag^{+}/Ag^{+} Cl^{-} scalp electrodes were positioned at sites: Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T7, T8, P7, P8, Fz, Cz, Pz, Oz, Fc1, Fc2, Cp1, Cp2, Fc5, Fc6, Cp5, Cp6, Tp9, and Tp10 in addition to a reference electrode on the nose and a ground electrode positioned between Fpz and Fz sites. Vertical (VEOG) and horizontal electro-oculographic (HEOG) activity were monitored via electrodes placed on the supra- and sub-orbital ridges of the right eye as well as on the external canthus of both eyes. Electrode impedance was kept below 5 kΩ throughout the recording session.

P50 ERP amplitude and latency measures to S_1 and S_2 were extracted following offline processing and analyses using Brain Vision Analyzer® (Brain Products, Germany) software. The raw signals were initially re-referenced to mastoid electrodes (Tp9 and Tp10), digitally filtered (24 dB/octave) with low-high cutoff window of 10 – 50 Hz, segmented into epochs of 400 ms (beginning 100 ms pre-stimulus), ocular-corrected (Gratton et al., 1983), and submitted to automatic artifact rejection which excluded epochs with amplitude voltages exceeding ± 75 µV.

The electrical activity recorded during the 100 ms pre-stimulus window was used to baseline-correct the remaining segments before final ERP averaging for P50. Typically, amplitude and latency measures from the central vertex (Cz) site are used for P50 peak detection and for deriving gating indices as higher P50 amplitudes are usually recorded from Cz (vs. Fz, C3 and C4) and it has been shown that measures from Cz are best at demonstrating response differences between patients suffering from SCZ and their matched non-patient healthy participants (Clementz, 1998). However, due to the speech nature and novelty of this type of P50 paradigm, the peak detection guidelines and criteria described by Boutros et al. (Boutros et al., 2004) were slightly modified to take into account the speech/linguistic nature of the stimuli. Semiautomatic peak detection was conducted separately for Cz, C3 and C4 channels in order to verify that maximal amplitudes were indeed at Cz. The selected S_1P50 peak at Cz was chosen between 40 – 80 ms after stimulus onset, was the second of possibly two positive peaks or the P50 maximal amplitude, had to be present at an additional site (C3 or C4, if not both) and had to be higher than 0.5 μV measured from peak to the averaged baseline. Typically the preceding N40 negative peak is used to calculate the relative P50 amplitude (peak minus trough), but due to the variability in the N40 onset and its appearance, P50 amplitude was measured with respect to the averaged baseline voltage. Previous work has shown that baseline-to-peak measurement of P50 is more reliable than peak-to-trough measurement (Dalecki et al., 2015). S_2P50 peaks had to be within a latency window of ± 10 ms relative to the paired S_1P50 peak onset latency. Following S_1P50 and S_2P50 peak amplitude detection, P50 gating indices were calculated for rP50 (S_2/S_1) and dP50 ($S_1 – S_2$).

2.5.7 Adverse events

At the end of each testing session, a checklist of physical and psychological adverse events was administered. Participants were asked to rate the severity of symptoms experienced following treatment administration on a scale from 1 (no symptom at all) to 5 (severe symptom).

2.5.8 Vital signs

Heart rate, systolic and diastolic blood pressure were assessed before treatment administration, at peak absorption time, and at the end of testing for safety purposes only.

2.5.9 Statistical analysis

rP50 scores were used to stratify participants into low and high suppressors based on a median split under placebo conditions. The primary gating measures, rP50 and dP50, were analyzed using separate univariate mixed analyses of variance (ANOVA) with group (two levels) as a between-subjects factor and with treatment (two levels), and scalp site (three levels) as within-subjects repeated measures factors. As any group differences in treatment response may reflect a 'regression to the mean' effect, similar ANOVAs were conducted with participants stratification using treatment (i.e., not placebo) rP50 scores. The secondary measures of amplitude and latency for S_1P50 and S_2P50 were also analyzed using separate univariate mixed ANOVAs with group (two levels) as a between-subjects factor, and with treatment (two levels), stimulus (two levels), and site (three levels) as within-subjects repeated measures factors. Greenhouse-Geisser corrected significant effects ($p < .05$) were followed up with Bonferroni-adjusted pairwise treatment comparisons for both primary and secondary measures. Placebo dependency of CDP-choline/galantamine effects was additionally examined with Pearsons bivariate correlations to assess relationships between the placebo condition and treatment change scores (treatment values minus placebo values) for all primary and secondary measures.

2.6 Results

Demographic data for the total sample group and the high and low suppressor subgroups are presented in Table 2.1. T-test and Chi-square analyses confirmed that low suppressors were not statistically different from high suppressors regarding age, gender ($X^2(1,30) = .833$, $p = .361$), and smoking status ($X^2(1,30) = .536$, $p = .464$).

Table 2.1 Demographics for the total sample, and high and low suppressor subgroups F/M: female/male; NS/S: non-smokers/smokers.

	Total Sample (N = 30)	High Suppressors (N = 15)	Low Suppressors (N = 15)
Age (mean ± SE)	39.7 (2.18)	39.9 (3.13)	39.5 (3.14)
Sex	6 F / 24 M	4 F / 11 M	2F / 13M
Smoking status	16 NS / 14 S	9 NS / 6 S	7 NS / 8 S

S_1P50 and S_2P50 grand averaged waveforms under the placebo conditions for all participants, and the low and high suppressor groups (based on placebo data) are shown in Figure 2.1 (a: full group; b,c: low and high suppressor waveforms subgrouped according to rP50 placebo data). As displayed in the waveforms, S_2P50 amplitude attenuation (vs. S_1) was significant and consistent with previous studies.

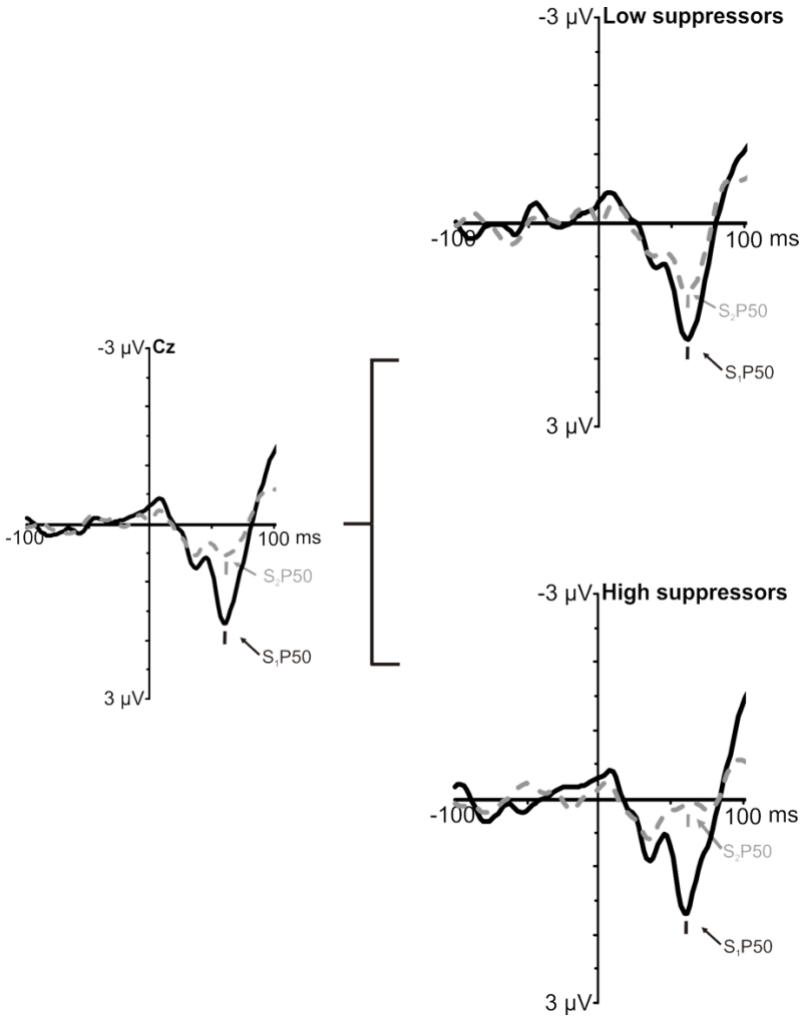

Figure 2.1 Baseline (placebo) grand average waveforms for S_1P50 and S_2P50 response for the total sample (a) and for stratified low (b) and high (c) suppressor subgroups.

2.6.1 rP50 gating

As expected, a main overall group effect was observed, F(1, 28) = 6.96, p = .013, with the high suppressors exhibiting smaller (better gating) rP50 scores (rP50 M = 0.42, SE ±0.075) than the low suppressors (M = 0.70, SE ±0.075).

For a significant group x treatment interaction, F(1, 28) = 6.63, p = .016, follow-up comparisons of treatment effects (Figure 2.2) in the low suppressor group revealed a significant (p = .005) reduction of rP50 (improved gating) under CDP-choline/galantamine (rP50 M = 0.46,

SE ±0.085) compared to placebo (rP50 M = 0.94, SE ±0.13). High suppressors did not show a significant rP50 gating change with treatment (vs. placebo).

No significant treatment or interaction effects were observed when group stratification was based on treatment (i.e., not placebo) rP50 values.

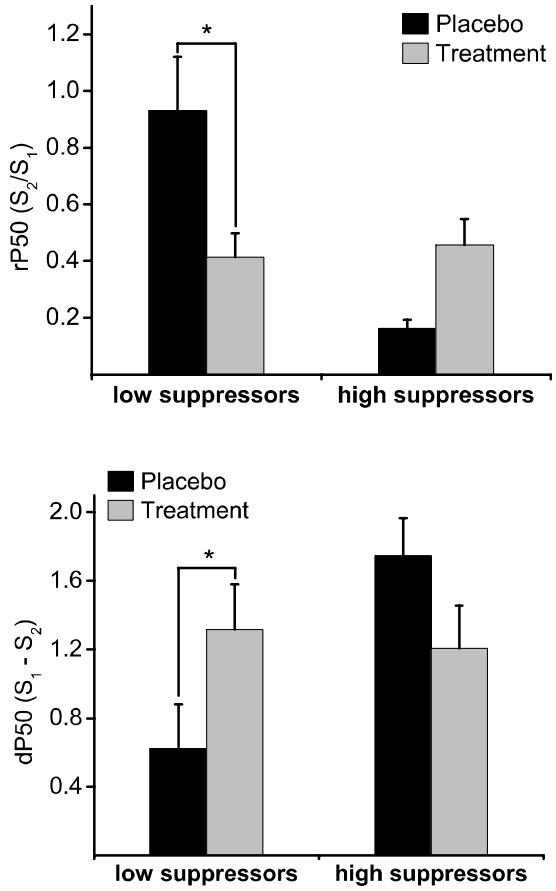

Figure 2.2 Mean (±SE) P50 ratio (S_2/S_1) and difference ($S_1–S_2$) scores, recorded at the Cz scalp site for high and low suppressor groups in response to CDP-choline (500mg)/galantamine (16mg) treatment in comparison to placebo. *p < 0.05; SE: standard error.

2.6.2 dP50 gating

As expected, a main overall group effect was observed, $F(1, 28) = 7.35$, $p = .011$, with low suppressors exhibiting smaller dP50 scores (M = 0.71 µV, SE ±0.14) compared to dP50 scores of high suppressors (M = 1.25 µv, SE ±0.14).

In a significant group x treatment interaction, $F(1, 28) = 9.13$, $p = .005$, follow-up comparisons of treatment effects (Figure 2.2) in the low suppressors group revealed a significant ($p = .011$) increase of dP50 (improved gating) under CDP-choline/galantamine (M = 1.03 µV, SE ±0.18) compared to placebo (M = 0.39 µv, SE ±0.18). High suppressors did not show a dP50 gating change with CDP-choline/galantamine treatment (vs. placebo).

No significant treatment or interaction effects were observed when group stratification was based on the treatment (i.e., not placebo) dP50 values.

2.6.3 P50 amplitudes

Analyses of treatment effects on S_1P50 and S_2P50 amplitudes revealed significant main effects for stimulus $F(1, 28) = 97.01$, $p < .001$, and significant stimulus x group $F(1, 28) = 7.35$, $p < .011$, treatment x group $F(1, 28) = 6.19$, $p = .019$, and treatment x stimulus x group $F(1, 28) = 9.13$, $p = .005$ interaction effects.

Regarding the main stimulus effect, greater S_1P50 amplitudes (M = 1.87 µV, SE ±0.13) were observed compared to S_2P50 amplitudes (M = 0.89 µV, SE ±0.076) with groups collapsed.

Follow-up comparisons for the main stimulus x group effect revealed that both suppressor groups, low (S_1P50 M = 1.82 µV, SE ±0.18; S_2P50 M = 1.11 µV, SE ±0.11) and high (S_1P50 M = 1.92 µV, SE ±0.18; S_2P50 M = 0.68 µV, SE ±0.11), exhibited significantly ($p < .001$) greater S_1P50 (vs. S_2P50) amplitudes (Figure 2.1) and that high suppressors showed significantly ($p = .008$) smaller S_2P50 amplitudes (M = 0.68 µV, SE ±0.11) than low suppressors (M = 1.11 µV, SE ±0.11).

Follow-up of the treatment x group interaction showed that high suppressors (M = 1.14 µV, SE ±0.14) expressed significantly lower (p = .033) P50 amplitudes (S_1 and S_2 collapsed) compared to low suppressors (M = 1.58 µV, SE ±0.14) under placebo condition.

Follow-up comparisons of the treatment x stimulus x group interaction revealed that high suppressors (M = 0.43 µV, SE ±0.12) expressed significantly smaller (p < .001) S_2P50 amplitudes compared to low suppressors (M = 1.39 µV, SE ±0.12) under placebo. When comparing treatment effects, CDP-choline/galantamine (vs. placebo) significantly increased S_2P50 amplitudes (Figure 2.3) in high suppressors (placebo M = 0.43 µV, SE ±12; treatment M = 0.92 µV, SE ±0.16) while it lowered it in low suppressors (placebo M = 01.39 µV, SE ±12; treatment M = 0.83 µV, SE ±0.16). S_1P50 amplitudes were significantly greater than S_2P50 amplitudes for low and high suppressors under placebo (low suppressors p = 0.043; high suppressors p < .001) and treatment (low suppressors p < .001; high suppressors p < .001) conditions while treatment did not modulate S_1P50 amplitudes.

No significant effects were observed with latency analyses.

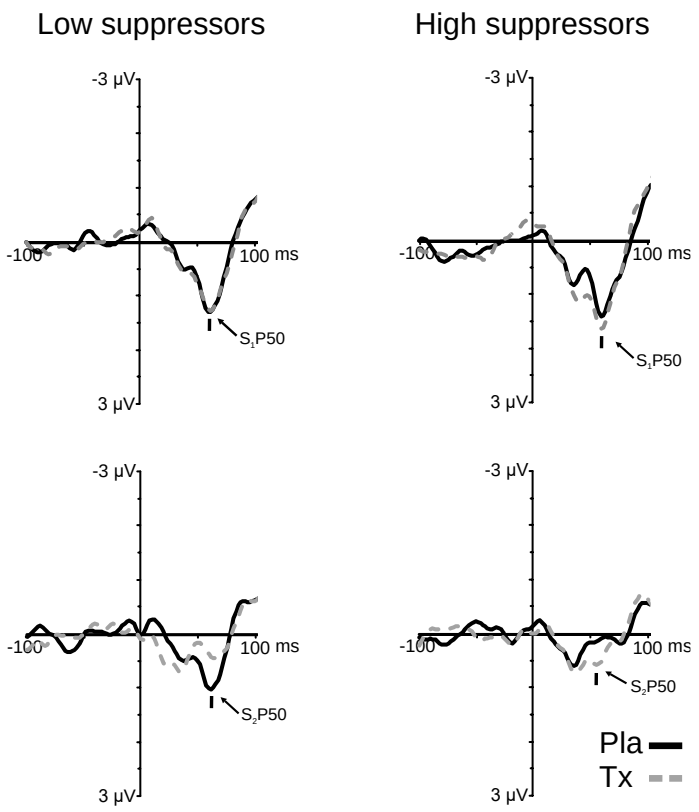

Figure 2.3 Mean (±SE) S_1P50 (top) and S_2P50 (bottom) amplitudes in low and high suppressors during placebo and CDP-choline (500 mg)/ galantamine (16mg) treatment.

2.6.4 Placebo vs. treatment effect correlations

Treatment-induced changes in gating (rP50 and dP50) and amplitude measures were found to be inversely related to placebo values, indicating that individuals with reduced gating (and amplitude) scores benefit most from the CDP-choline/galantamine treatment (Figure 2.4).

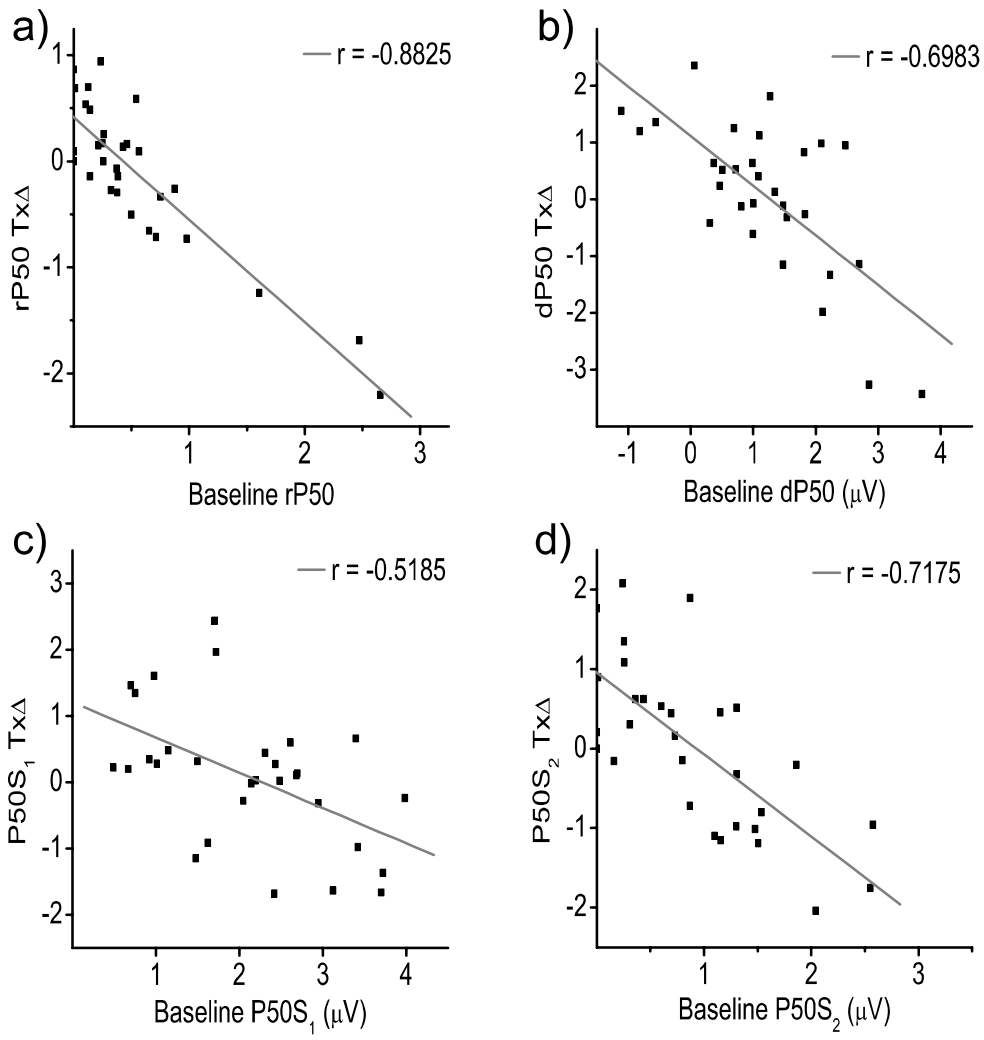

Figure 2.4 Scattergrams between treatment effect (TxΔ) scores (treatment – placebo) and placebo scores for P50 ratio (S_2/S_1; a), P50 difference ($S_1–S_2$; b), S_1P50 (c) and S_2P50 (d) amplitudes. TxΔ scores negatively correlated with placebo scores for rP50 (rho = −0.88, p < 0.0001), dP50 (rho = −0.70, p < 0.0001), S_1P50 (rho = −0.52, p = 0.003) and S_2P50 (rho = −0.72, p < 0.0001).

2.6.5 Adverse events

Self-reports of adverse events related to the administration of the active treatment (CDP-choline/galantamine) did not reflect any significant difference compared to the placebo condition. No severe symptoms were reported throughout the study experiments.

2.6.6 Vital signs

No significant differences were observed for systolic and diastolic blood pressure measures at placebo compared to measures at CDP-choline/galantamine. Pre- and post- treatment administration heart rate measures were not significantly different under the CDP-choline/galantamine condition in comparison to placebo. However, the last heart rate measure (at the end of the testing session before participant departure) during the placebo session ($M = 61.8$ bpm, $SE \pm 2.13$) was significantly ($t(19) = -2.47$, $p = .023$) lower than during the active treatment ($M = 65.4$ bpm, $SE \pm 1.84$).

2.7 Discussion

The primary objective of this study was to examine the effect of a novel cholinergic treatment, consisting of CDP-choline and galantamine on speech P50 gating indices, rP50 (S_2/S_1) and dP50 ($S_1 – S_2$), in healthy humans. Our findings demonstrated that CDP-choline/galantamine (vs. placebo): 1) improved rP50 and dP50 gating and reduced S_2P50 amplitudes in low suppressors; 2) did not modulate gating indices in high suppressor; however, it significantly increased S_2P50 amplitudes; 3) treatment effect scores (treatment minus placebo) revealed significant negative correlations for S_1P50, S_2P50, rP50 and dP50 measures. These findings indicate a baseline-dependency effect, with individuals expressing relatively reduced P50 gating indices benefitting most from the cholinergic treatment. These results also implicate that CDP-choline/galantamine treatment might impair P50 SG and amplitude values in individuals who show optimal SG scores

at baseline. Due to the receptor selectivity nature of CDP-choline, these results conclusively showed that the α7 nAChRs are implicated in SG modulation.

Improved P50 SG in low suppressors was in line with our expectations and, adopting the low suppressors group strategy as a surrogate model of SCZ is in line with previous studies reporting that 40% of healthy individuals elicit rP50 scores within ± 1 SD of the mean rP50, .79, expressed by SCZ patients (Fuerst et al., 2007; Patterson et al., 2008). Our findings complement the similar outcomes of previous clinical research that examined CDP-choline effects on P50 SG in low suppressor groups of SCZ patients (Aidelbaum et al., 2018) and healthy individuals (Knott, Smith, et al., 2014). Our results also parallel the increased sensory inhibition findings in studies examining the effect of perinatal choline administration in DBA/2 mice and newborn infants (Ross et al., 2013; Stevens et al., 2014). These results are also in line with findings from studies examining the effects of nicotine, an agonist that binds and activates all subtypes of neural nAChRs, on P50 gating indices in low and high suppressors groups (Adler et al., 1992; de La Salle et al., 2013; Knott et al., 2010, 2013; Millar et al., 2011). Only a few studies to date have examined the effect of selective α7 PAMs on P50 gating in humans and mice. Pre-clinical studies employing JNJ-1930942 on hippocampal slices and in DBA/2 mice observed increases in neurotransmission and reversal of SG deficits respectively (Dinklo et al., 2011). In parallel JNJ-39393406, another α7 selective PAM, was also shown to reverse SG deficits in DBA/2 mice, however, when examined on SCZ patients, JNJ-39393406 did not ameliorate P50 auditory gating impairments (Winterer et al., 2013). Participants were not subgrouped for baseline performance, a strategy repeatedly shown to be useful due to performance variability in healthy volunteers and SCZ patients (Patterson et al., 2008).

CDP-choline's effects have been shown to be mediated by increased calcium influx and by modulating the release of GABA, dopamine, ACh, glutamate, and kynurenic acid (Agut et al., 2000; Koukouli & Maskos, 2015). Increased GABA neurotransmission in the hippocampus (Albuquerque et al., 1998) following CDP-choline administration is an important and relevant neural mechanism as previous and recent evidence associated the hippocampus with repetition suppression (Boutros et al., 1999, 2013; Freedman et al., 1991; Javitt & Freedman, 2015). Individual differences in dopamine activity may also underlie variations in suppressor group response to nicotinic treatment as nicotine effects on SG in the suppressor groups vary with dopamine genotype (de La Salle et al., 2013; Millar et al., 2011). Furthermore, paralleling our findings of CDP-choline/galantamine mediated decreases of S_2P50 amplitudes in low suppressors, S_2P50 mediated gating improvements have been previously evidenced following increased inhibitory interneuronal activity on hippocampal pyramidal neurons mediated by DMXB-A treatment, a selective α7 nAChR agonist, in mice and SCZ patients (Frazier et al., 1998; Miller & Freedman, 1995). The implication of acetylcholine and nicotinic receptors in the hippocampus was recently examined, outlining the role of astrocytes in inhibiting neuronal activity in an extensive research study employing optogenetics, in-vivo and in-vitro patch-clamp and single-unit recordings, and multiphoton imaging techniques (Pabst et al., 2016). Deutsch's initiative of combining CDP-choline and galantamine, a strategy aimed to sustain a longer activation state of α7 receptors countering the desensitizing impact observed with high doses of α7 nAChRs agonists (Dani & Bertrand, 2007; Wallace & Bertrand, 2015), yielded significant improvements of global functioning scores and free verbal recall tests in SCZ patients (Deutsch et al., 2013). Furthermore, a recent clinical research study on Alzheimer's disease patients with mild cognitive impairments revealed significant cognitive improvement, measured by the mini-

mental state examination (MMSE), following CDP-choline/galantamine treatment (Gareri et al., 2017).

Our study is the first to examine the effect of CDP-choline/galantamine treatment on P50 SG. While galantamine can be criticized for its lack of α7 receptor selectivity, it is important to note that although CDP-choline is highly selective for α7 receptors, it modulates the release of numerous other neurotransmitters and its metabolism yields cytidine and choline (Secades, 2011). Choline can produce betaine that can then produce S-adenosyl-L-methionine that in turn is a precursor for serotonin (Adibhatla et al., 2001). This elucidates the complexity of biological processes and in part demonstrates that although this treatment selectively targets α7 receptors, ultimately and theoretically it can modulate multiple other neural receptor systems. The use of a highly selective compound, targeting neuronal nicotinic receptors for cognitive enhancements, was recently viewed as a reductionist approach in a recent review attempting to explain the nature of the lack of significant neuropharmacological breakthroughs in this system (Bertrand & Terry, 2018).

Employing a speech P50 ERP paradigm was a novelistic feature of this study as a speech (vs. clicks/tones) P50 paradigm has only been previously employed in a magnetoencephalography (MEG) experiment that revealed a correlation between impaired P50m SG to speech and AVH severity in SCZ (Hirano et al., 2010). While the association between P50 SG (to clicks) and AVH has previously been examined (Faugere et al., 2016; Smith et al., 2013; Thoma et al., 2017), the associations between speech processing, P50 gating, nicotinic acetylcholinergic deficits, and AVHs in SCZ have not been systematically evaluated and thus remain poorly understood. Inherent to SCZ symptomatology, high-level language processing and low-level speech perception have been characterized with several dysfunctional aspects and have

been associated with AVHs and thought disorders (Brown & Kuperberg, 2015). Furthermore, brain regions activated during AVHs have also been shown to be implicated in the nuclear auditory repetition suppression apparatus, responsible for sensory gating, which includes the temporal neocortex, the prefrontal cortex and hippocampus (Boutros et al., 2013; de Leede-Smith & Barkus, 2013). These regions are highly innervated by nAChRs (Dani & Bertrand, 2007) and have been reported to express α7 cholinergic deficits in SCZ (Wallace & Bertrand, 2015). Therefore, lower speech P50 gating scores in low suppressors (vs. high suppressors) under placebo and improvements following CDP-choline/galantamine treatment in this study also suggest that speech processing is associated with α7 nAChR functioning in SCZ.

2.7.1 Limitations

This study is characterized by many strengths including the use of double-blinded and randomized treatment administration, a cross-over repeated measures design, and the assessment of male and female smokers and non-smokers in order to support the generalizability of the data and results to SCZ. Certain limitations are to be considered including a relatively small sample size in our stratified gating groups, which could have limited the statistical power.

This was a pilot study testing a single dose level of CDP-choline/galantamine. Thus, future studies need to assess different dosages and in different combinations for each treatment in order to better define the dose-response curve of these separate and combination approaches. An extended treatment regimen will give a better outlook on the long-term efficacy of this strategy, and multiple doses will help optimize the effectiveness of this treatment. A recent clinical study, examining the effect of CDP-choline and an acetylcholine esterase inhibitor (donepezil, rivastigmine or galantamine) on cognitive measures in patients with Alzheimer's Disease, reported time-related cognitive performance enhancement when the acetylcholine esterase

inhibitor was combined with CDP-choline (vs. the acetylcholine esterase inhibitor alone) (Gareri et al., 2017).

The inclusion of smokers could also be considered as a limitation arguing that gating impairments can be related to nicotine withdrawal and therefore active treatment effects in smokers could be a factor of alleviating withdrawal symptoms. However, smokers (in comparison to non-smokers) did not express significantly different rP50 and dP50 gating scores or S_1P50 and S_2P50 amplitudes.

Our participants were stratified into low and high subgroups based on their rP50 scores under the placebo session which were also used in the statistical analysis and could have contributed to a "regression to the mean" effect. However, the counterbalanced design of this study could have helped to eliminate this effect as results from analyses using the stratification based on treatment session rP50 values yielded no significant interaction or treatment effects. Future study design could incorporate a preliminary testing session for stratification purposes.

Finally, gating of speech stimuli should be compared to gating of click/tone stimuli to assess auditory gating specificity and to better understand early auditory processing mechanisms affected by nicotinic neurotransmission.

2.8 Conclusion

The single administration of this combined cholinergic treatment strategy of CDP-choline and galantamine was shown to alleviate P50 gating impairments in a SCZ gating surrogate group of healthy low suppressors. These ERP results are in line with previous preclinical, clinical and neurobiological evidence suggesting deficient α7 nAChR functioning in SCZ (Hashimoto, 2015; Leonard et al., 1996, 2002; Smucny et al., 2015) and support the use of rP50 as a biomarker and endophenotype for examining this treatment strategy on sensory impairments in SCZ. These

findings also support the future testing of this pharmacological approach on SG in SCZ patients and in the schizotypal spectrum as an adjunct treatment that might help alleviate the burden of sensory processing deficiencies previously associated with higher-order cognitive and functional outcome (Javitt & Freedman, 2015).

Chapter 3

Effects of CDP-Choline and Galantamine on P50 Sensory Gating in Individuals with Schizophrenia

3.1 Preface

Overview

This pilot study in patients with SCZ assessed the modulating effect of a single moderate dose of CDP-choline and galantamine on P50 ERPs and sensory gating indices (rP50 and dP50) to speech sounds in patients with SCZ stratified into low and high gaters based on their baseline gating performance.

Statement of author contribution

This study was designed by Dr. Verner Knott, with contributing input from Joelle Choueiry. The study setup was done by Joelle Choueiry and Dhrasti Shah. Paradigm programming with auditory speech stimuli was done by Joelle Choueiry, Derek Fisher, and Dylan Smith. Participant recruitment and screening were done by Joelle Choueiry and Crystal Blais. Recruited participants were clinically interviewed by Dr. Alain Labelle. Administration of study tasks and ERP recording were done by Joelle Choueiry and Crystal Blais. ERP processing and analyses, statistical analyses, tables and figures and manuscript writing were done by Joelle Choueiry. The final manuscript was reviewed by all authors.

3.2 Title page

Combining CDP-choline and galantamine, an optimized α7 nicotinic strategy, to ameliorate sensory gating to speech stimuli in schizophrenia

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Declaration of interest: All authors declare not conflict of interest.

3.3 Abstract

Neural α7 nicotinic acetylcholine receptor (nAChR) expression and functioning deficits have been extensively associated with cognitive and early sensory gating (SG) impairments in schizophrenia (SCZ) patients and their relatives. SG, the suppression of irrelevant and redundant stimuli, is measured in a conditioning-testing (S_1-S_2) paradigm eliciting electroencephalography-derived P50 event-related potentials (ERPs), the S_2 amplitudes of which are typically suppressed relative to S_1. Despite extensive reports of nicotine-related improvements and several decades of research, an efficient nicotinic treatment has yet to be approved for SCZ. Following reports of SG improvements in low P50 suppressing SCZ patients and healthy participants with the α7 agonist, cytidine diphosphocholine (CDP-choline), this pilot study examined the combined modulatory effect of CDP-choline (500 mg) and galantamine (16 mg), a nAChR positive allosteric modulator and acetylcholinesterase inhibitor, on SG to speech stimuli in twenty-four SCZ patients in a randomized, double-blind and placebo-controlled design. As expected, in low P50 suppressors CDP-choline/galantamine (vs. placebo) improved (decreased) the ratio P50 (rP50; S_2/S_1) and (increased) the difference P50 (dP50; $S_1 – S_2$) scores by increasing inhibitory mechanisms as reflected by S_2P50 amplitude reductions. Results also suggest a moderating role for auditory verbal hallucinations in treatment response. These preliminary findings provide supportive evidence for the involvement of α7 nAChR activity in speech gating in SCZ and support additional trials, examining different dose combinations and repeated doses of this optimized and personalized targeted α7 cholinergic treatment for SG dysfunction in subgroups of SCZ patients.

3.4 Introduction

3.4.1 Nicotinic receptor and sensory cognitive impairments in schizophrenia

Nicotine, initially, then followed by a multitude of other nicotinic acetylcholine receptor (nAChR) agonists have been the subject of extensive research in schizophrenia (SCZ). Although cigarette smoking rates in healthy populations (10 – 15%) are at an all time low, ~ 60-80% of individuals with SCZ (Cather et al., 2017) are still attempting to alleviate cognitive impairments one deep and sustained cigarette puff at a time, as hypothesized by the nicotine self-medicating hypothesis (Kumari & Postma, 2005). Although this hypothesis has recently been challenged (Boggs et al., 2014, 2018), nicotinic modulation of cognitive processes has been supported by numerous animal and human research studies (Featherstone & Siegel, 2015). Cholinergic system abnormalities have been implicated in substance (i.e. nicotine and cocaine) abuse and dependence and in multiple brain disorders notably SCZ (Grasing, 2016; Nees, 2015). The CHRNA7 gene, responsible for α7 nAChR expression in the brain, has been identified as a risk gene in SCZ (Bertelsen et al., 2015; Sinkus et al., 2015) with lower post-mortem expression of α7 receptors reported in the frontal cortex (Guan et al., 2000), the hippocampus (Freedman et al., 1995; Olincy & Stevens, 2007), and the thalamus (Court et al., 1999). Furthermore, multiple single nucleotide polymorphisms and variants in the core promoter region of the CHRNA7 gene have been associated with deficits in neurophysiological measures of information processing in SCZ (Freedman et al., 1997, 2000, 2003; Leonard et al., 2002; Olincy & Freedman, 2012; Tregellas, 2014; Turetsky et al., 2007).

The National Institute of Mental Health identified cognitive impairments as a pressing target in SCZ often experienced before the onset of positive symptoms (i.e. hallucinations) and, due to the anti-dopaminergic nature of neuroleptics, continue to negatively impact patients' quality of life despite the remission of psychosis (Addington & Addington, 1993; Green et al.,

2000, 2004; Hofer et al., 2005; Reichenberg et al., 2010; Tandon et al., 2009). Furthermore, deficiencies in early low-level processes of sensory gating (SG**;** responsible for filtering/gating out redundant and irrelevant environmental stimuli/information (Javitt et al., 2008; Javitt & Freedman, 2015)) have been associated with poor functional outcome, the severity of auditory verbal hallucinations (AVH), and aberrant attentional processing and have been used as biomarkers in the development of cognitive pharmacological treatments in SCZ (Azzopardi et al., 2013; Braff, 2011; Javitt, 2009a; Jones et al., 2016; Mackowick et al., 2014; Smith et al., 2013). Following associations of the cholinergic system, the α7 nAChR specifically, with cognitive processes and SG mechanisms, the Measure and Treatment Research To Improve Cognition in Schizophrenia (MATRICS)' guidelines identified α7 nACh as a major molecular and neuropharmacological target (Azzopardi et al., 2013; Braff, 2011; Jones et al., 2016; Mackowick et al., 2014).

3.4.2 Measuring SG deficits in schizophrenia

Measures of SG are acquired from, non-invasive and high-temporal resolution, recordings of electrical activity at the scalp using brain electroencephalography (EEG)-derived event-related potentials (ERPs). A conditioning-testing P50 auditory paradigm indexes SG following the presentation of a pair of identical auditory clicks or tones. The conditioning stimulus (S_1) evokes an early positive potential (S_1P50; approximately 50 ms post-stimulus onset) while efficient neural mechanisms in healthy individuals typically suppress responses to repetitive auditory stimuli and yield reduced testing stimulus (S_2P50) amplitudes. Calculated P50 amplitude ratio score (rP50, S_2/ S_1) and difference score (dP50, $S_1 – S_2$) typically index SG efficiency with evidence suggesting that the rP50 index more closely reflects S_2P50 suppression (Boutros et al., 2013). The rP50 is now being recognized as a valuable biomarker and endophenotype in the SCZ spectrum disorder (Braff et al., 2007; Braff & Freedman, 2002; Brockhaus-Dumke et al., 2008;

Hall et al., 2006; Patterson et al., 2008; Turetsky et al., 2007) where significantly higher rP50 scores (~.80**,** reflecting ~20% suppression in comparison to ~.40 in healthy controls, reflecting ~60% suppression) were measured in chronic patients (Bramon et al., 2004; Patterson et al., 2008; Su et al., 2012), their non-clinically affected relatives (Clementz et al., 1998), in first-episode patients (Brockhaus-Dumke et al., 2008; Oranje et al., 2013) and in individuals with schizotypal personality disorder (Cadenhead et al., 2000; Giakoumaki, 2012). Furthermore, auditory P50 SG deficits have been associated with the emergence of psychotic (Javanbakht, 2006) and cognitive symptoms (Thoma et al., 2003), attentional difficulty, working memory impairments and reduced processing speed (Hamilton, Williams, et al., 2018) and also evidenced to impact SCZ patient's quality of life (Micoulaud-Franchi et al., 2016). The CHRNA7 gene on chromosome 15q14, has also been genetically linked with P50 SG deficits in SCZ patients and in healthy controls (Freedman et al., 1997, 2003; Hashimoto, 2015; Javitt & Freedman, 2015; Stephens et al., 2009).

3.4.3 Targeting α7 nAChRs to alleviate P50 SG impairments in schizophrenia

Current neuroleptics do not alleviate P50 SG deficits in SCZ (Su et al., 2012), despite previous positive reports (Adler et al., 2004; Oranje et al., 2013). In contrast, clinical trials with nicotine have reported improvements of impaired P50 SG measures in SCZ patients, their unaffected relatives, and in healthy individuals with reduced SG (Adler et al., 1992; de La Salle et al., 2013; Knott et al., 2010; Millar et al., 2011). Analogously, nicotine corrected auditory gating deficiencies in a DBA/2 (dilute brown, non-agouti; H-2^d haplotype) mouse strain, an inbred mouse model of SCZ expressing low levels of hippocampal α7 nicotinic receptors and SG impairments (Adler et al., 1998; Light & Braff, 1999; Olincy et al., 2006; Stevens & Wear, 1997). However, nicotine (smoke inhaled nicotine in particular) is not considered a safe, feasible

alternative treatment for SCZ patients, in part because of the diseases associated with smoking and because elevated smoking rates (Mackowick et al., 2014) have been associated with a shorter lifespan (~28 years) of smokers diagnosed with SCZ (Olfson et al., 2015). Furthermore, in addition to the highly addictive property of nicotine and the poorly known impact of long-term nicotine exposure, recent clinical trials and reviews have reported a lack of nicotine-related improvements/deterioration of cognitive functioning following nicotinic treatments/periods of nicotinic abstinence, respectively (Boggs et al., 2014, 2018). It has been suggested that the confounding impact of the heterogeneity of SCZ may account for these inconsistent findings and raises the importance and validity of conducting smaller size clinical trials that have the capacity to foster precise and strictly controlled patient inclusion/exclusion criteria (Bertrand & Terry, 2018).

Cytidine diphosphocholine (CDP-choline), has the capacity to increase choline metabolism and in turn increase GABA neurotransmission in the hippocampus following selective α7 nAChR activation (Albuquerque et al., 1998; Secades, 2011). In individuals with senile disease and traumatic brain injuries, chronic CDP-choline treatment significantly improved higher order attentional and memory functioning (Gareri et al., 2015; Sarkar et al., 2012; Secades, 2011). Given CDP-choline's α7 receptor selectivity, our laboratory examined its acute effect on SG and cognition in healthy individuals and SCZ patients. In healthy participants showing relatively lower cognitive and SG scores at baseline, CDP-choline was found to enhance multiple domains of cognitive functioning (Knott, de La Salle, et al., 2015) and improve SG (Knott, Smith, et al., 2014). Also, our laboratory reported CDP-choline-mediated improvements of P50 SG scores in SCZ patients who exhibited impaired (rP50 > .70) gating (Aidelbaum et al., 2018). Also, improved SG scores following gestational choline

supplementation, in DBA/2 mice that carried the wild-type α7 nAChR gene (chrna7) (Stevens et al., 2014), and in newborn infants (Ross et al., 2013), highlighted choline's benefits on the neurodevelopmental risks of SCZ as deficits in P50 inhibition have been associated with greater risks of developing attentional impairments and SCZ-like symptoms (Ross et al., 2013; Stevens et al., 2014).

3.4.4 Utilizing positive allosteric modulators to improve P50 SG and cognition in schizophrenia

Although the selective α7 receptor agonist approach yielded positive SG outcomes, this strategy naturally encompasses a limitation stemming from the α7 nAChR's fast desensitization rate when exposed to a full agonist (Albuquerque et al., 1998; Mike et al., 2000; Zhang et al., 1994). As an alternative, positive allosteric modulators (PAM) have been examined in mice models and clinical populations for their capacity to modulate receptor functioning by increasing binding affinity to agonists (Type-I), and by slowing the rate at which the receptor desensitizes and remains in the de-activated state (Type-II) (Wallace & Bertrand, 2015). While PAMs seem theoretically promising, in practice, not many PAMs have completed human clinical trials and only few have been examined on SG and response suppression yielding reports of improved P20-N40 (a P50 SG analogue) scores in DBA/2 mice (Hashimoto, 2015; Smucny et al., 2015). Galantamine, a type-I PAM and an acetylcholinesterase inhibitor (Bertrand & Gopalakrishnan, 2007; Williams et al., 2011), has been shown to improve inhibition scores in rats with deficient sensory motor gating (Hohnadel et al., 2007; Shao et al., 2014) while alleviating cognitive dysfunction and reducing rates of disease progression in patients with Alzheimer's disease (Scott & Goa, 2000), in addition to enhancing processing speed and verbal memory in SCZ patients (Buchanan et al., 2008). Therefore, combining the dual modulatory action of galantamine with an α7 nAChR agonist would be an optimized strategy that counters the tendency of nAChRs to desensitize following amplified agonist exposure.

To the best of our knowledge, the combination of CDP-choline and galantamine has only been examined in clinical and healthy non-clinical control populations in two studies that yielded mixed findings of non-significant clinical (positive and negative symptoms) improvements and minor auditory verbal memory performance improvements (Deutsch et al., 2013; Deutsch et al., 2008a,b). A decade later, experimental studies examining CDP-choline and other nAChR agonists converged on a "less is more" outcome as the dose-response curve, taking the shape of an inverted U, determined maximized effects when nicotinic agonists were administered in low doses (Castner et al., 2011; Hahn et al., 2002; Prickaerts et al., 2012; Werkheiser et al., 2011). Furthermore, our laboratory's previous findings suggest optimal benefits with low-to-moderate CDP-choline doses (Knott, de La Salle, et al., 2015; Knott et al., 2014). We recently examined the effects of a low dose of CDP-choline and moderate dose of galantamine and found significantly enhanced P50 gating measures to speech stimuli in a sub-group of healthy participants that expressed relatively lower P50 response suppression scores at baseline (Choueiry et al., 2019a).

3.4.5 Study objectives and hypotheses

The enhancing effect of this optimized strategy on SG in healthy participants supports its examination in SCZ patients. Thus, the primary objective of this study was to assess the acute combined effect of CDP-choline and galantamine, on rP50 and dP50 indices of SG in this population, which, to the best of our knowledge, has not yet been explored. As nicotinic modulation of P50 gating has previously been shown to be 'baseline-dependent', and evidencing enhanced and diminished gating in low and high P50 suppressors, respectively, SCZ patients were accordingly stratified into low and high baseline suppressor groups. Analogously to studies examining P50 SG modulation by nicotine (Knott et al., 2013) and CDP-choline (Aidelbaum et al., 2018; Knott, Smith, et al., 2014), greater rP50 improvements (lower rP50 scores) are

expected in individuals who express greater rP50 gating impairments (higher rP50 scores) at baseline. The active cholinergic treatment consists of the administration of a lower (500 mg) dose of CDP-choline and a moderate (16 mg) dose of galantamine (Deutsch et al., 2013) similar to the doses administered to healthy participants. These optimized doses were initially selected based on previous reports showing most effective modulation when lower-moderate (500 mg, 1000 mg) acute doses of CDP-choline were assessed in relation to cognitive performance (Knott, de La Salle, et al., 2015), on P50 gating (Aidelbaum et al., 2018; Knott, Smith, et al., 2014) and on attentional and sensory memory processing indexed by respective neural ERP components (Hyde et al., 2016; Knott, Impey, et al., 2015). CDP-choline has a well-tolerated daily dose range of 500 – 4000 mg/day. Oral and intravenous administration methods show analogous bioavailability ranging between 92 - 94% (Agut et al., 1983). A single acute administration of CDP-choline increases choline plasma levels in a dose-dependent rate with metabolites reaching brain tissue in thirty minutes and plasma peaking approximately 2-3 hours after ingestion (Wurtman et al., 2000). Galantamine has a bioavailability range between 85 to 100% and plasma levels reach peak value in 0.5 to 2 hours (Jann et al., 2002). CDP-choline and galantamine at these doses have no reports of serious adverse events.

The onset and occurrence of positive clinical symptoms (i.e. hallucinations and delusions) are still not well understood, and it's been suggested in a tentative model that SG is one of the main components underlying their emergence (Javanbakht, 2006). Furthermore, a recent P50 SG study examining neural regions implicated in response suppression highlighted a significant role for the frontal lobe in addition to the involvement of cingulate areas (Boutros et al., 2013), notably, these regions have also been associated with the occurrence of AVHs in SCZ patients (de Leede-Smith & Barkus, 2013).The clicks/tones P50 paradigm has been extensively examined

in healthy individuals and in those with SCZ (Adler et al., 1998; Boutros et al., 2004; Clementz et al., 1998; Freedman et al., 1991; Nagamoto et al., 1991; Patterson et al., 2008), therefore, presenting speech (instead of click/tone) stimuli while maintaining the tested and recommended presenting, recording, and processing parameters might provide more insight into the previously reported associations between P50 SG and the occurrence and severity of AVHs in SCZ (Faugere et al., 2016; Hirano et al., 2010; Javanbakht, 2006; Smith et al., 2013; Smucny et al., 2013; Thoma et al., 2017). P50m (the magnetoencephalographic [MEG] measure of P50 SG) has previously been examined with verbal phonemes instead of the typical click/tone stimuli (Hirano et al., 2010). Compared to healthy controls, SCZ patients expressed greater rP50m scores (deficient gating) in the left temporal hemisphere, which also correlated with greater AVH scores. Results from our recent study measuring speech P50 SG indices in healthy participants did not yield a hemispheric lateralization at the scalp level, however, low suppressors exhibited increased speech gating following CDP-choline/galantamine treatment (Choueiry et al., 2019a).

Given previous evidence of a relationship between SG to click (Smith et al., 2013) and speech (Hirano et al., 2010) stimuli and auditory hallucinations, a second objective of this study was to examine the relationship of self-ratings of AVHs to speech gating and their change with treatment, focusing on primary (rP50 and dP50) and secondary (S_1P50 and S_2P50 amplitudes) measures of SG in SCZ patients. Given that previous studies on the relationship between positive and negative symptoms and SG to click stimuli have been inconsistent (Adler et al., 1990; Boutros et al., 2004, 2009; Potter et al., 2006; Thoma et al., 2005; Zhu et al., 2017), we also assessed the relationship between positive and negative symptoms and speech gating and their change with treatment.

3.5 Materials and methods

3.5.1 Study participants

Twenty-six SCZ patients were recruited from the SCZ Outpatient Program at The Royal Ottawa Mental Health Centre. Recruited patients had a SCZ diagnosis according to DSM-IV criteria, were clinically stable for at least three months (assessed with the Positive and Negative Symptom Scale; PANSS)(Kay et al., 1987), and had been on a stable antipsychotic regimen for at least four weeks consisting of one or a combination of different neuroleptics (i.e., aripiprazole, risperidone, flupentixol, haloperidol, paliperidone, levomepromazine, olanzapine, perphenazine, quetiapine, trifluoperazine, ziprasidone). Participants were excluded from this study if they were diagnosed with other DSM-IV disorders or a medical illness, were taking clozapine (as some studies have shown clozapine modulation of P50 gating although later meta-analyses confirmed the lack of significant clozapine and other first- and second-generation antipsychotic medication mediated effect on P50 gating (Sanchez-Morla et al., 2009; Su et al., 2012)), had a recent (past six months) head injury with loss of consciousness, or displayed a hearing impairment. All study participants had normal laboratory and drug screen tests, normal weight, normal hearing, no significant medical/neurological illness (including head trauma/seizure), signed an informed consent form prior to study participation and received $100 upon testing completion. Only one participant dropped out of the study and another participant's data was discarded due to marked artifact EEG recordings. The final group (7 females and 17 males; mean age of 45.12; SE ± 1.98) included 16 smokers and 8 non-smokers, with the later being defined as having smoked less than one hundred cigarettes in their lifetime and had not consumed any tobacco products during the past year. Smokers smoked on average M = 16.6, SE ±1.9 cigarettes per day for an average of M = 24.3, SE ±2.0 years. Fifteen SCZ patients were taking antipsychotic medication with an anticholinergic effect (i.e. cogentin, olanzapine, seroquel). In the screening session, auditory

hallucinations were assessed with the Psychotic Symptom Rating Scales (PSYRATS) (Haddock et al., 1999). Participants rated, on a scale from 0-4, eleven items that characterize experiences of auditory hallucinations (i.e. frequency, duration, location, loudness, beliefs re-origin of voices, amount of negative content of voices, degree of negative content, amount of distress, intensity of distress, disruption to life caused by voices, and controllability of voices). Study procedures and recruitment of SCZ patients for this study were undertaken in compliance with the Research Ethics Boards of The Royal Ottawa Mental Health Care Group and the University of Ottawa.

3.5.2 Experimental design

Volunteers were assessed during a placebo session and a treatment (CDP-choline + galantamine) session within a randomized, double-blinded, and counterbalanced design that permitted an equal number of participants to start with the placebo session as with the treatment session. A minimum of seven days separated testing sessions to allow for treatment washout.

3.5.3 Treatment administration

All active treatment capsules matched the non-active placebo capsules (250 mg of cellulose) in shape, size, and colour. Participants ingested two cellulose-filled capsules (placebo session) or 500 mg (2 x 250 mg capsules) of CDP-choline (treatment session) and sixty minutes later, ingested another cellulose filled capsule (placebo session) or 16 mg (250 mg capsule filled with 234 mg of cellulose) of galantamine (treatment session).

3.5.4 Experimental procedures

Participants were initially assessed in a screening session and subsequently completed two testing sessions. Abstinence from food, drugs (neuroleptics for treating SCZ were taken as usual), alcohol, caffeine, and tobacco was verbally confirmed upon participant's arrival to the laboratory (between 8:00 a.m. and 11:30 a.m.) followed by a measurement of exhaled carbon monoxide (CO) to verify smoking abstinence (< 3 p.p.m. for non-smokers and less than the

exhaled CO level at the screening session for smokers). Participants then received either placebo or CDP-choline (time 0 minutes) and were invited to sit and relax in a dimly lit, sound-attenuated chamber where they watched an emotionally neutral movie during the treatment absorption period. Sixty minutes after receiving placebo or CDP-choline, participants were administered placebo or galantamine and continued to watch their movie for an additional thirty minutes. At peak CDP-choline/galantamine absorption (time 120 minutes), participants were presented with the P50 gating paradigm.

For safety purposes only, blood pressure and heart rate were measured at three intervals, before drug administration, two hours after drug administration and at the end of the testing session where drug adverse events checklist was also administered to assess potential drug-related symptoms.

3.5.5 P50 paradigm

120 consonant-vowel pairs te-te (/te:/; F = 101 Hz; 170 ms duration; Pakarinen et al., 2009) were administered binaurally through headphones at 80 dB (SPL). Consonant-vowel pairs (te-te; S_1-S_2) were presented at intra-pair intervals of 0.5 s and inter-pair intervals of 10 s totalling approximately 16 minutes of auditory stimuli presentation. During the paradigm presentation, patients were instructed to ignore the sounds and to visually fixate on the center of a black computer screen while remaining seated and relaxed.

3.5.6 ERP recording and processing

Two electrodes, one on the nose and one placed between Fpz and Fz sites, were used as references and ground, respectively. Thirty Ag+/Ag+ Cl- electrodes were positioned at scalp sites: Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T7, T8, P7, P8, Fz, Cz, Pz, Oz, Fc1, Fc2, Cp1, Cp2, Fc5, Fc6, Cp5, Cp6, Tp9, and Tp10; in addition to a reference electrode placed on the nose and a ground electrode placed between Fpz and Fz sites according to the 10/10 international

system (Jurcak et al., 2007). Electrodes placed on the supra- and sub-orbital ridges of the right eye were used to monitor vertical electro-oculographic (VEOG) activity while electrodes on the external canthus of both eyes monitored horizontal electro-oculographic (HEOG) activity. Brain Vision Quickamp® (Brain Products, Gmbh, Munich, Germany) amplifier (amplifier bandpass filters set at 0.1 to 70 Hz) and Brain Vision Recorder® software (continuous digitization sampling rate of 500 Hz) were used to record EEG activity. Electrode impedance was kept below 5 kΩ throughout the recording session.

Brain Vision Analyser® (Brain Products, Germany) software was used offline to process and analyze P50 ERP amplitude and latency measures to S_1 and S_2 stimuli. The raw signals were initially re-referenced to electronically linked mastoid electrodes (Tp9 and Tp10). Subsequent processing consisted of digital filtering (24 dB/octave) with a low-high cut-off window of 10 – 50 Hz, segmenting into 150 ms epochs beginning at 50 ms pre-stimulus, ocular correction (Gratton et al., 1983), and automatic artifact rejection of epochs with amplitudes exceeding ± 75 µV. The remaining artifact-free segments were then baseline corrected using the electrical activity recorded during the 50 ms pre-stimulus window. The processed epochs were finally averaged for P50 ERP processing. P50 amplitudes are usually higher at the central vertex (Cz vs. Fz, C3 and C4), where SG differences between SCZ patients and healthy controls have been best elucidated (Clementz et al., 1998). Although amplitude and latency measures from Cz are typically used for P50 peak detection, the traditional peak detection guidelines and criteria (Boutros et al., 2004) were slightly modified to take into account the speech/linguistic nature of this speech P50 paradigm. Using the semiautomatic peak detection tool of Brain Vision Analyser®, S_1P50 peaks were identified separately for Cz, C3 and C4 channels. P50 peaks were selected within the 40 – 80 ms post-stimulus onset timeframe and were the second of two

positive peaks or the maximal P50 amplitude. As per traditional guidelines, the chosen S_1P50 peaks at Cz were also required to be present at C3 or C4 (or at both channels) and had to be greater than 0.5 µV measured from peak to the averaged baseline. Typically, P50 peak amplitudes are calculated as the difference between the P50 peak value and the preceding N40 negative peak (peak-to-trough). P50 peaks in this study were measured with respect to the averaged baseline voltage due to the inconsistent appearance of the N40 and its onset variability and in accordance to recent work (Dalecki et al., 2015). All selected S_1P50 and S_2P50 peaks displayed positive amplitudes at Cz, C3, and C4 scalp electrode sites. S_2P50 peaks were selected within a latency window of ± 10 ms relative to the onset latency of the paired S_1P50 peak. rP50 (S_2/S_1) and dP50 ($S_1 – S_2$) gating indices were calculated following P50 S_1 and S_2 peak quantification.

Studies have repeatedly shown that nicotinic agonists effects can be baseline-dependent thus analogous to our previous studies (Aidelbaum et al., 2018; de La Salle et al., 2013; Knott et al., 2013; Knott, Smith, et al., 2014) and to studies from other laboratories (Csomor et al., 2008), participant segmentation into low and high suppressor groups was based on baseline (placebo session) rP50 scores. Based on the findings of an extensive meta-analysis validating that SCZ patients report a mean rP50 score of .79 (ranging between .56 – 1.58) in comparison to a mean rP50 score of .38 (ranging between .09 – .73) in healthy humans (Patterson et al., 2008), a baseline (placebo) rP50 score of .70 was employed for participant stratification into low and high suppressor subgroups. Participants with baseline (placebo) rP50 scores above .70 µV were classified as low suppressors while the high suppressors group consisted of participants that expressed baseline (placebo) rP50 scores below .70 µV.

3.5.7 Adverse events

A self-report of adverse events was obtained using a checklist of physical and psychological symptoms that participants were asked to rate on a scale from 1 (no symptom at all) to 5 (severe symptom).

3.5.8 Vital signs

Sitting vital signs consisted of heart rate, systolic and diastolic blood pressure measurements before treatment administration, at peak absorption time, and at the end of testing were assessed for safety purposes only.

3.5.9 Statistical analysis

The Statistical Package for the Social Sciences software (SPSS, IBM Corporation, New York, USA) was used for all data analyses. Separate univariate, mixed analysis of variance (ANOVA) with treatment (two levels) and electrode scalp position (three levels) as within-subject factors were used to initially analyze the overall effect of CDP-choline/galantamine treatment on the primary rP50 and dP50 gating measures. A stimulus factor (two levels) was used in addition in these ANOVAs to analyze the overall CDP-choline/galantamine treatment effect on our secondary measures of $P50S_1$ and $P50S_2$ amplitudes and latencies.

CDP-choline/galantamine treatment effect on rP50 and dP50 gating indices were analyzed separately for the low and high suppressors subgroups using univariate mixed analyses of variance (ANOVA) with group (two levels) as a between-subjects factor and with treatment (two levels), and scalp site (three levels) as within-subjects repeated measures factors. Secondary S_1P50 and S_2P50 amplitude and latency measures were also analyzed using separate univariate mixed ANOVAs with group (two levels) as a between-subjects factor, and with treatment (two levels), stimulus (two levels), and scalp site (three levels) as within-subjects repeated measures factors.

Greenhouse-Geisser corrected significant effects ($p < .05$) for primary and secondary measures were followed up with Bonferroni-adjusted pairwise treatment comparisons.

Chi-square analyses were conducted to compare high and low participant subgroups based on gender, smoking status, and the use of neuroleptics that interact with the cholinergic system. T-test analyses were employed to assess whether high and low subgroups differed based on psychometric measures of PANSS and PSYRATS scores. Also, Spearman's rho analysis was used for the correlation between SG to speech (placebo score) and PSYRATS/PANSS scores as well as change (treatment values minus placebo values) in SG with treatment and PSYRATS/PANSS scores.

3.6 Results

3.6.1 Demographic and psychometric measures

Study participants' demographic and psychometric data are presented in Table 3.1 for the total sample group and for the high and low suppressor subgroups. Chi square and T-test analyses confirmed that low suppressors were not statistically different from high suppressors regarding gender ($X2(1,24) = 0.23$, $p = .633$), age ($t(22) = 0.56$, $p = .583$), smoking status ($X2(1,24) = 2.14$, $p = .143$), neuroleptics that interact with the cholinergic system ($X2(1, 24) = 0.046$, $p = .831$), and chlorpromazine equivalent dose means (presented in supplementary material in Annex 2). T-test analyses also confirmed that sub-groups did not differ on PANSS or PSYRATS scores (see Table 3.2). The PANSS measures include the total score (the sum of scores for the three subscales), the positive symptoms subscale score (range 7 – 49 indicates the severity of positive symptoms including delusions, hallucinations, and grandiosity), the negative symptoms subscale (range 7 – 49 indicates the severity of negative symptoms such as blunted affect, emotional withdrawal, and poor rapport), and the general psychopathology subscale (range 16 – 112 indicates symptoms such as anxiety, tension, and depression) (Kay et al., 1987). The PANSS

total score and subscale scores for the whole sample group (M = 61.79, SE ±2.87) is indicative of SCZ patients that express stable and managed symptoms classified amongst the 20-35th percentile ranks. These scores also demonstrate that these patients were not more or less classified as positive/negative SCZ type as their subscale positive/negative scores are not different.

The PSYRATS measures included the total score (the sum of scores for the eleven items regarding the AVH subscale; ranging from 0 - 44), the total distress score (the sum of scores (0-8) reported for the amount of distress (0-4) and intensity of distress (0-4) attributed to AVHs, and the controllability score (0-4) reporting the level of control that the participant experiences over the occurrence of AVHs (Haddock et al., 1999).

Table 3.1 Demographic and psychometric mean (±SE) scores for the total sample, and low and high suppressor subgroups.

	Total Sample (N = 24)	High Suppressors (N = 14)	Low Suppressors (N = 10)
Sex	6 F / 18 M	3 F / 11 M	3F / 7M
Age	45.13 (1.98)	46.07 (1.86)	43.8 (4.09)
Smoking status	8 NS / 16 S	3 NS / 11 S	5NS / 5S
Anti- cholinergic neuroleptics	15 I / 9 NI	9 I / 5 NI	6 I / 4 NI
PANSS total	61.79 (2.87)	63.28 (3.52)	59.7 (4.98)
Positive scale	15.96 (0.71)	16.28 (1.13)	15.5 (0.69)
Negative scale	16.25 (1.03)	16.57 (1.49)	15.8 (1.43)
General scale	29.75 (1.89)	30.43 (1.86)	28.8 (3.84)
PSYRATS total	26.12 (1.57)	25.86 (2.21)	26.5 (2.30)
Distress total	4.79 (0.54)	4.57 (0.79)	5.1 (0.72)
Controllability	2.75 (0.26)	2.5 (0.37)	3.1 (0.35)

The positive, negative, and general scales are subscales from the Positive and Negative Symptom Scale (PANSS).
The distress total and controllability scales are subscales from the Psychotic Symptom Rating Scales (PSYRATS).
F/M: female/male; NS/S: non-smokers/smokers; I/NI: neuroleptics that are known to interact (i.e., aripiprazole, risperidone, flupentixol, haloperidol, paliperidone, levomepromazine, olanzapine,

perphenazine, quetiapine, trifluoperazine;(Chew et al., 2008)*) or not interact with the cholinergic system.*

Table 3.2 T-test results comparing low and high suppressor subgroups for PANSS and PSYRATS scales and subscales.

	t	df	Sig. (2-tailed)
PANSS total	0.607	22	.550
Positive scale	0.536	22	.597
Negative scale	0.361	22	.722
General scale	0.417	22	.681
PSYRATS total	-0.197	22	.846
Distress total	-0.473	22	.641
Controllability	-1.127	22	.272

3.6.2 CDP-choline/galantamine effects on rP50 gating

Grand averaged placebo ERP waveforms displaying S_1P50 and S_2P50 for all participants and for the low and high suppressor groups are displayed in Figure 3.1.

In line with our expectations, a main overall group effect was observed, $F(1, 22) = 5.83$, $p = .024$. High suppressors displayed smaller (better gating) rP50 scores (rP50 M = 0.52, SE ±0.072) than low suppressors (M = 0.79, SE ±0.085).

A significant group x treatment interaction, $F(1, 22) = 19.30$, $p < .001$, was detected with follow-up comparisons of treatment effects (Figure 3.2) in the low suppressor group showing that CDP-choline/galantamine (rP50 M = 0.49, SE ±0.11) significantly ($p = .001$) reduced rP50 scores (improved gating) in comparison to placebo (rP50 M = 1.09, SE ±0.12) scores which is in line with our predictions. Follow-up comparisons for high suppressors revealed a trend ($p = .055$) toward a decline in gating under CDP-choline/galantamine (rP50 M = 0.65, SE ±0.09) conditions in comparison to placebo (rP50 M = 0.39, SE ±0.1).

3.6.3 CDP-choline/galantamine effects on dP50 gating

As expected, a main overall group effect was observed, $F(1, 22) = 7.09$, $p = .014$. High suppressors displayed larger (better gating) dP50 scores (dP50 M = 1.14 µV, SE ±0.16) than low suppressors (M = 0.48 µV, SE ±0.19).

As indicated in Figure 3.2, significant group x treatment interaction, $F(1, 22) = 31.07$, $p < .001$, was observed with follow-up comparisons revealing that low suppressors experienced a significant ($p = .001$) dP50 increase (improved gating) under CDP-choline/galantamine (M = 0.95 µV, SE ±0.22) compared to placebo (M = 0.015 µv, SE ±0.24). Whereas decreased dP50 gating scores ($p < .001$) in high suppressors were detected under CDP-choline/galantamine treatment (M = 0.68 µV, SE ±0.18) compared to placebo (M = 1.6 µV, SE ±0.20).

3.6.4 CDP-choline/galantamine effects on P50 amplitudes and latencies

Grand averaged placebo ERP waveforms displaying S_1P50 and S_2P50 for all participants and for the low and high suppressor groups are displayed in Figure 3.2.

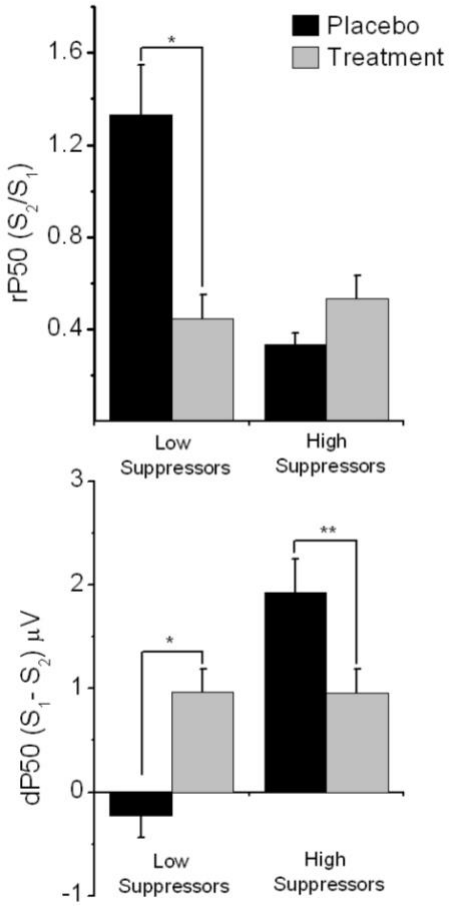

Figure 3.1 Mean (±SE) P50 ratio (S_2/S_1) and difference ($S_1–S_2$) (µV) gating scores, recorded at the Cz scalp site for high and low suppressor groups in response to CDP-choline (500 mg)/galantamine (16 mg) treatment in comparison to placebo.
****p < 0.001; *p = .001; SE: standard error**

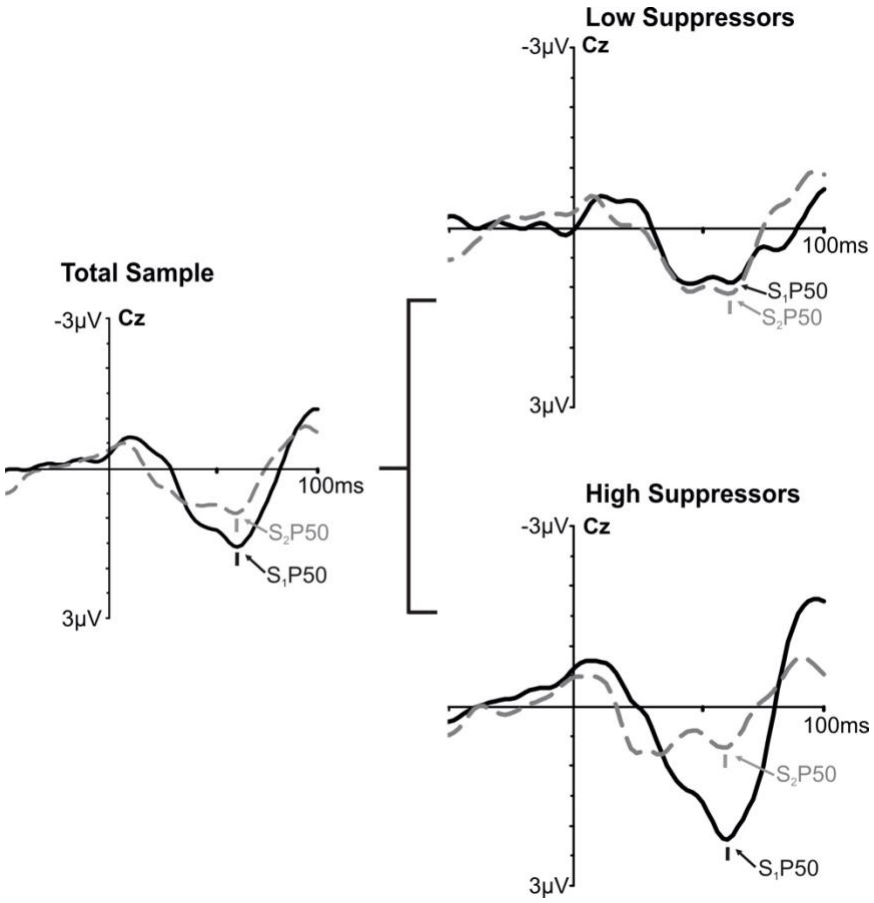

Figure 3.2 S_1P50 and S_2P50 response grand average waveforms at baseline (placebo) for the total sample (left; N = 24) and for stratified low (top right; N = 10) and high (bottom right; N = 14) suppressor subgroups.

Table 3.3 Mean (±SE) S_1P50 and S_2P50 amplitudes for high and low suppressor groups by drug conditions

Suppressor group	Drug condition	S_1P50 mean (±SE) amplitude (μV)	S_2P50 mean (±SE) amplitude (μV)
High	Placebo	2.62 (0.25)	1.01 (0.14)
	CDP-cho/Gal	2.01 (0.22)	1.33 (0.19)
Low	Placebo	1.40 (0.30)	1.39 (0.17)
	CDP-cho/Gal	1.77 (0.26)	0.82 (0.22)

(CDP-cho: CDP-choline; Gal: galantamine).

Analyses of treatment effects on S_1P50 and S_2P50 amplitudes revealed significant main effects for stimulus $F(1, 22) = 43.23$, $p < .001$, and significant stimulus x group $F(1, 22) = 7.09$, $p = .014$, and treatment x stimulus x group $F(1, 22) = 31.07$, $p < .001$ interaction effects.

Follow-up comparisons of the main stimulus effect across suppressor groups revealed greater S_1P50 amplitudes (M = 1.95 μV, SE ±0.16) compared to S_2P50 amplitudes (M = 1.14 μV, SE ±0.11) as expected.

Analysis of the main stimulus x group effect across treatments revealed that high suppressors (M = 2.31 μV, SE ±0.21) showed significantly ($p = .039$) larger S_1P50 amplitudes than low suppressors (M = 1.59 μV, SE ±0.25). Both suppressor groups, low (S_1P50 M = 1.59 μV, SE ±0.25; S_2P50 M = 1.11 μV, SE ±0.18) and high (S_1P50 M = 2.31 μV, SE ±0.21; S_2P50 M = 1.17 μV, SE ±0.15), exhibited significantly (low $p = .018$; high $p < .001$) greater S_1P50 (vs. S_2P50) amplitudes (Figure 3.1).

Follow-up comparisons of the treatment x stimulus x group interaction revealed that under baseline (placebo) conditions, low suppressors (M = 1.40 μV, SE ±0.30) expressed smaller ($p = .005$) S_1P50 amplitudes compared to high suppressors (M = 2.62 μV, SE ±0.25). Examination of treatment effects revealed that CDP-choline/galantamine (vs. placebo) significantly ($p = .006$) decreased S_2P50 amplitudes (Figure 3.3) in low suppressors (placebo M = 1.39 μV, SE ±0.17; treatment M = 0.82 μV, SE ±0.22). In high suppressors (S_1P50: placebo M = 2.62 μV, SE ±0.25; treatment M = 2.01 μV, SE ±0.22), CDP-choline/galantamine (vs. placebo) significantly lowered S_1P50 amplitudes ($p = .007$) and showed a trend ($p = .051$) toward increased S_2P50 amplitudes (S_2P50: placebo M = 1.01 μV, SE ±0.14; treatment M = 1.33 μV, SE ±0.19).

S_1P50 amplitudes were significantly greater than S_2P50 amplitudes for high suppressors under placebo ($p < 0.001$) and CDP-choline/galantamine ($p = .001$) conditions. Low suppressors expressed significantly greater S_1P50 (vs. S_2P50 amplitudes) under the active treatment conditions ($p < .001$) only.

Latency analyses yielded no significant findings.

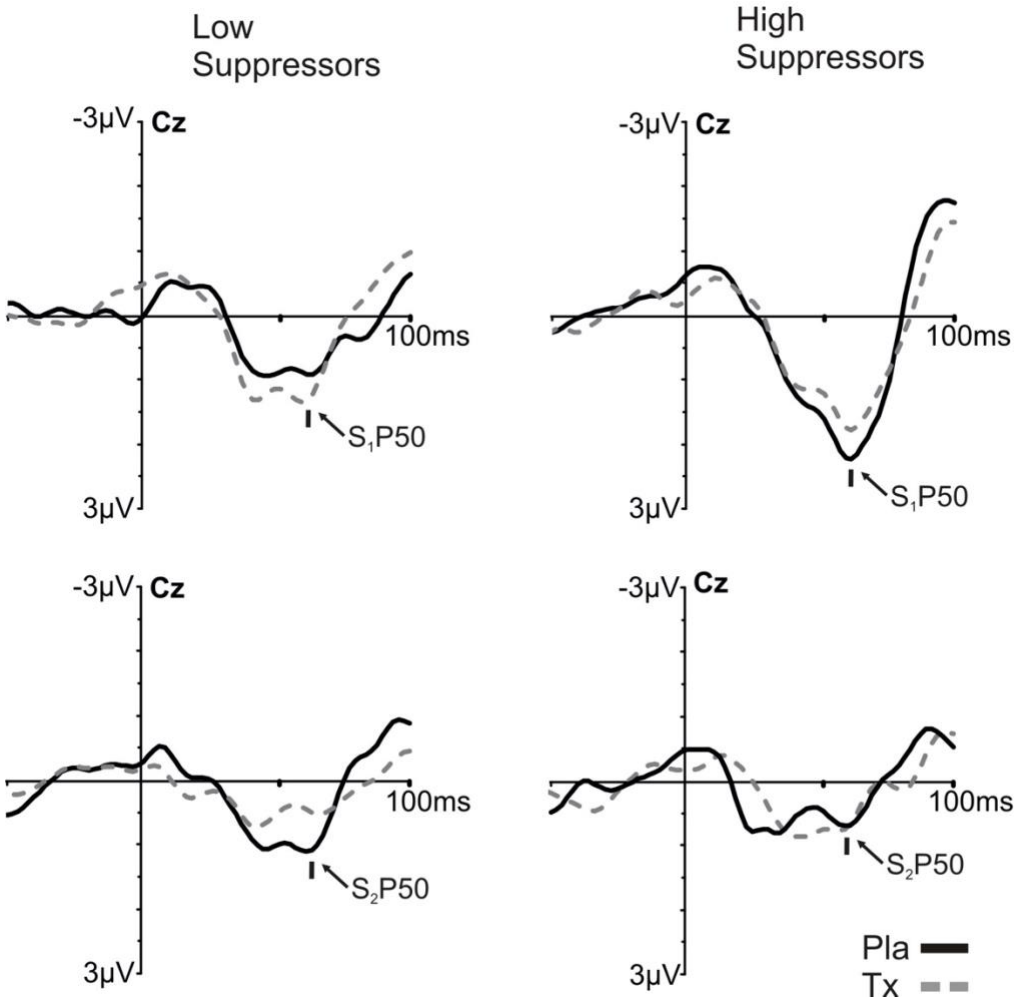

Figure 3.3 Grand averaged S_1P50 (top) and S_2P50 (bottom) ERP waveforms in low and high suppressors during placebo and CDP-choline (500 mg)/galantamine (16 mg) treatment.

3.6.5 PSYRATS – speech gating relationships

Spearman's rho analysis revealed that baseline (placebo) measures of P50 SG (rP50 and dP50) and S_2P50 amplitudes did not significantly correlate with PSYRATS total, distress, or controllability scores. S_1P50 amplitudes at baseline were negatively correlated ($\rho = -0.44$, $p = .015$) with the total PSYRATS score only.

Treatment-induced changes (derived by subtracting placebo values from treatment values) in dP50 gating and S_1P50 amplitude measures significantly correlated (dP50: $\rho = 0.40$, $p = .026$; S_1P50: $\rho = 0.38$, $p = .033$) to total distress subscale scores (Figure 3.4). These correlations indicate that participants reporting greater AVHs distress ratings expressed a better treatment response with respect to dP50 gating scores and S_1P50 amplitudes. Also, treatment-induced changes in rP50 gating and S_2P50 amplitude measures significantly correlated (rP50: $\rho = -0.41$, $p = .025$; S_2P50 $\rho = -0.40$, $p = .025$) to controllability subscale scores (Figure 3.5). Controllability scores range from 0 (controllability over the occurrence of voices) to 4 (no control over when the voices occur and no ability to dismiss them) therefore, participants reporting weaker controllability over voices (higher scores), expressed better treatment response with respect to rP50 gating scores and S_2P50 amplitudes. No relations were observed between treatment-induced changes in gating and amplitude measures and the PSYRATS total score.

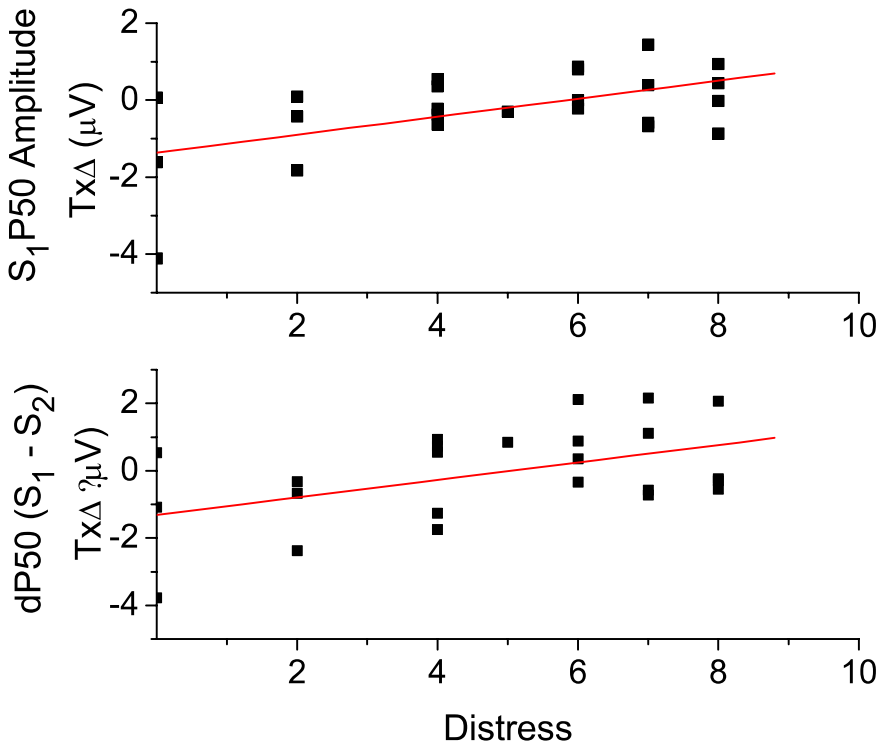

Figure 3.4 Scattergrams reflecting correlations of PSYRATS total distress scores with treatment effect (TxΔ) scores (treatment – placebo) for P50 difference (S_1–S_2; μV) and S_1P50 amplitudes. dP50 (ρ = 0.40, p = .026) and S_1P50 (ρ = 0.38, p = .033) TxΔ scores positively correlated with total distress ratings.

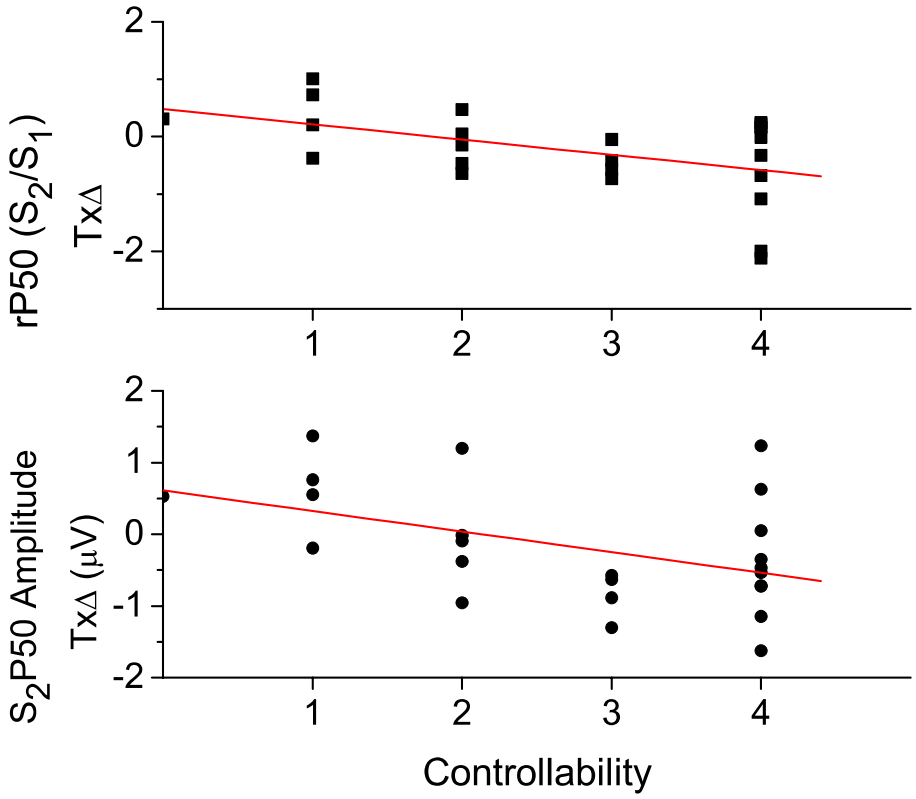

Figure 3.5 Scattergrams reflecting correlations of PSYRATS controllability scores with treatment effect (TxΔ) scores (treatment – placebo) for P50 ratio (S_2/S_1) and S_2P50 amplitudes (μV). rP50 (ρ = -0.41, p = .025) and S_2P50 (ρ = -0.40, p = .025) TxΔ scores negatively correlated with ratings of controllability (where scores 0-4 indicate reports of control - no control, respectively).

3.6.6 PANSS – speech gating relationships

Baseline (placebo) and treatment-induced changes in gating and amplitude measures were not related to PANSS total scores, or to any of the PANSS subscales scores based on two-tailed Spearman's analyses.

3.6.7 Adverse events

Analyses of the self-reports of adverse events related to the CDP-choline/galantamine administration, compared to the placebo condition, yielded no significant differences. There were no reports of severe symptoms during the course of the study.

3.6.8 Vital signs

Analyses of heart rate, systolic and diastolic blood pressure measures at placebo compared to measures at CDP-choline/galantamine yielded no significant findings.

3.7 Discussion

To the best of our knowledge, this study is the first to measure the modulatory effect of CDP-choline and galantamine on ERP measures of SG (rP50, dP50) to speech stimuli in patients with SCZ. Preliminary findings of improved speech SG indices in low P50 suppressors provide supportive evidence for additional trials, examining different dose combinations and repeated doses of this optimized α7 cholinergic treatment for the enhancement of sensory and cognitive dysfunction in SG biomarker defined patients with SCZ.

In line with our expectations, CDP-choline/galantamine (vs. placebo) significantly improved sensory inhibition (decreased rP50 and increased dP50 scores) of speech stimuli in low suppressors, while it exerted a tendency to increase rP50 and significantly reduce dP50 scores in high suppressors, paralleling our recent observations in healthy participants (Choueiry et al., 2019a). Previous examination of the combined CDP-choline and galantamine treatment in SCZ patients yielded improved scores on measures of global functioning and free verbal recall (Deutsch et al., 2013), and improved cognition, measured by the mini-mental state examination (MMSE), in patients with Alzheimer's disease with mild cognitive impairments (Gareri et al., 2017).

These results parallel our previous findings with CDP-choline (alone) on P50 SG to simple auditory stimuli (clicks) in healthy (Knott, Smith, et al., 2014), and SCZ (Aidelbaum et al., 2018) low suppressors subgroups and they compliment SG benefits of choline reported in neurodevelopmental studies in mice and humans (Ross et al., 2013; Stevens et al., 2014). Galantamine (alone) has also been shown to improve cognitive impairments in SCZ (Buchanan

et al., 2008) with additional synergistic effects shown when combined with memantine (Koola, 2018), an NMDA receptor antagonist, also recently shown to improve sensorimotor gating in SCZ (Swerdlow et al., 2016). The non-selective nAChR agonist nicotine has also been shown to modulate auditory sensory gating differently in low and high suppressors (Adler et al., 1992; de La Salle et al., 2013; Knott et al., 2010; Knott et al., 2013; Millar et al., 2011) and together, these observations suggest that selecting patients with specific SG criteria may be a more targeted and fruitful approach for the development of novel cholinergic agents aimed at treating sensory and cognitive processing deficits in SCZ.

A few compounds remain under active examination today and have shown cognitive and sensory gating benefits relevant for SCZ despite the challenges in drug development (i.e. receptor selectivity, drug potency and potential clinical benefit (vs. placebo), and critical adverse event) (Yang et al., 2017). BMS-933043, a partial α7 nAChR agonist that has advanced for phase-I clinical trial in humans, improved sensory gating in preclinical rodent models (Bristow et al., 2016). However, while AVL-3288, a type-I PAM, yielded inconclusive modulatory effects on P50 SG in SCZ patients examined in a phase-I clinical trial (Gee et al., 2017), increased neurotransmission in hippocampal slices and improved P50 SG deficits following JNJ-1930942, α7 selective PAM, administration were reported (Dinklo et al., 2011). Analogously JNJ-39393406 showed reversal of SG deficits in DBA/2 mice which did not translate in patients with SCZ (Winterer et al., 2013). Also, CCMI (Type-I α7 PAM), PNU120596 (Type-II α7 PAM) and A582941 (α7 agonist) all reversed induced sensorimotor impairments in a rat model of evoked cognitive disturbances (Potasiewicz et al., 2017). Notably, none of these clinical trials stratified participants based on baseline SG performance, a factor which could be of importance in

moderating treatment effects given the marked inter-individual variability in SG that has been extensively reported in SCZ and healthy individuals (Patterson et al., 2008).

In earlier studies examining 3-(2,4-dimethoxybenzylidene) anabaseine (DMXB-A), a selective α7 nAChR agonist, modulation of SG indices in SCZ mice models and patients showed S_2P50 mediated SG enhancements where increased inhibition of hippocampal pyramidal neurons was mediated by choline-enhanced interneuronal activity (Frazier et al., 1998; Miller & Freedman, 1995). In addition to increased activity in the hippocampus, SG-related modulation by neural cholinergic inputs has been reported in the pre-frontal and the temporal cortices (Boutros et al., 1999, 2013; Freedman et al., 1991; Javitt & Freedman, 2015). While the precise neural mechanism underlying SG processing and its response to cholinergic treatment in SCZ remain under examination today, increased α7 nAChR activation, following CDP-choline modulation, has been shown to mediate higher calcium influx and the release of multiple neurotransmitters including GABA, dopamine, Ach, glutamate, and kynurenic acid (Agut et al., 2000; Koukouli & Maskos, 2015). Recent experiments employing advanced technological procedures such as optogenetics, in vivo and in vitro patch-clamping techniques combined with single-unit recordings and multiphoton imaging have shown the involvement of nicotinic acetylcholine modulation of hippocampal astrocytes in higher order neuronal inhibition (Pabst et al., 2016).

Neuroimaging and neuroelectrophysiological experiments in SCZ continue to explore the neural mechanisms associated with deficient gating of auditory input in general, and speech/language stimuli in particular, and their modulation by α7 neurotransmission. The brain regions recently implicated in the human "nuclear auditory repetition suppression apparatus" (NARSA), thought to participate in SG (Boutros et al., 1999, 2013), have also been shown to be active during AVHs (de Leede-Smith & Barkus, 2013) and are associated with extensive nAChR

input (Dani & Bertrand, 2007) shown to be deficient (specifically α7) in SCZ (Wallace & Bertrand, 2015). AVHs and thought disorders have recently been associated with several anomalies in high-level language processes and low level-speech perception mechanisms in addition to structural (grey and white matter) anomalies inherent to SCZ (Brown & Kuperberg, 2015; Cavelti et al., 2018). Furthermore, deficiencies in the neural mechanisms responsible for speech detection were observed following multiple MEG-evoked oscillatory activity differences between SCZ patients and healthy participants (Hirano et al., 2008). While P50 SG deficits were previously shown to positively correlate with inhibitory deficits in the semantic memory network (Vinogradov et al., 1996), to date only a single study has examined speech P50m gating in SCZ and reported a correlation with the experienced severity of AVHs (Hirano et al., 2010). Of important relevance to speech, DMXB-A and galantamine have been previously shown to decrease alogia scores (a subscale measure of the Scale for the Assessment of Negative Symptoms) in SCZ patients (Buchanan et al., 2008; Freedman et al., 2008). Improvements of deficient speech P50 gating scores, measured in low suppressing SCZ patients, following CDP-choline/galantamine administration outlines the involvement of the cholinergic system in aberrant SG of speech in SCZ.

To the best of our knowledge, relationships between state/trait reports of AVHs and measures of P50 SG to click/speech stimuli have not been thoroughly examined. Relative to the associations between early SG, AVHs, and speech/language processing in SCZ, a secondary objective of this study was to investigate the modulation of treatment-response by ratings of AVHs in SCZ. P50 SG measures to click stimuli recently failed to correlate with AVH PSYRATS scores (Thoma et al., 2017), however, an earlier experiment in our laboratory was the first to reveal significantly greater AVHs PSYRATS scores in relation to reduced/impaired P50

gating indices to clicks (Smith et al., 2013). These results were recently supported by a study that found a negative correlation between PANSS item P3 ratings and P50 suppression scores in SCZ patients (Faugere et al., 2016). Our earlier results also showed PSYRATS distress scores to positively correlate with S_1P50 (to clicks) latency measures, in comparison, our current findings (P50 to speech stimuli) revealed positive correlations between greater emotional distress scores and treatment-change scores of dP50 scores and S_1P50 amplitudes. Emotional distress, has not been explicitly examined in relation to P50 SG in SCZ, however it has been associated with the experience and severity of negative symptoms (Ritsner et al., 2002; Selten et al., 2000). Furthermore, negative correlations between PSYRATS controllability scores and measures of dP50 SG and S_1P50 amplitudes in SCZ patients (Smith et al., 2013) were in line with earlier associations of PSYRATS controllability scores with sensorimotor deficits measured by the prepulse inhibition (PPI) of the startle response, repeatedly shown to be deficient in SCZ (Kumari et al., 2008). While AVHs controllability scores in the current study did not correlate with baseline (placebo) P50 SG measures and amplitudes, they negatively correlated with rP50 and S_2P50 treatment-change scores possibly reflecting varying speech-mediated (vs. clicks) suppression mechanisms. Moreover, the severity of AVHs and their associations with S_1 response-mediated gating, were related to neurophysiological processes in the temporal lobe (Smith et al., 2013). In comparison, our current results, highlighting associations of AVHs with rP50 and S_2P50-mediated treatment response, potentially implicate the frontal lobe and suggest interactions between AVHs and the cholinergic system. Contrary to an earlier report of positive correlations between P50m ratios and positive and negative symptoms (Hirano et al., 2010), speech P50 ERP SG indices and amplitudes did not correlate with PANSS total or sub-scale scores at baseline or with treatment-change scores which is in accordance with the results from

previous research studies employing similar experimental conditions (i.e. chronic SCZ patients and stable antipsychotic regimen) (Boutros et al., 2009; Thoma et al., 2005; Zhu et al., 2017).

3.7.1 Limitations

The cross-over repeated measures design and the double blinded and randomized treatment administration in chronic SCZ patients add to our study's strength and scientific validity, however, there are various limitations that need to be considered. The total sample size of twenty-four participants was further divided into rP50-based sub-groups potentially limiting the statistical power. Moreover, baseline SG, used to stratify participants into low/high suppressor groups, was derived from the placebo session, an additional preliminary/baseline session could eliminate any statistical interference. A single dose level of CDP-choline/galantamine was administered to SCZ patients in this pilot study. The positive findings support further examinations that assess different dose levels and different combinations of dose levels of each drug separately and in combination so as to better define a dose-response curve in patients. In addition, the long-term efficacy of these doses also needs to be evaluated in SCZ as it was recently examined in patients with Alzheimer's Disease where increasing cognitive performance enhancements were observed as the length of treatment increased (Gareri et al., 2017). This was only observed when an acetylcholine esterase inhibitor (donepezil, rivastigmine, or galantamine) was combined with CDP-choline (vs. exclusive acetylcholine esterase inhibitor administration).

Although galantamine can be criticized for not being highly selective to α7 nAChRs, a recent review deemed the use of highly selective compounds as a reductionist approach while comparing it to current successful neuroleptics that grant their success to their ability to modulate several receptor systems (Bertrand & Terry, 2018). In parallel it is also important to clarify that

while CDP-choline is highly selective for α7 nAChRs, several neurotransmitter systems are activated following α7 receptor activation (as previously discussed) and following the metabolism of CDP-choline. Cytidine and choline are derivatives of metabolized CDP-choline, and in turn choline can produce betaine which can increase serotonin levels in the brain by increasing the levels of its precursor S-adenosyl-L-methionine (Adibhatla et al., 2001). This suggests that while this combined CDP-choline/galantamine treatment targets α7 nAChRs specifically, the complex nature of the resulting pharmacodynamics implicates and may benefit other neural receptor systems.

Moreover, our combination treatment was examined in chronic SCZ patients with moderate PANSS and AVHs scores. The effectiveness of CDP-choline/galantamine in alleviating SG impairments also needs to be examined in first episode patients and other clinically defined subtypes of patients (e.g. hallucinating vs. non-hallucinating) in order to generalize these treatment effects and document treatment efficacy in the broad spectrum of SCZ disorder. The differential effect of this treatment strategy should also be examined in neuroleptic-naïve patients and patients who are not taking neuroleptics having an anti-cholinergic load in order to further assess possible drug interaction effects. Although low/high suppressor subgroups did not significantly differ in terms of patient smoking status (i.e., number of smokers and number of non-smokers in each group were not significantly different), the inclusion of smokers might be a limiting factor as any beneficial treatment effects in smokers may be attributed to the relief of smoking withdrawal symptoms despite the lack of significant differences between smokers and non-smokers for all P50 SG measures.

Importantly, while the speech P50 stimuli assessment in SCZ patients was a novel feature of this study, a direct comparison with the typical click/tone paradigm would benefit our

understanding of auditory gating specificity and potentially further expand our understanding of early speech processing mechanisms and how they might be modulated by nAChR-mediated neurotransmission enhancement. Lastly, this study focused solely on SG and how benefits in SG with this combined treatment may possibly impact other sensory and/or cognitive processes is unknown and requires examination. Previous work in healthy controls has shown CDP-choline to increase the mismatch negativity (MMN) ERP, an index of sensory memory (Knott, Impey, et al., 2015), to enhance performance across multiple cognitive domains in healthy volunteers with relatively poor performance ability (Knott, de La Salle, et al., 2015), and to facilitate executive function in SCZ patients expressing reduced SG (Aidelbaum et al., 2018).

3.8 Conclusion

The combined CDP-choline/galantamine treatment was well tolerated by all participants with no reports of adverse events. This optimized cholinergic treatment strategy was beneficial in alleviating SG impairments and improving SG rP50 and dP50 gating scores in SCZ patients expressing low baseline suppression. These findings also support the use of rP50 as a biomarker for facilitating precision α7 treatment, allowing for targeted evaluation of nicotinic cholinergic modulation of SG deficits in selected subgroups of SCZ patients, and suggesting potentially better treatment outcome in individuals experiencing little to no control over AVHs. Our findings tentatively support the involvement of α7 nAChR activity in speech gating in SCZ and the effectiveness of selectively targeting the α7 receptor with an adjunct cholinergic treatment to ameliorate this deficit.

Chapter 4

Effects of CDP-Choline and Galantamine on MMN Deviance Detection in Healthy Volunteers

4.1 Preface

Overview

The following manuscript aimed to examine in thirty-three healthy participants the effect of a single moderate dose of CDP-choline and galantamine on deviance detection of speech sounds indexed by MMN ERPs with participants stratified into low, medium, and high groups based on baseline MMN amplitudes.

Statement of author contribution

This study was designed by Dr. Verner Knott, with contributing input from Joelle Choueiry. The study setup was done by Joelle Choueiry and Dhrasti Shah. Paradigm programming with auditory speech stimuli was done by Joelle Choueiry, Derek Fisher, and Dylan Smith. Participant recruitment and screening were done by Joelle Choueiry and Crystal Blais. Recruited participants were clinically interviewed by Dr. Vadim Illivitsky. Administration of study tasks and ERP recording were done by Joelle Choueiry and Crystal Blais. ERP processing and analyses, statistical analyses, tables and figures and manuscript writing were done by Joelle Choueiry. The final manuscript was reviewed by all authors.

4.2 Title page

CDP-choline and galantamine, a personalized α7 nicotinic acetylcholine receptor targeted treatment for the modulation of speech MMN indexed deviance detection in healthy volunteers: A pilot study

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Declaration of interest: All authors declare not conflict of interest.

4.3 Abstract

The combination of CDP-choline, an α7 nicotinic acetylcholine receptor (α7 nAChR) agonist, with galantamine, a positive allosteric modulator of nAChRs, is believed to counter the fast desensitization rate of the α7 nAChRs and may be of interest for schizophrenia (SCZ) patients. Beyond the positive and negative clinical symptoms, deficits in early auditory prediction-error processes are also observed in SCZ. Regularity violations activate these mechanisms that are indexed by electroencephalography-derived mismatch negativity (MMN) event-related potentials (ERPs) in response to auditory deviance.

This pilot study in thirty-three healthy humans assessed the effects of an optimized α7 nAChR strategy combining CDP-choline (500 mg) with galantamine (16 mg) on speech elicited MMN amplitude and latency measures. The randomized, double-blinded, placebo-controlled, and counterbalanced design with a baseline stratification method, allowed for assessment of individual response differences.

Increases in MMN generation mediated by the acute CDP-choline/galantamine treatment in individuals with low baseline MMN amplitude for frequency, intensity, duration, and vowel deviants were revealed.

These results, observed primarily at temporal recording sites overlying the auditory cortex, implicate α7 nAChRs in the enhancement of speech deviance detection and warrant further examination with respect to dysfunctional auditory deviance processing in individuals with SCZ.

4.4 Introduction

4.4.1 Cognition in schizophrenia

Neurocognitive deficits across the schizophrenia (SCZ) spectrum disorder are now well established and reported over multiple cognitive domains including attention, memory, learning, and executive functioning, and are associated with poor functional outcome (Addington & Addington, 1993; Green et al., 2000, 2004; Hofer et al., 2005; Reichenberg et al., 2010; Tandon et al., 2009). Although not included in standard neurocognitive assessment batteries for SCZ, behavioural and electrophysiological measures of basic functions such as early auditory information processing (EAIP) have shown that cognitive dysfunction in SCZ encompasses a profound disturbance in low-level sensory processing that contributes substantially to the core clinical symptoms and impaired social and cognitive functioning (Javitt & Freedman, 2015; Javitt & Sweet, 2015). Despite the success in reducing and managing positive symptoms (e.g. hallucinations and delusions) with anti-dopaminergic antipsychotic drugs, these pharmacological approaches have been inadequate in treating sensory processing and cognitive impairments in SCZ, thus requiring the identification of new therapeutic targets following the initiatives and guidelines of the National Institute of Mental Health's Measure and Treatment Research To Improve Cognition in Schizophrenia (MATRICS) (Bertrand & Terry, 2018).

4.4.2 Targeting α7 nAChRs in schizophrenia

Initially, increased smoking rates in SCZ (40-90% vs. ~ 20% of the general population) (Cather et al., 2017; D'Souza & Markou, 2012) was suggested to reflect self-medication (but for alternative hypothesis see (Boggs et al., 2014, 2018; Wing et al., 2012)) for sensory/cognitive deficits mediated via nicotinic acetylcholine receptor (nAChR) pathophysiology (Kumari & Postma, 2005). Subsequently, nicotine (the primary psychoactive ingredient in tobacco and the

prototypical nAChR ligand) administration was also shown to mediate these improvements in SCZ and healthy individuals (Mackowick et al., 2014; Newhouse et al., 2011).

In parallel, the MATRICS identified α7 nAChRs selective targeting as a potential therapeutic strategy for ameliorating sensory/cognitive impairments following cumulative evidence suggesting the association of α7 nACHR pathophysiology with SCZ (Azzopardi et al., 2013; Braff, 2011; Jones et al., 2016; Mackowick et al., 2014). Reduced α7 nAChR expression in post-mortem brain regions (e.g. hippocampus, frontal cortex) important for sensory/cognitive processing (Court et al., 1999; Freedman et al., 1995; Guan et al., 2000) to the degree of global cognitive dysfunction (Martin-Ruiz et al., 2003). In addition, genetic studies have supported a chromosome 15q13-14 locus, the α7 nAChR coding site carrying the CHRNA7 gene, as a candidate region for both SCZ and the associated sensory (P50 gating) processing deficits (Leonard & Freedman, 2006). And, evidence suggesting the involvement of low (nicotine) affinity α7 nAChR in learning, memory, attention, and sensory processing (Azzopardi et al., 2013; Braff, 2011; Jones et al., 2016; Mackowick et al., 2014).

Pre-clinical and clinical experiments examining the effect of α7 nAChR orthosteric agonists on sensory/cognitive measures revealed mixed findings thus far with relatively greater success rates in pre-clinical mouse models of SCZ examining non-selective nicotine and α7-selective agonists (Hashimoto, 2015; Levin, 2012; Marcus et al., 2016; Poorthuis & Mansvelder, 2013; Potasiewicz et al., 2017; Stevens et al., 2015; Uteshev, 2014; Wallace & Bertrand, 2015; Yang et al., 2017). The translation to human studies has been challenging, and only minor sensory/cognitive enhancements are reported with failure to reach clinical significance (Lewis et al., 2017). U-shaped dose responses are often associated with nAChR agonists, differences in treatment dose (clinical studies), and α7 nAChR genetic, pharmacological, and expression

characteristics are thought to be potential factors that may account for translation barriers between rodent and human studies (Lewis et al., 2017). Also, the α7 nAChR has a fast desensitization rate under prolonged exposure to agonists (Bertrand & Gopalakrishnan, 2007; Changeux et al., 1998). As an alternate strategy, a recent interest in examining positive allosteric modulators (PAMs), which have been shown to increase receptor's binding affinity to agonists (Type-I) and to slow the desensitization rate (Type-II) (Wallace & Bertrand, 2015), resulted in the rescue of SCZ-like sensory/cognitive impairments in rodents (Levin, 2012; Marcus et al., 2016; Poorthuis & Mansvelder, 2013; Potasiewicz et al., 2017; Stevens et al., 2015; Uteshev, 2014; Wallace & Bertrand, 2015; Winterer et al., 2013; Yang et al., 2017). However, PAMs have failed to reproduce these effects in clinical trials (Winterer et al., 2013).

4.4.3 Auditory sensory processing in schizophrenia

EAIP deficits in SCZ are widely studied with the mismatch negativity (MMN) event related potential (ERP). Typically observed in the context of an auditory "oddball" paradigm, the MMN negative potential (peaking at 150-250 ms) is maximal at frontal-central scalp sites (with phase reversal at mastoids). The interruption of a sequence of standard identical auditory stimuli by a stimulus that deviates from the standard in any physical dimension (e.g. pitch, duration, intensity) or even by its omission elicits the MMN ERP. Recorded under conditions requiring no behavioural response or attention by the participants, the MMN reflects the pre-attentive processing of an acoustic change in the environment. The auditory change detection requires a sensory memory trace of the sound environment and the violation of the regularity elicits a prediction-error indexed by the MMN generated in tandem in the temporal auditory and frontal cortices (El Karoui et al., 2015; Javitt, 1996, 2000; Rosburg et al., 2005). With more than 200 citations, the MMN response's high replicability in SCZ has also yielded associations of SCZ trait aspects and pathological processing with MMN amplitude reductions following duration

and frequency deviants respectively (Näätänen et al., 2016). In children at high-risk, the MMN ERP has been shown to be a strong predictor of conversion to psychosis (Bodatsch et al., 2011; Perez et al., 2014) and, although it is not affected by antipsychotic treatment, the MMN is able to predict the likelihood of treatment response (Light et al., 2015). MMN is considered one of the few mature translatable brain markers for developing new drugs or therapeutic methods for SCZ (Butler et al., 2012; Green et al., 2009; Nagai et al., 2013; Tada et al., 2019; Todd et al., 2013) , with evidence associating MMN improvement with significant improvements in higher-order cognitive processing measures of attention and memory (Javitt et al., 2018).

4.4.4 MMN modulation via nAChR

Deviance detection is robustly modulated by NMDA (N-methyl-D-aspertate) receptor agonists (Greenwood et al., 2018; Kantrowitz, Epstein, et al., 2018; Kantrowitz et al., 2016) and antagonists in animal and human studies (Javitt, 1996; Swerdlow et al., 2016; Tikhonravov et al., 2008). Pursuing pharmacotherapies aiming for NMDA receptor activity enhancement is supported by the glutamatergic hypothesis in SCZ which highlights the association of glutamatergic system impairments (i.e. Lower glutamate levels and decreased functioning of NMDA receptors) with decreased measures of deviance detection which is also associated with lower levels of cognitive functioning and the severity of negative symptoms (Coyle et al., 2012; Javitt et al., 2012; Kantrowitz & Javitt, 2010; Moghaddam & Javitt, 2012). Furthermore, it was recently highlighted that α7 nAChR have the potential to modulate glutamatergic and NMDA receptor signaling in the hippocampal CA1 region (Bali et al., 2017, 2019).

Multiple findings have supported nicotine-mediated MMN improvements in healthy individuals (Baldeweg et al., 2006; Dunbar et al., 2007; Featherstone & Siegel, 2015; Hamilton, D'Souza, et al., 2018; Harkrider & Hedrick, 2005; Inami & Kirino, 2019; Martin et al., 2009) while other studies failed (Inami et al., 2005, 2008; Knott et al., 2011; Martin et al., 2009;

Mathalon et al., 2014). Similar mixed findings were observed in SCZ (Dulude et al., 2010; Featherstone & Siegel, 2015; Fisher, Grant, et al., 2012; Inami et al., 2008; Inami & Kirino, 2019). Inter-study differences in dose and route of nicotine administration (smoke, transdermal patch, gum), deviant type (pitch, duration, intensity), and smoker vs. non-smoker status (Inami & Kirino, 2019) are contributing factors to the lack of consistancySelective α7 agonists also exerted mixed effects on MMN response in rodent models of SCZ and clinical trials. EVP-6124 is a recent example of a potent α7 nAChR agonist that illustrated a tendency to modulate MMN amplitudes in a dose-depend manner (although it failed to reach statistical significance)(Kohlhaas et al., 2015; Preskorn et al., 2014). However, α7 nAChRs are characterized with a fast desensitization rate when exposed to an agonist (Albuquerque et al., 1998; Mike et al., 2000; Zhang et al., 1994), despite employment of a slow-release method (Kem et al., 2018), suggesting a role for optimizing α7 nAChR's pharmacokinetics in future studies by targeting α7 receptors with PAMs or with concurrent α7 agonist and PAM treatments.

To date, few PAMs have completed human clinical trials and only JNJ39393406, a selective α7 PAM, has been examined on MMN in patients with SCZ which failed to yield significant findings even after participants were subgrouped with respect to CHRNA7 genotype (Winterer et al., 2013).

A novel activation strategy consisting of the combination of a nAChR agonist and a PAM (Deutsch et al., 2008a) was introduced by combining choline (the precursor and metabolite of acetylcholine which has α7 nAChR agonist actions), in the form of the dietary supplement cytidine 5'-diphosphocholine (CDP-choline) with galantamine (a nAChR PAM and cholinesterase inhibitor). Initially examined in clinical and healthy non-clinical control populations, this combination treatment also yielded mixed findings of non-significant clinical

(positive and negative symptoms) improvements and significant minor auditory verbal memory performance improvements (Deutsch et al., 2013; Deutsch et al., 2008a,b). Our laboratory recently reported on the acute enhancing effects of this optimized strategy on EAIP, with ERP measures of auditory (P50) sensory gating (the ability to suppress or inhibit response to irrelevant/redundant stimuli) being improved both in healthy participants (Choueiry et al., 2019a) and individuals with SCZ (Choueiry et al., 2019b) in a baseline-dependent manner (selectively enhancing gating in poor gaters).

The neurodevelopmental effect of CDP-choline showed improved SG scores following gestational choline supplementation, in DBA/2 mice that carried the wild-type α7 nAChR gene (chrna7) (Stevens et al., 2014), and in newborn infants (Ross et al., 2013). CDP-choline administered alone improved higher-order cognitive functioning in neurological disorders (Gareri et al., 2015; Sarkar et al., 2012; Secades, 2011). Its acute administration was shown by our laboratory to enhance multiple domains of cognitive functioning (Knott, de La Salle, et al., 2015) in a baseline-dependent manner (i.e., increasing cognition in low performers) and to improve SG (Knott, Smith, et al., 2014) in healthy individuals and in SCZ patients who exhibited impaired P50 gating measures (Aidelbaum et al., 2018). CDP-choline also exerted MMN amplitude increases in healthy individuals with low baseline deviance detection(Knott, Impey, et al., 2015) .

Galantamine alone has been shown to improve cognitive impairments (Buchanan et al., 2008) and has been suggested to be a potential EAIP enhancer when combined with memantine (Koola, 2018), an NMDA receptor antagonist that has been shown to improve sensorimotor gating in SCZ (Swerdlow et al., 2016).

4.4.5 Individual differences in response to nicotinic treatments

Genetics, smoking status, personality, and level of functioning are trait factors previously shown to influence response variability to treatments and to nicotine specifically (Gilbert & Gilbert, 1995; Kupferschmidt et al., 2010; Li et al., 2009; Perkins, 1995, 2009; Poltavski & Petros, 2005). Nicotinic modulation of performance on behavioural and cognitive tasks in animal models and human studies has been shown to depend on baseline performance levels: individuals with low-performance levels tend to show increases in performance with nAChR stimulation, while those with optimum performance levels show decreases in performance (Newhouse et al., 2004; Perkins, 1999; Picciotto, 2003). Nicotinic effects on neurophysiological indices of cognitive functioning (antisaccades and sensory gating) have also been shown to be baseline-dependent (Ettinger et al., 2009; Knott et al., 2010, 2013; Petrovsky et al., 2012). In light of developing targeted and personalized treatments, stratification with baseline performance or electrophysiological biomarkers (P50 and MMN) into low, medium, and high functioning groups is an increasingly informative approach. Baseline stratification has a translatable potential for identifying types of individuals who are most responsive to the sensory/cognitive enhancing properties of nAChR stimulation. Most recently, this translational approach has been applied in healthy volunteers to assess the effects of nicotine/CDP-choline on sensory gating (Knott et al., 2013; Knott, Smith, et al., 2014), MMN (Knott, Impey, et al., 2014, 2015), P300 (Hyde et al., 2016), and cognition (Knott, de La Salle, et al., 2015). Baseline stratification was also used to assess the effects of antipsychotics on sensory gating in SCZ (Adler et al., 2004, 2005). In general, nAChR stimulation resulted in enhanced sensory/cognitive responses in low responding/performing individuals. Recent results from our laboratory with this translational approach reported that combined low-dose CDP-choline and galantamine benefitted healthy individuals with poor baseline gating while hindering those with optimal baseline sensory gating

(Choueiry et al., 2019a). These findings were subsequently extended with reports of significantly enhanced sensory gating in SCZ patients with low (vs. high) gating following CDP-choline and galantamine(Choueiry et al., 2019b). This stratification strategy based on individual performance/neurophysiological measures was recently highlighted as a support for implementing personalized interventions with synergy between targeted therapy (which targets specific neural systems) and targeted individuals expected to better respond and benefit from the given treatment/therapy (Fisher & Salisbury, 2019).

4.4.6 Objectives and hypotheses

Prior to implementing clinical trials on individuals with SCZ to determine if the enhanced auditory sensory gating seen with our optimized nicotinic treatment, consisting of CDP-choline and galantamine, extends to other sensory functions, we aimed to use this translational model in healthy volunteers to examine its effects on auditory deviance detection with MMN. Employing an advocated within-subject challenge dose design (placebo vs. active) in biomarker (MMN) defined low, medium, and high subgroups (surrogate populations, the full group was split into three subgroups given that the full sample size allowed for subgroups of 11 participants) that have no symptom profile and without the confounds (e.g. medication, disease chronicity, symptom variability) associated with the SCZ disorder (Chou et al., 2012; Koychev et al., 2012). In order to increase the translational relevance of this study, we assessed MMN in response to speech (vs. simple tone) stimuli as abnormalities in language perception, interpretation, and production are integral to the SCZ syndrome and have been associated with auditory hallucinations (Brown & Kuperberg, 2015). Speech and language impairments have been extensively studied using MMN (Fisher et al., 2008; Kasai et al., 2002; Kawakubo et al., 2006, 2007; Yamasue et al., 2004), where speech (vs. non-speech) MMN stimuli have illustrated more robust MMN impairments in SCZ in comparison to healthy individuals (Fisher et al., 2008;

Kasai et al., 2002). The underlying neural mechanisms involved in speech abnormalities seen in SCZ are not yet well understood and further examination of their modulation by nAChR agonist in a speech MMN paradigm might yield more insight into the potential association of this neurotransmitter system with speech discrimination impairments. Based on previous work with this approach, the combined nicotinic treatment is expected to alter MMN response to speech stimuli relative to placebo, with increased MMN being observed in low MMN responders and reduced MMNs being elicited in moderate-high MMN responders.

4.5 Materials and methods

4.5.1 Subjects

Thirty-three healthy male (26) and female (7) volunteers (mean age of 40.2; SE ± 2.02) were recruited in this study. Participants underwent a medical and psychiatric interview following eligibility screening with the DSM-IV Structured Clinical Interview, non-patient version (SCID-NP; (Williams et al., 1992)) and the Family Interview for Genetic Studies (FIGS; (Maxwell, 1992)). The SCID-NP assessed participants for illicit substance abuse/dependence and personal psychiatric history. The FIGS questionnaire was employed to confirm that eligible volunteers have no history of psychiatric illnesses in their first-degree relatives. Eligible volunteers verbally confirmed having no past or current DSM-IV disorders, no significant medical/neurological illness (including head trauma/seizure), and that they were not currently consuming any prescription medications, any herbal medicines/supplements or any over-the-counter medications.

Recruited volunteers (17 smokers; 16 non-smokers) had normal laboratory and drug screen tests, normal weight, and normal hearing as verified by audiometric testing. Non-smokers were defined as having smoked less than one hundred cigarettes in their lifetime and had not consumed any tobacco products during the past year. Smokers smoked on average M = 14, SE

±1.3 cigarettes per day for an average of M = 22, SE ±3.5 years. Recruitment of healthy volunteers and study procedures were approved and complied with the guidelines of the Research Ethics Boards of The Royal Ottawa Mental Health Care Group and the University of Ottawa. Participants signed an informed consent form before taking part in the study and obtained $75 upon completion.

4.5.2 Experimental design

Healthy volunteers were assessed during two separate sessions (a placebo and a CDP-choline + galantamine session) in a randomized, repeated-measures, double-blind, placebo-controlled, crossover, and counterbalanced design. A minimum of seven days separated testing sessions in order to allow for treatment (CDP-choline) washout.

4.5.3 Drug administration

While typical daily doses in clinical trials range from 1000 to 4000 mg, in general, lower doses of nicotinic agonists have been evidenced to have optimal effects, with dose-response curves of nAChR agonists taking the shape of an inverted U (Castner et al., 2011; Hahn et al., 2002; Prickaerts et al., 2012; Werkheiser et al., 2011). As our previous studies with CDP-choline and combination treatment (CDP-choline plus galantamine) showed EAIP and cognitive improvements with relatively low (500 mg, 100mg) of CDP-choline, this study administered a 500 mg (2 x 250 mg capsules) dose of CDP-choline and 16 mg of galantamine (250 mg capsule filled with 234 mg of cellulose) were administered orally in capsules identical to the placebo (250 mg of cellulose) capsules in shape, size and colour. CDP-choline and galantamine have no reports of serious adverse events at these administered doses. In healthy subjects, CDP-choline (Citicoline) peaks in the plasma ~2-3 hours after administration while galantamine has a maximum plasma concentration-time range between 0.5 to 2 hours (Wurtman et al., 2000).

4.5.4 Experimental procedures

Participants attended a screening session and two testing sessions. They received a reminder and informative phone call the evening before a testing session instructing them to abstain from food, drugs, alcohol, caffeine, and cigarettes from midnight until their arrival to the laboratory (between 8:00 a.m. and 11:30 a.m.). Smoking abstinence was verified, by measuring exhaled carbon monoxide (CO) levels (< 3 p.p.m. for non-smokers and less than the exhaled CO level at the screening session for smokers), before administration of placebo CDP-choline or active CDP-choline capsules (time 0 minutes). Participants were then asked to remain seated and relaxed in a dimly lit and sound-attenuated testing chamber while watching an emotionally neutral movie for a 60-minute absorption period, after which time placebo galantamine or active galantamine capsules were administered, and an additional treatment absorption period of 30 minutes followed. The speech MMN paradigm and ERP recordings were subsequently initiated near peak CDP-choline/galantamine absorption time (at ~ 90 minutes). Vital signs (before treatment administration and at peak absorption time) and adverse events (at the end of testing) were collected for safety reasons only.

4.5.5 MMN paradigm

4.5.5.1 Stimuli

Participants were instructed to remain seated and relaxed as they watched a silent video (The Blue Planet by BC, 2001) during the presentation of a fast multi-feature speech MMN paradigm using tested and validated semi-synthetic Finnish-language consonant-vowel /te:/ and /pi:/ stimuli (Pakarinen et al., 2009) projected binaurally through noise cancelling headphones. The standard stimuli were syllables /te:/ and /pi:/, had a fundamental frequency (F0) of 101 Hz, a syllable duration of 170 ms, and an intensity of 70 dB (SPL). Five types of deviant stimuli were used and differed from standard stimuli either in syllable frequency (FRE), intensity (INT),

vowel duration (VOWDUR), and consonant (CONS) or vowel (VOW) change. FRE deviants were 8% higher or lower (F0 ±8%, 93/109 Hz;). INT deviants were 50% quieter and 50% louder by 6dB. VOWDUR deviants were shorter by 70 ms. CONS deviants in the two blocks using /te/ standards were /pe/ syllables, while in the other two blocks using /pi/ standards the deviants were /ti/ syllables. VOW deviants in the two blocks using /te/ standards were /ti/ syllables, while in the other two blocks using /pi/ standards the deviants were /pe/ syllables.

4.5.5.2 Presentation

The stimuli were presented in accordance to the presentation sequence employed in the Optimum-1 MMN paradigm (Näätänen et al., 2004) where every other syllable was a standard (p = 0.5) and every other was one of the 5 deviant syllables (p = 0.1, each deviant type). Four 5-minute sequence blocks were presented, each including 465 syllables for a total of 1860 stimuli. The first 5 syllables in each block were always standards. /te:/ syllables were the standard syllables in two of the sequence blocks with deviants consisting of FRE/te:/, INT/te:/, VOWDUR/te/, CONS/pe:/, and VOW/ti:/. In the other two sequences, /pi:/ syllables were the standard syllables with the deviants consisting of FRE/pi:/, INT/pi:/, VOWDUR/pi/, CONS/ti:/, and VOW/pe:/. In an array of ten successive stimuli, all five deviants were pseudo-randomized to appear once and the same deviant was never repeated after the standard following it. The presentation order of the /te:/ and /pi:/ sequence blocks was randomized amongst participants.

4.5.6 ERP recording and processing

EEG signals were recorded using Brain Vision Quickamp® (Brain Products, Gmbh, Munich, Germany) amplifier and Brain Vision Recorder® software with amplifier bandpass filters set at 0.1 to 70 Hz and continuous digitization at 500 Hz. Thirty Ag^{+}/Ag^{+} Cl^{-} scalp electrodes were positioned at sites: Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T7, T8, P7, P8, Fz, Cz, Pz, Oz, Fc1, Fc2, Cp1, Cp2, Fc5, Fc6, Cp5, Cp6, Tp9, and Tp10 according to the 10/10 international

system (Jurcak et al., 2007). A reference electrode was placed on the nose and a ground electrode was positioned at AFz site. Electrodes on the supra- and sub-orbital ridges of the right eye, and on the external canthus of both eyes were used to monitor vertical (VEOG) and horizontal electro-oculographic (HEOG) activity. Electrode impedance was kept below 5 kΩ throughout the recording session.

EEG signals were processed offline and analyzed using Brain Vision Analyzer® (Brain Products, Gmbh, Munich, Germany) software. The raw signals were digitally filtered (24 dB/octave) with low-high cutoff window of 1 – 20 Hz, ocular-corrected (Gratton et al., 1983), segmented into 500 ms epochs (beginning 100 ms pre-stimulus), submitted to automatic artifact rejection (eliminating epochs with voltage exceeding ± 75 µV), and baseline-corrected relative to the 100 ms pre-stimulus electrical activity. The epochs were then separately averaged for each stimulus type. To delineate the MMN ERP, the standard waveform voltage values were subtracted digitally point-by-point from the values of each respective deviant waveform. For the main purpose of our study, MMN peak amplitude (quantified relative to the average pre-stimulus amplitude) and latency were measured as the greatest negative peak occurring at 100–250 ms (based on grand average waveforms) after stimulus-onset. Peak amplitudes and latencies were extracted for frontal (F_z, F_3, and F_4) and also mastoids (TP_9 and TP_{10}) sites where prominent polarity-inverted peaks are observed in reference to electrical activity at the nose as previously observed (Näätänen et al., 2004). The original study employing the fast multi-feature Finnish speech paradigm used the left and right mastoids for reference purposes hence did not use these for analysis (Pakarinen et al., 2009).

4.5.7 Adverse events

At the end of each testing session, a checklist of physical and psychological adverse events was administered. Participants were asked to rate the severity of symptoms experienced following treatment administration on a scale from 1 (no symptom at all) to 5 (severe symptom).

4.5.8 Vital signs

Sitting heart rate, systolic and diastolic blood pressure measures were assessed before treatment administration (at time 0 minutes) and at peak absorption time (~ 90 minutes) for safety purposes only.

4.5.9 Statistical analysis

The Statistical Package for the Social Sciences software (SPSS, IBM Corporation, New York, USA) was used for all data analyses. All data were analyzed using recorded MMN measures from frontal (Fz, F3, F4) and temporal (TP9, TP10) electrode sites separately.

Separate univariate, mixed analysis of variance (ANOVA) with treatment (two levels, placebo treatment vs. CDP-choline/galantamine treatment) and electrode scalp position (three levels: Fz, F3, F4; or two levels: TP9, TP10) as within-subject factors were used to initially analyze the overall effect of the active CDP-choline/galantamine treatment on measures of MMN amplitudes for each deviant type. MMN latency ANOVAs were performed separately for each site (Fz, TP9, and TP10) comparing placebo treatment to the active CDP-choline/galantamine treatment. Significant (Greenhouse-Geisser corrected when appropriate) effects ($p < 0.05$) were followed up with Bonferroni-adjusted planned comparisons.

In order to assess treatment effects within our translational approach, MMN activity during the placebo treatment condition was used to sub-group the total sample of participants into groups of low, medium, and high amplitude individuals separately for each deviant type. For this purpose, placebo session amplitudes at midline frontal (Fz) were used to rank participants from

the lowest to the highest for each of the 5 MMN deviant types. The sample of 33 individuals was divided into three groups of 11 participants. The “low” group (LG) consisted of the 11 participants with the smallest amplitudes, while the “high” (HG) group consisted of the 11 participants with the largest amplitudes. The remaining 11 participants consisted the “medium” (MG) group. To assess treatment effects at the temporal sites, the same stratification method was used to rank participants into LG, MG, and HG based on the left and right temporal sites (TP9 and TP10) amplitudes, averaged and sorted from lowest to highest. CDP-choline/galantamine treatment effects on each speech MMN were analyzed using separate univariate mixed ANOVAs for each deviant, with group (three levels: low, medium, high) as a between-subjects factor and treatment (two levels: placebo, CDP-choline/galantamine), and scalp site (three levels: Fz, F3, F4; or two levels: TP9, TP10) as within-subjects repeated measures factors. Significant (Greenhouse-Geisser corrected when appropriate) effects ($p < 0.05$) were followed up with Bonferroni-adjusted planned comparisons. As any group differences in treatment response may reflect a ‘regression to the mean' effect, similar ANOVAs were conducted with participants stratification using active treatment (i.e., not placebo) MMN scores.

Fisher’s test and chi-square analyses were conducted to compare LG, MG, and HG subgroups in relation to gender, and smoking status. One-Way ANOVA analyses were used to compare subgroups based on age. The Spearman’s correlation statistic was additionally used to examine the relationship between baseline MMN measures with treatment-induced MMN change (indexed by difference scores [CDP-choline/galantamine MMN amplitude – placebo MMN amplitude]). Correlations were conducted with MMNs recorded from the mid-frontal recording site (Fz) and with the right, and left temporal sites (TP9, TP10) separately and combined.

4.6 Results

The total sample of participants (N = 33; M_{age} = 40.2 years, SE ±2.02) consisted of 7 females and 26 males, 16 non-smokers and 17 smokers. Demographic data for each deviant-specific baseline low (LG), medium (MG), and high (HG) amplitude responder subgroups are presented in Table 4.1. One-Way ANOVA, Fisher's exact test (FET), and Chi-square analyses confirmed that low, medium and high sub-groups were not statistically different regarding age, gender, and smoking status (respectively) for all deviants.

Table 4.1 Demographics for LG (N=11), MG (N=11), and HG (N=11) amplitude subgroups for each MMN deviant type.

Deviant type	Group	Age (mean ± SE)	Sex (F/M)	Smoking status (NS/S)
Frequency	LG	39 (3.44)	3/8	4/7
	MG	41.6 (3.89)	1/10	6/5
	HG	39.9 (3.46)	3/8	6/5
		F(2,30) = 0.138, p = .871	FET = 1.521, p = .649	$X^2(2)$ = .971, p = .616
Intensity	LG	40.6 (3.60)	2/9	3/8
	MG	38.8 (3.09)	3/8	7/4
	HG	41.1 (4.06)	2/9	6/5
		F(2,30) = 0.111, p = .895	FET = 0.499, p = 1.00	$X^2(2)$ = .971, p = .616
Duration	LG	39 (3.25)	3/8	6/5
	MG	38.9 (4.20)	1/10	4/7
	HG	42.6 (3.20)	3/8	6/5
		F(2,30) = 0.354, p = .705	FET = 2.332, p = .439	$X^2(2)$ = 4.610, p = .100
Consonant	LG	42 (3.04)	5/6	4/7
	MG	38.3 (4.01)	1/10	5/6
	HG	40.3 (3.64)	1/10	7/4
		F(2,30) = 0.271, p = .765	FET = 0.499, p = 1.00	$X^2(2)$ = .971, p = .616
Vowel	LG	39.1 (3.97)	3/8	5/6
	MG	40.1 (3.76)	2/9	4/7
	HG	41.4 (3.03)	2/9	7/4
		F(2,30) = 0.100, p = .905	FET = 2.332, p = .439	$X^2(2)$ = .243, p = .886

F/M: female/male; NS/S: non-smokers/smokers; LG/MG/HG: low, medium, high amplitude groups; FET: Fisher's exact test.

4.6.1 MMN amplitude measures

4.6.1.1 Frontal (Fz, F3, and F4) electrode sites

Total group

Grand averaged deviant minus standard difference waveforms for each deviant type during placebo and CDP-choline/galantamine treatment are shown in Figure 4.1. A significant ($p < 0.05$) main site effect was observed for all deviant types indicating that larger MMN amplitudes were recorded at the mid-frontal (Fz) electrode site in comparison to the left- and right-frontal hemisphere sites (F3 and F4). Also, significantly larger MMN amplitudes at the right F4 electrode site (vs. F3) were recorded for frequency (M_{F3} = -1.04 µV, SE ±.10; M_{F4} = -1.24 µV, SE ±.11; p = 0.004) and duration deviants (M_{F3} = -1.11 µV, SE ±.07; M_{F4} = -1.34 µV, SE ±.07; p = 0.008). CDP-choline/galantamine treatment showed no significant impact on MMN amplitudes for all deviant types, and no interaction effects were observed.

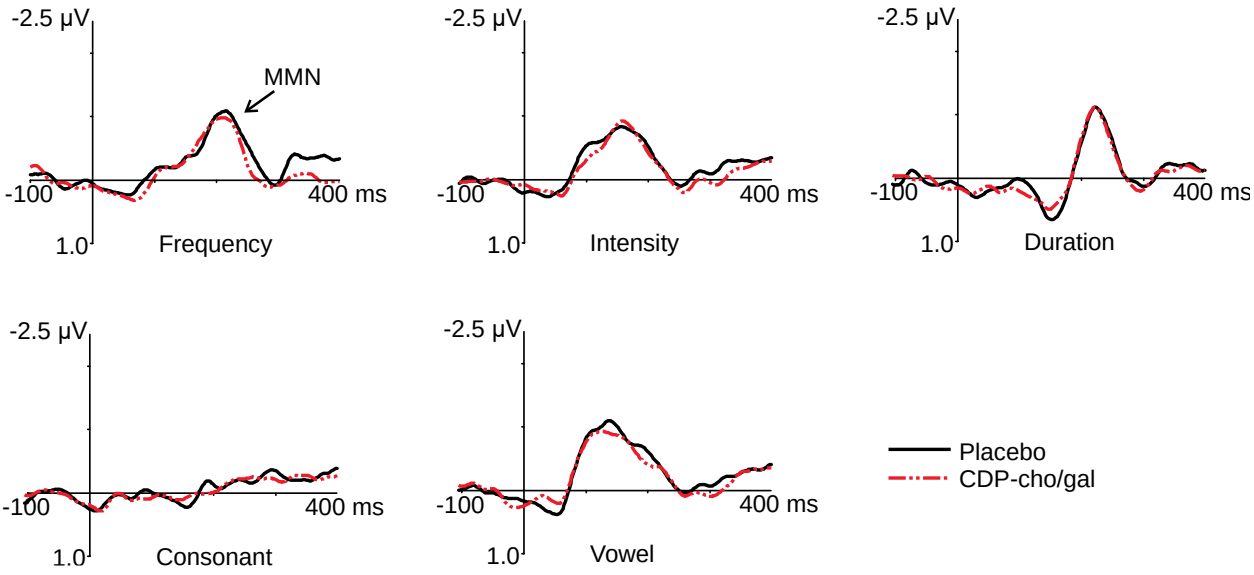

Figure 4.1 Frontal (Fz) ERP grand averaged subtracted difference waveforms (deviant minus standard) for the 5 mismatch negativity deviants during placebo and CDP-choline/galantamine (CDP-cho/gal) conditions

Group comparisons

Independent MMN analyses for each deviant type at frontal Fz, F3, and F4 sites revealed no main treatment effect for any of the 5 deviants. Significant ($p < 0.01$) main site effects were observed for all deviant types with greater MMN amplitudes at the mid-frontal (Fz) site in comparison to left (F3) and right (F4) frontal hemisphere sites.

As expected, main group effects were observed for frequency ($F(2,30) = 34.16$, $p < 0.001$), intensity ($F(2,30) = 19.07$, $p = 0.001$), vowel duration ($F(2,30) = 14.05$, $p < 0.001$), consonant change ($F(2,30) = 21.56$, $p < 0.001$) and vowel change ($F(2,30) = 10.36$, $p < 0.001$) deviants (Figure 4.2). LG individuals expressed significantly smaller MMN amplitudes (across placebo and active treatment conditions) in comparison to MG and HG individuals, for pitch ($p = 0.038$; $p < 0.001$), intensity ($p = 0.001$; $p < 0.001$), consonant ($p = 0.010$; $p < 0.001$), and vowel ($p = 0.009$; $p < 0.001$). For duration deviants the LG was only significantly ($p < 0.001$) different from the HG. MG individuals showed smaller MMN amplitudes in comparison to HG

individuals for frequency ($p < 0.001$), duration ($p = 0.005$), and consonant ($p = 0.006$) deviants only.

Significant group x treatment interactions were observed for consonant $F(2,30) = 4.84$, $p = .015$ and vowel $F(2,30) = 5.06$, $p = .013$ change deviants. LG participants displayed greater vowel MMN amplitudes ($p = .050$) under CDP-choline/galantamine treatment conditions ($M = -1.10$ µV, SE ±.20) in comparison to placebo ($M = - 0.70$ µV, SE ±.08) (Figure 4.3). The active treatment did not impact MMN amplitudes for any other deviant in the LG. HG individuals demonstrated reduced MMN amplitudes in response to consonant ($p = .010$) and vowel ($p = .022$) deviants under the active treatment condition ($M_{con} = -0.77$ µV, SE ±.16; $M_{vow} = -1.40$ µV, SE ±.20) in comparison to placebo ($M_{con} = -1.30$ µV, SE ±.13; $M_{vow} = -1.87$ µV, SE ±.08). No significant interactions were observed for MG participants.

A significant site x group interaction was observed for consonant deviants only $F(4,60) = 3.12$, $p = .027$. Planned follow-up comparisons revealed that MMN amplitudes for the LG, MG, and HG groups were significantly ($p < .05$) different at all frontal sites (Fz, F3, F4) with an exemption at F3, where MG and HG groups were not shown to be significantly different. Also, HG participants were the only group to express significantly ($p = .001$) larger amplitudes at Fz ($M = -1.19$ µV, SE ±.13) in comparison to F3 ($M = -0.85$ µV, SE ±.11).

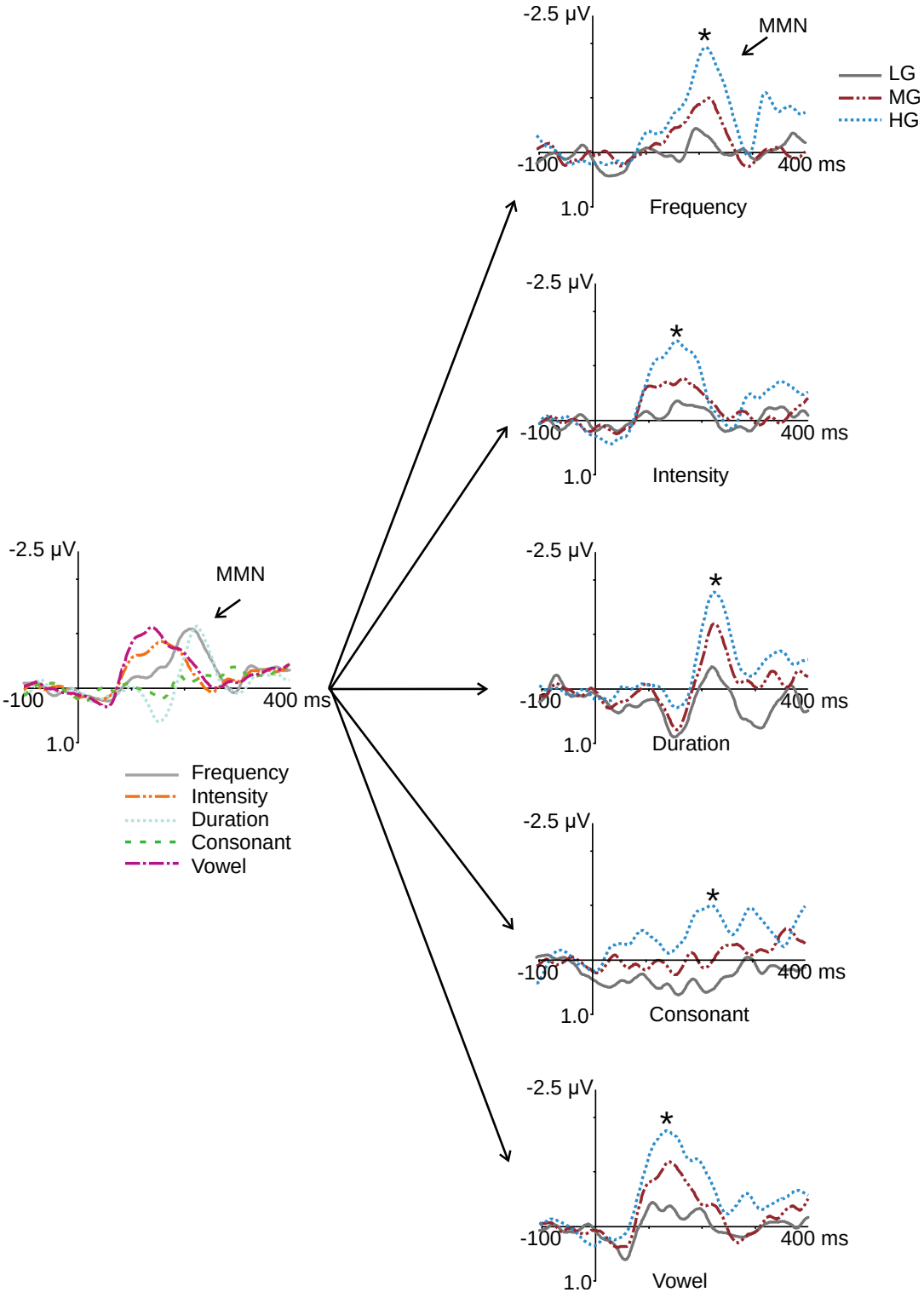

Figure 4.2 Baseline (placebo) grand averaged frontal (Fz) difference waveforms (deviant minus standard) for the 5 deviants in the total sample and in LG (low), MG (medium), and HG (high) amplitude MMN subgroups

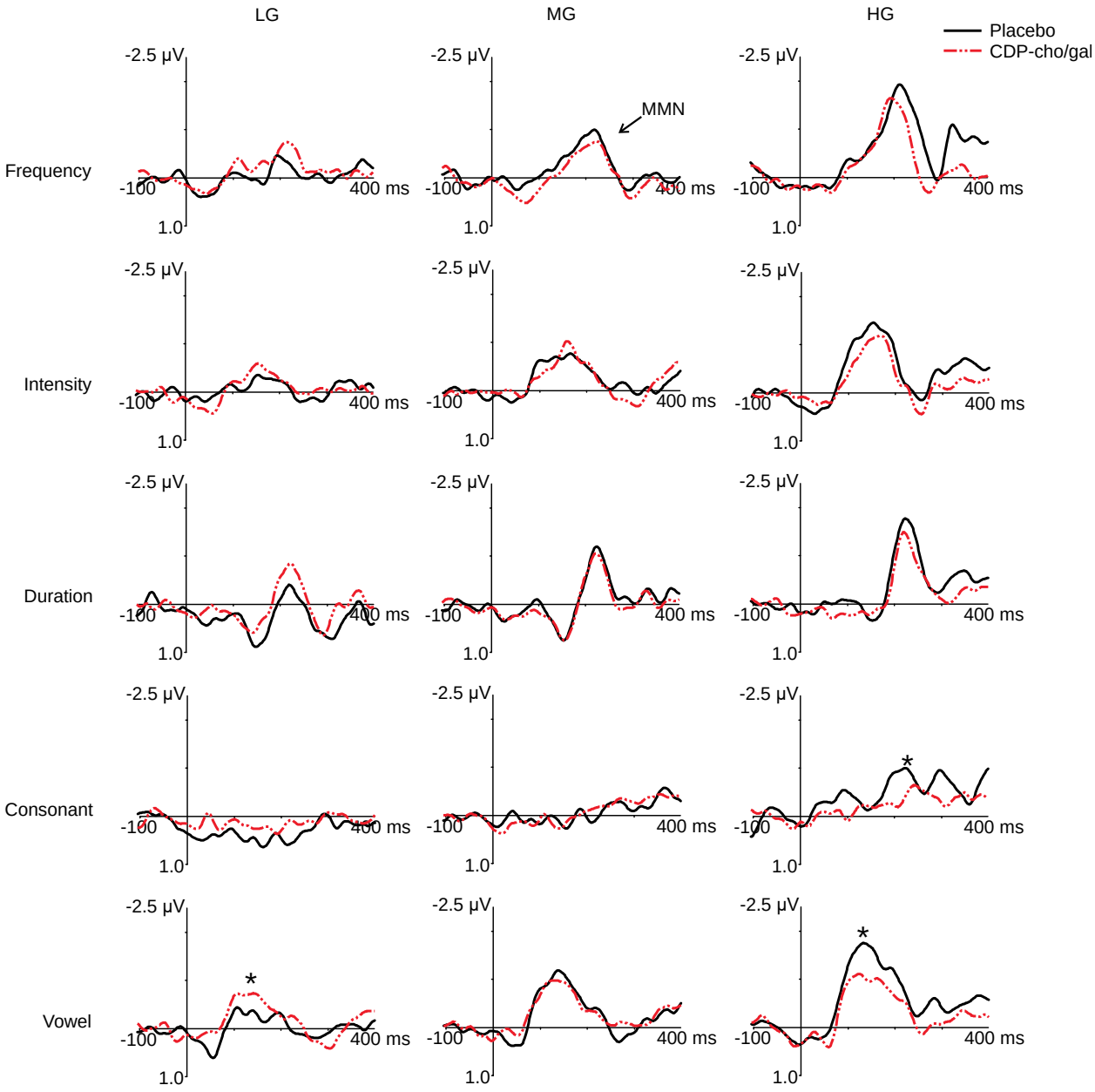

Figure 4.3 Frontal (Fz) grand averaged difference waveforms (deviant minus standard) for the 5 deviants in LG (low), MG (medium), and HG (high) participants during placebo and CDP-choline/galantamine (CDP-cho/gal) conditions

4.6.1.2 Temporal (TP9 and TP10) electrode sites

Total group

Pooled temporal (TP9 and TP10) grand averaged difference waveforms for each deviant type during placebo and CDP-choline/galantamine treatment are shown in Figure 4.4. A significant ($p < 0.01$) main site effect, $F(1,32) = 15.76$, was only observed for vowel MMN deviants indicating that larger MMN amplitudes were recorded at the left-temporal (TP9) hemisphere electrode site ($M = 1.93$ µV, SE ±.09) in comparison to the right-temporal site (TP10; $M = 1.54$ µV, SE ±.11). A close to significant ($p = 0.052$) main treatment effect, $F(1,32) = 4.06$, was observed for consonant MMN deviants where MMN amplitudes were larger during CDP-choline/galantamine treatment condition ($M = 0.66$ µV, SE ±.11) in comparison to placebo ($M = 0.37$ µV, SE ±.15).

A significant ($p = 0.013$) site x treatment interaction was observed for consonant MMN deviants (Figure 4.5). Follow-up planned pairwise comparisons indicated that at TP9, significantly ($p = .005$) greater MMN amplitudes were observed under the CDP-choline/galantamine condition ($M = 0.78$ µV, SE ±.13) in comparison to placebo ($M = 0.30$ µV, SE ±.16). Also, only during the CDP-choline/galantamine treatment significantly ($p = 0.034$) greater MMN amplitudes were observed at TP9 ($M = 0.78$ µV, SE ±.13) in comparison to TP10 ($M = 0.54$ µV, SE ±.12).

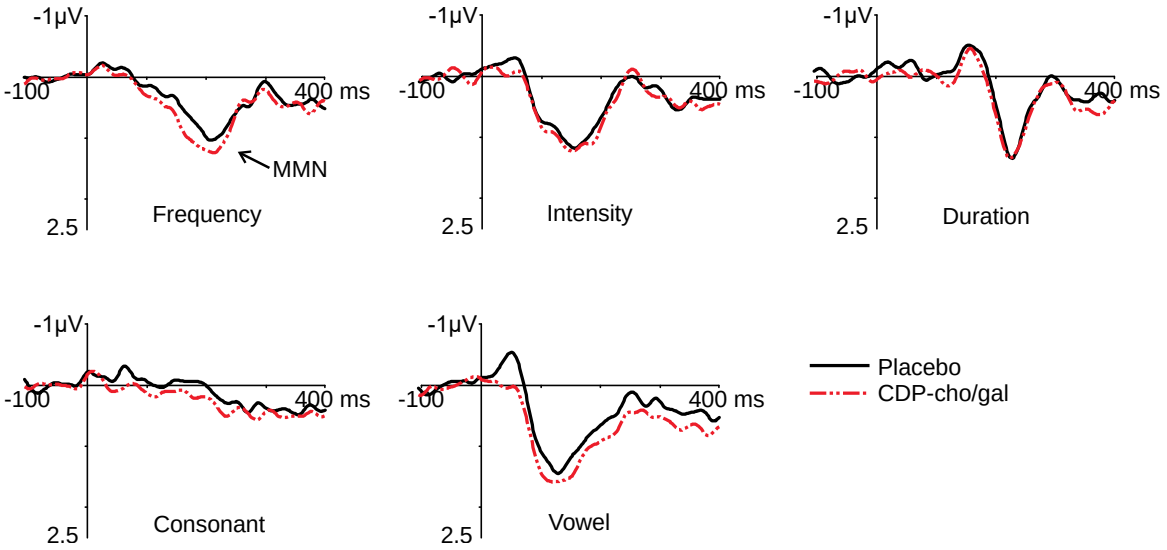

Figure 4.4 Pooled left and right temporal-parietal (TP9, TP10) ERP grand averaged difference waveforms (deviant minus standard) for the 5 deviants during placebo and CDP-choline/galantamine (CDP-cho/gal) treatment conditions

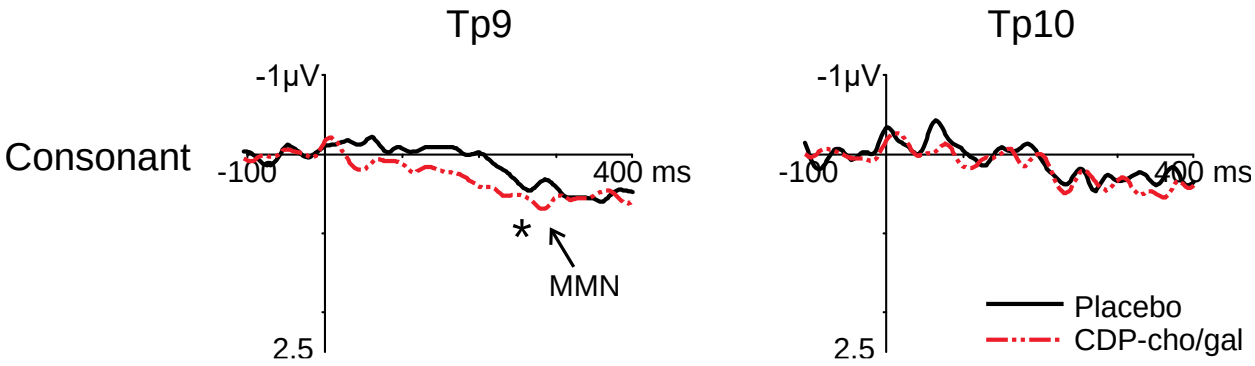

Figure 4.5 Left and right temporal-parietal (TP9, TP10) MMN ERP grand averaged difference waveforms (deviant minus standard) to consonant deviants during placebo and CDP-choline/galantamine (CDP-cho/gal) treatment conditions

Group comparisons

Significant main treatment effects were observed, with CDP-choline/galantamine increasing MMN generation in response to intensity $F(1,30) = 4.71$, $p = 0.04$ ($M_{Pla} = 1.26$ μV, SE ±.06; $M_{CDP\text{-}cho/gal} = 1.53$ μV, SE ±.12), consonant $F(1,30) = 4.59$, $p = 0.04$ ($M_{Pla} = 0.37$ μV, SE ±.11;

$M_{CDP\text{-}cho/gal}$ = 0.66 µV, SE ±.11), and vowel F(1,30) = 5.36, p = 0.03 (M_{Pla} = 1.60 µV, SE ±.04; $M_{CDP\text{-}cho/gal}$ = 1.86 µV, SE ±.12) deviant types.

A significant main site effect was observed for vowel F(1,30) = 14.88, p = 0.001 deviants only, with larger amplitudes at TP9 (M = 1.93µV, SE ±.07) in comparison to TP10 (M = 1.54 µV, SE ±.10).

Main group effects were observed in response to frequency (F(2,30) = 16.76, p < 0.001), intensity (F(2,30) = 8.71, p = 0.001), duration (F(2,30) = 18.64, p < 0.001), consonant (F(2,30) = 14.25, p < 0.001) and vowel (F(2,30) = 9.84, p = 0.001) deviants (Figure 4.6, Table 4.2). LG individuals expressed significantly smaller MMN amplitudes in comparison to MG and HG individuals for frequency (p = 0.019, p < 0.001), intensity (p = 0.039, p = 0.001), duration (p = 0.005, p < 0.001), and vowel (p = 0.035, p < 0.001) deviants. MG also showed smaller amplitudes than HG individuals for frequency (p = 0.024), and duration (p = 0.036) deviants. For consonant deviants, LG and MG showed smaller amplitudes in comparison to HG (p < 0.001, p = 0.024), a close to significant trend (p = 0.056) was observed between LG and MG.

Table 4.2 Mean (±SE) MMN amplitudes (µV) for LG (low), MG (medium), and HG (high) amplitude groups for each deviant type

	Frequency	Intensity	Duration	Consonant	Vowel
LG	0.72 (.15)	0.98 (.12)	0.81 (.12)	-0.21 (.15)	1.32 (.12)
MG	1.34 (.15)	1.46 (.12)	1.40 (.12)	0.49 (.15)	1.79 (.12)
HG	1.94 (.15)	1.72 (.12)	1.86 (.12)	1.08 (.15)	2.09 (.12)
LG < MG	p = .019	p = .039	p = .005	p = .056	p = .035
LG < HG	p < .001	p = .001	p < .001	p < .001	p < .001
MG < HG	p = .024	p = .447	p = .036	p = .024	p = .292

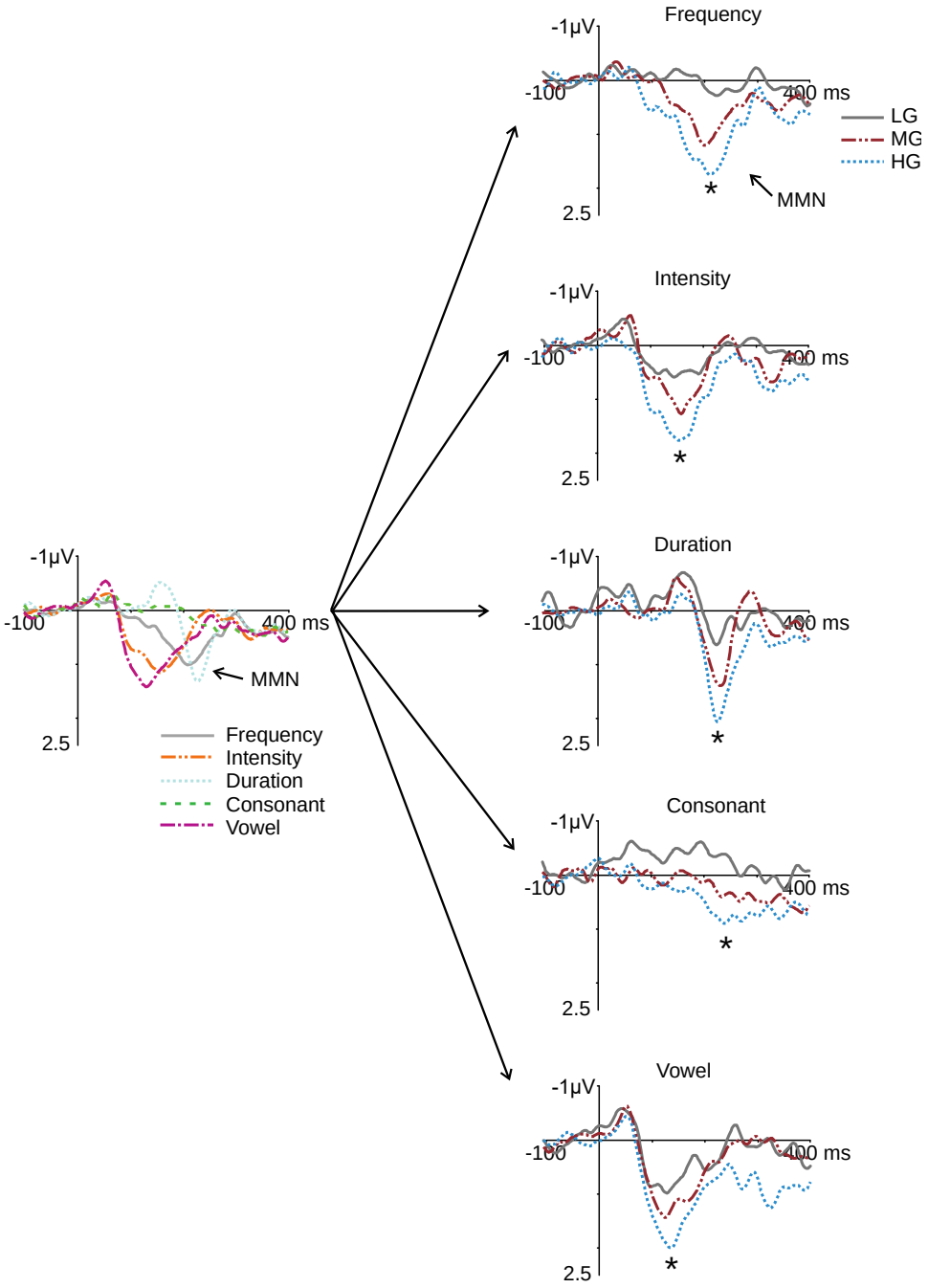

Figure 4.6 Baseline (placebo) grand averaged pooled left and right temporal (TP9 and TP10) difference waveforms (deviant minus standard) for the 5 deviants in the total sample and in LG (low), MG (medium), and HG (high) amplitude MMN subgroups

Significant treatment x group interactions were observed for frequency ($F(2,30) = 4.68$; $p = 0.017$), intensity ($F(2,30) = 10.25$; $p < 0.001$), duration ($F(2,30) = 7.04$; $p = 0.003$), and vowel ($F(2,30) = 7.84$; $p = 0.002$) deviant types. Planned follow-up comparisons revealed that CDP-

choline/galantamine treatment (vs. placebo) significantly increased MMN amplitudes in LG participants for frequency ($p = 0.003$), intensity ($p < 0.001$), duration ($p = 0.002$), and vowel ($p = 0.001$) deviants and also in the MG ($p = .034$) for vowel deviants only (Figure 4.7). No significant treatment x group interactions were observed for consonant deviants and for HG individuals.

A significant site x treatment interaction $F(1,30) = 6.78$, $p = .014$ was observed for consonant deviants where significantly ($p = 0.004$) greater MMN amplitudes were observed under CDP-choline/galantamine treatment (M = 0.78 μV, SE ±.12) in comparison to placebo (M = 0.30 μV, SE ±.11) at TP9 (Figure 4.5). Also, under the active treatment only, MMN amplitudes were significantly larger at TP9 (M = 0.78 μV, SE ±.12) than at TP10 (M = 0.54 μV, SE ±.12).

A significant site x treatment x group interaction was observed for frequency deviants $F(2,30) = 4.10$, $p = .027$, with greater ($p = .002$) MMN amplitudes during CDP-choline/galantamine treatment (M = 1.30 μV, SE ±.27) compared to placebo (M = 0.33 μV, SE ±.26) being observed for the LG group at TP9 , and a close to significant treatment difference ($p = .051$) was noted at TP10 where the LG demonstrated greater frequency MMN amplitudes under CDP-choline/galantamine (M = 0.92 μV, SE ±.28) compared to placebo (M = 0.37 μV, SE ±.17). Also, at TP9, a close to significant ($p = .056$) interaction revealed that smaller syllable frequency MMN amplitudes (M = 1.94 μV, SE ±.27) were recorded under CDP-choline/galantamine in comparison to placebo (M = 2.53 μV, SE ±.26) for the HG group (Figure 4.8). Under placebo treatment, HG individuals demonstrated significantly ($p = 0.014$) larger MMN amplitudes to frequency deviants at the TP9 electrode (M = 2.53 μV, SE ± .26) compared to TP10 (M = 1.58 μV, SE ± .17).

No significant treatment or interaction effects were observed when group stratification was based on treatment (i.e., not placebo) for all MMN deviant types.

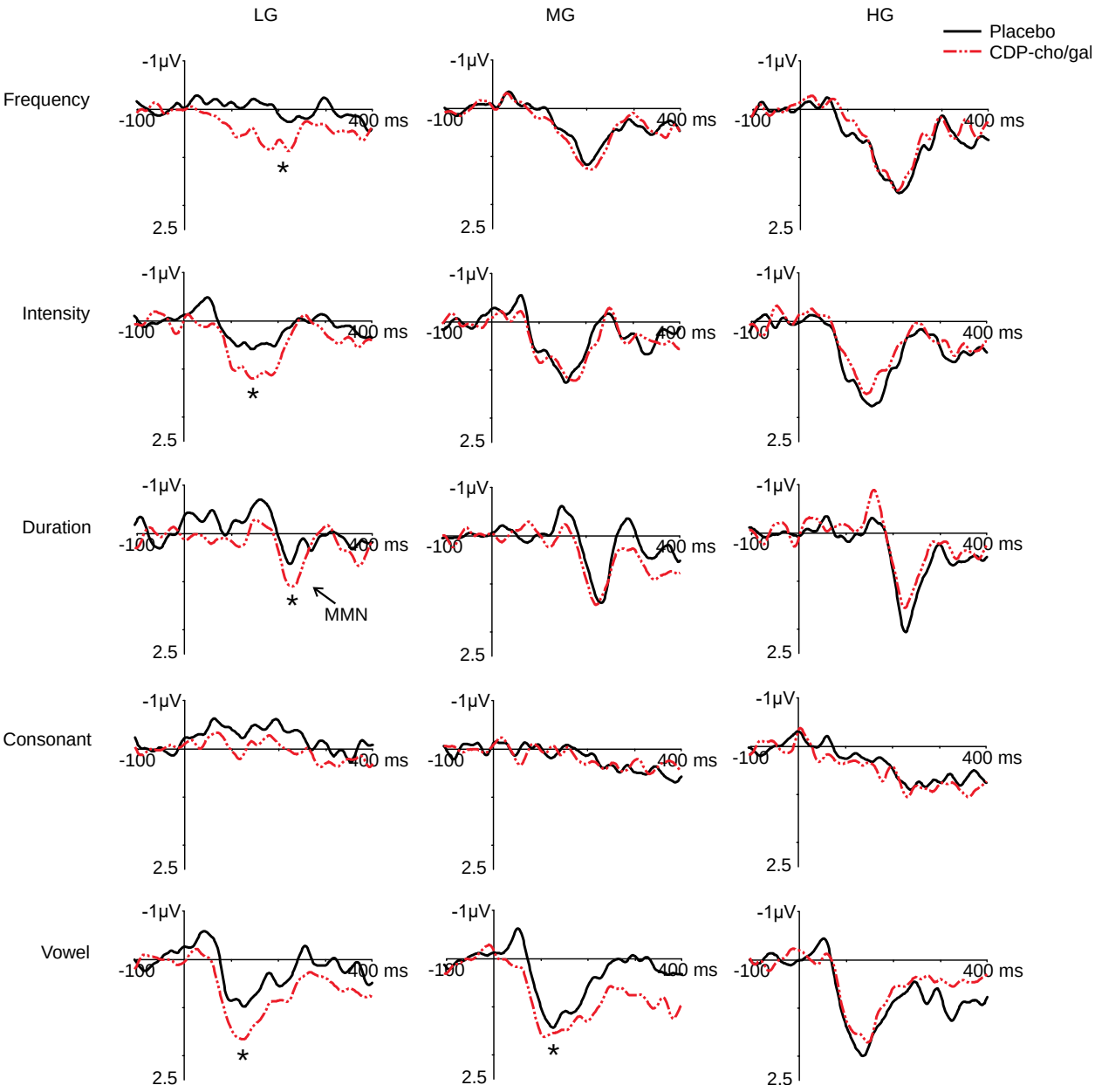

Figure 4.7 Pooled Left and right temporal-parietal (TP9, TP10) grand averaged difference waveforms (deviant minus standard) for the 5 deviants in LG (low), MG (medium), and HG (high) participants during placebo and CDP-choline/galantamine (CDP-cho/gal) conditions

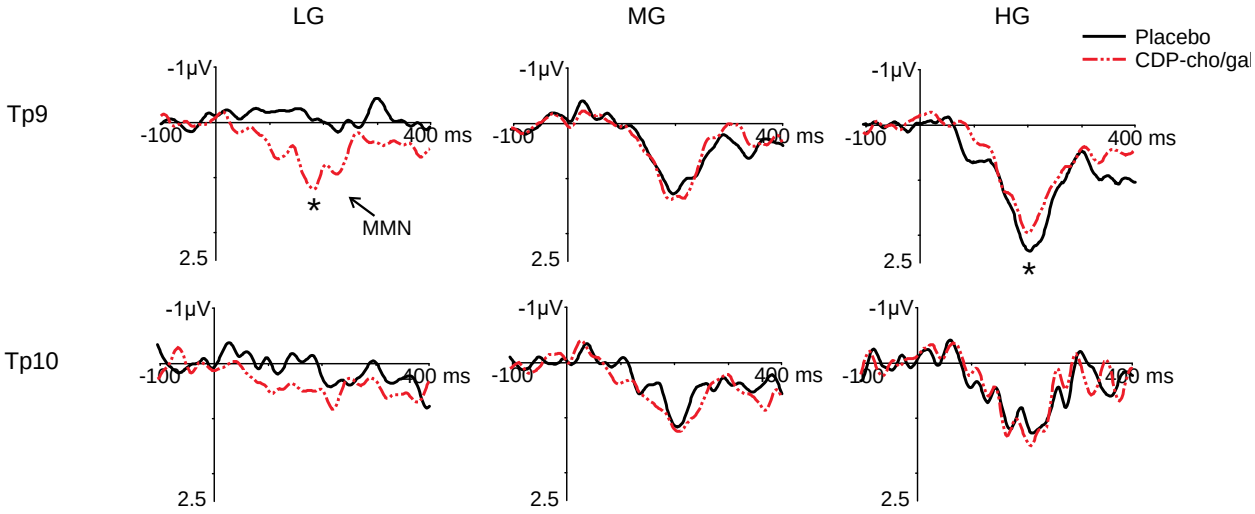

Figure 4.8 Left and right temporal-parietal (TP9, TP10) MMN ERP grand averaged difference waveforms (deviant minus standard) for frequency deviants in LG (low), MG (medium), and HG (high) participants during placebo and CDP-choline/galantamine (CDP-cho/gal) conditions

4.6.2 MMN latency measures

4.6.2.1 Frontal (Fz, F3, and F4) electrode sites

Total group

Overall analysis of MMN latencies revealed no significant drug or site differences for all deviant types.

Group comparisons

Main group effects were observed for frequency $F(2,30) = 3.54$, $p = .042$, and consonant $F(2,30) = 3.99$, $p = .029$ deviants. Follow-up comparisons revealed no significant group differences for frequency deviants; while consonant change deviant subgroup analyses revealed that LG individuals (M = 174.8 ms, SE ±9.3) exhibited shorter response latencies compared to those in the HG (M = 211.4 ms, SE ±9.3).

A significant treatment x group interaction was observed for the duration deviant $F(2,30) = 4.18$, $p = .025$ only. Follow-up comparisons indicated that LG individuals displayed shorter latencies under placebo (M = 203.6 ms, SE ±7.4), in comparison to CDP-choline/galantamine (M = 223 ms, SE ±5.2).

4.6.2.2 Temporal (TP9 and TP10) electrode sites

Total group

General repeated measures analyses for MMN latency averages revealed no main drug or site effect for pooled left and right temporal-parietal latency measures.

Analyses of latencies separately for the left and right temporal-parietal hemisphere site revealed a main treatment effect $F(1,30) = 5.12$, $p = .031$ at TP10 for frequency deviants where shorter MMN latencies were observed under the CDP-choline/galantamine (M = 194.7 ms, SE ±6.09) condition in comparison to placebo (M = 209.5 ms, SE ±5.44).

Group comparisons

Analysis of MMN latency with pooled TP9 and TP10 measures for LG, MG, and HG individuals revealed no main treatment, site or group effect for any of the deviants.

A significant main treatment x group interaction was found for duration deviants only $F(2,30) = 4.06$, $p = 0.028$. Planned follow-up comparisons revealed that for the LG only, MMN latencies were significantly ($p = 0.011$) shorter under placebo conditions (M = 205.91 ms, SE ±7.61) in comparison to CDP-choline/galantamine treatment (M = 227.14 ms, SE ±4.66).

Analyses of latencies separately for the left and right temporal-parietal hemisphere site revealed a significant treatment x group interaction for duration deviants at TP9 $F(2,30) = 3.75$, $p = .035$ and TP10 $F(2,30) = 4.13$, $p = .026$. Follow-up analyses revealed that LG individuals displayed longer MMN responses under the CDP-choline/galantamine condition (M_{TP9} = 226.8 ms, SE ±4.73; M_{TP10} = 227.4 ms, SE ±4.88) in comparison to placebo (M_{TP9} = 205.6 ms, SE ±7.66; M_{TP10} = 206.2 ms, SE ±7.68).

No significant treatment or interaction effects were observed when group stratification was based on treatment (i.e., not placebo) for all deviant types.

4.6.3 Placebo vs. treatment effect correlations

Treatment-induced changes in MMN amplitude measures were found to be inversely related to placebo values for all deviant types at Fz, TP9 and TP10. These results suggest that subjects with relatively lower baseline MMN amplitudes exhibit greater amplitude incrementing effects with the CDP-choline/galantamine treatment (Figure 4.9). Findings for the separate analyses of TP9 and TP10 were the same as the pooled TP9 and TP10, therefore only the pooled TP9 and TP10 (TP) correlations are shown in Figure 4.9b.

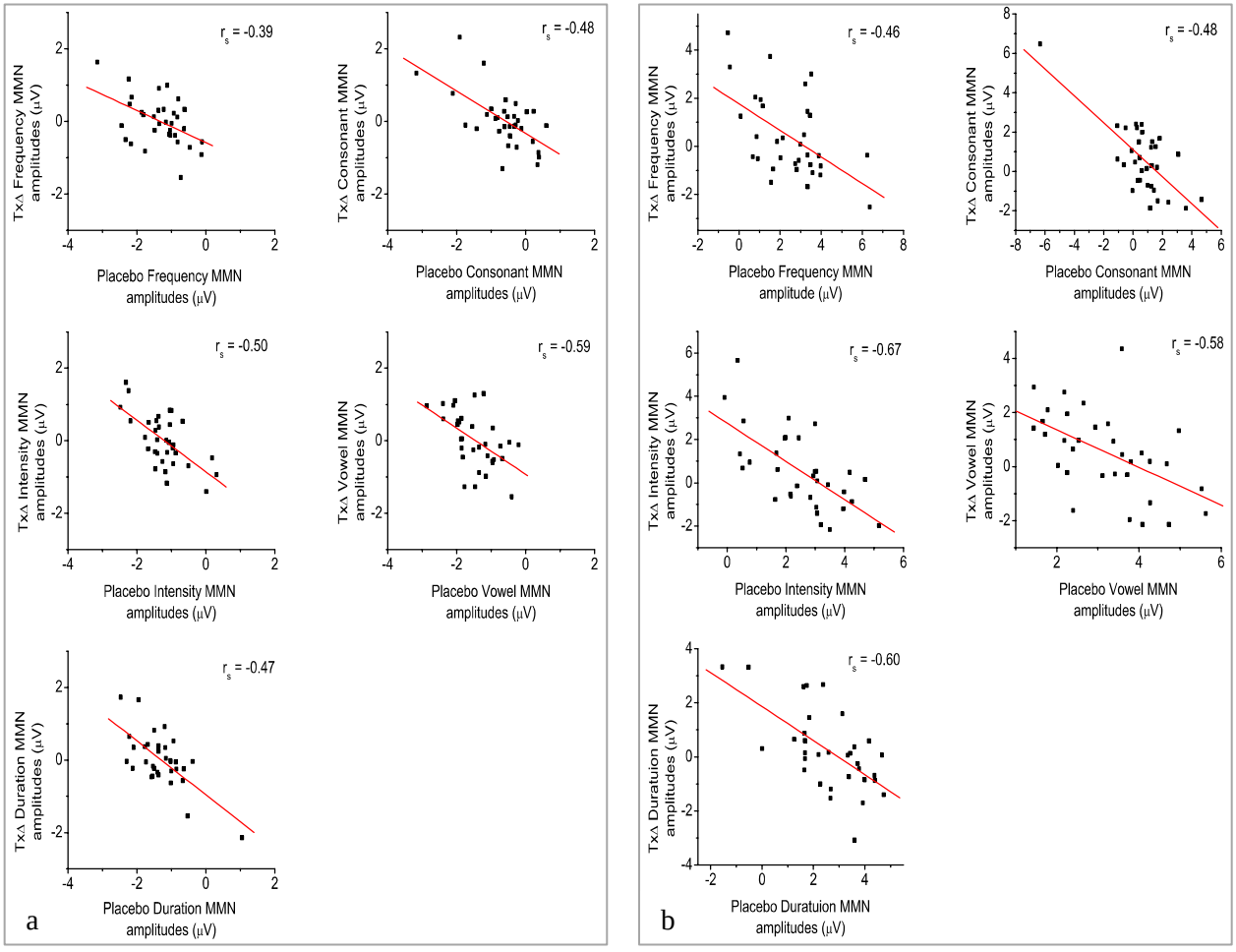

Figure 4.9 (a)Frontal (Fz) and (b) pooled left and right temporal-parietal (TP) treatment effect (TxΔ) (treatment – placebo) and placebo amplitudes for each MMN deviant. TxΔ scores significantly ($p < 0.05$; $df = 31$) correlated with baseline scores for all deviants

4.6.4 Adverse events

Self-reports of adverse events related to the administration of the active treatment (CDP-choline/galantamine) did not reflect any significant difference compared to the placebo condition. No severe symptoms were reported throughout the study experiments.

4.6.5 Vital signs

No significant differences were observed for systolic and diastolic blood pressure measures at placebo compared to measures at CDP-choline/galantamine. Pre- and post- treatment administration heart rate measures were not significantly different under the CDP-choline/galantamine condition in comparison to placebo. However, the last heart rate measure (at the end of the testing session before participant departure) during the placebo session (M = 61.5 bpm, SE ±2.15) was significantly ($t(21) = -2.44$, $p = .023$) lower than during the active treatment (M = 64.9 bpm, SE±1.96).

4.7 Discussion

Examination of the combined CDP-choline (a selective α7 nAChR agonist) and galantamine (a positive allosteric modulator shown to reduce nAChRs' fast desensitization rates) treatment on EAIP in healthy individuals had not been previously conducted with respect to MMN measures of auditory deviance detection. The CDP-choline/galantamine treatment, as predicted for healthy low MMN amplitude individuals (LG), significantly improved detection of vowel and consonant deviants at frontal sites and frequency, intensity, duration, and vowel deviants at temporal-parietal sites. These findings, presumably reflecting an enhancement in nicotinic cholinergic neurotransmission, which is known to be impaired in SCZ, supports the examination of this combined cholinergic approach as an adjunct treatment for deviance detection deficits in individuals with SCZ.

MMN amplitude improvements in LG individuals are analogous to results from our recent study examining the effect of this optimized CDP-choline/galantamine treatment on P50 sensory gating processing where improved P50 gating scores in healthy and SCZ participants were also baseline dependent (Choueiry et al., 2019a,b). Our results also extend previous MMN findings from our laboratory with CDP-choline (alone) (Knott, Impey, et al., 2015), and with nicotine (a non-selective nAChR agonist) (Knott, Impey, et al., 2014; Smith et al., 2015) showing increases in MMN generation in low MMN amplitude individuals. Other reports have also found nicotine-mediated MMN amplitude and/or latency improvements in healthy (Baldeweg et al., 2006; Inami et al., 2005; Inami & Kirino, 2019; Martin et al., 2009) and SCZ populations (Dulude et al., 2010; Fisher, Grant, et al., 2012; Inami & Kirino, 2019) in addition to opposing reports (Kohlhaas et al., 2015; Mathalon et al., 2014). Furthermore, nAChR modulation with selective and non-selective agonists and PAMs has previously been shown to improve measures of cognition (Dunbar et al., 2007; Featherstone & Siegel, 2015; Gee et al., 2017; Kantrowitz, Swerdlow, et al., 2018; Kohlhaas et al., 2015). Also evidenced by our correlational analyses, the most significant treatment effect is observed in individuals who at baseline exhibit poor deviance detection as expressed by relatively smaller MMN amplitudes. Primarily, genetics, smoking status, personality, and level of cognitive functioning are all factors that may explain inter-individual differences in treatment response variability (Gilbert & Gilbert, 1995; Kupferschmidt et al., 2010; Li et al., 2009; Perkins, 1995, 2009; Poltavski & Petros, 2005). As nicotinic receptor modulation across multiple response domains is also baseline dependent (Newhouse et al., 2004; Picciotto, 2003), our results support the value of baseline stratification in early pre-clinical translational approaches aiming to develop targeted and personalized treatments.

At the frontal site, only MMN amplitudes following vowel and consonant deviants were influenced by CDP-choline/galantamine with larger and smaller amplitudes evidenced for LG and HG individuals, respectively. In contrast, at the left and right temporal-parietal electrode sites (TP9 and TP10, respectively), CDP-choline/galantamine did not reduce MMN amplitudes in HG individuals. Also, in LG individuals, the optimized CDP-choline/galantamine treatment (vs. placebo) resulted in larger MMN amplitudes for frequency, intensity, duration, and vowel deviants. MG individuals also expressed larger MMN amplitudes mediated by the active treatment following vowel deviants only. The MMN ERP waveforms following each deviant type are similar to those reported in the original MMN study employing these speech stimuli (Pakarinen et al., 2009) and also to the frontal and temporal MMNs recorded in our recent study examining the effects of the NMDA receptor antagonist, ketamine, in healthy individuals (de La Salle et al., 2019b). Smaller MMN amplitudes with no discernable maximal peak in response to consonant deviants have been observed in previous studies with this type of stimulus and are believed to be smaller because of the greater difficulty in discriminating the change of consonant in comparison to the standard stimulus (de La Salle et al., 2019b; Kantrowitz et al., 2015; Pakarinen et al., 2009), in this case the change from /te/ to /pe/ or /pi/ to /ti/. These results suspect that the active treatment expressed differential effects on the different generators activated by the separate deviants. Although the specific neurobiological processes underlying the MMN generation are still debated (i.e., whether it is a function of prediction or anticipation), two main generators are recognized (see review: (Näätänen & Kähkönen, 2009)). Acoustic deviance detection at the frontal-cortical MMN generator, depends on the bilateral temporal generator from the auditory cortex and requires online comparison with information stored in

echoic memory traces and relies on fronto-temporal mechanisms implicating hippocampal input (El Karoui et al., 2015; Javitt, 1996, 2000; Rosburg et al., 2005).

Glutamate and NMDA receptors are heavily implicated in MMN generation with a consistent history of reports of deviance detection modulation by NMDA receptor agonists (Kantrowitz, Epstein, et al., 2018) and antagonists in animal and human studies (Javitt, 1996; Swerdlow et al., 2016; Tikhonravov et al., 2008). However, it was recently suggested that not to expect other receptors to modulate MMN response would be a limiting approach as additional data supports the involvement of nAChRs (Askew & Metherate, 2016) with evidence of α7 nAChR mediated modulation of NMDA receptor signalling in the CA1 hippocampal region (Bali et al., 2017, 2019). Furthermore, substantial evidence suggest that α7 nAChRs and NMDAR may complement each other in neuronal signal regulation especially in the modulation of learning mechanisms (Broide & Leslie, 1999; Kantrowitz, Swerdlow, et al., 2018), further implying that α7 nAChR modulation is a promising therapeutic strategy for the alleviation of sensory/cognitive impairments (Yang et al., 2017). Interestingly, while the optimized CDP-choline/galantamine treatment had no impact on frequency, intensity, and duration deviants at frontal sites, it significantly normalized smaller amplitudes in LG at temporal-parietal sites, indicating enhanced acoustic change detection in the bilateral auditory cortex and potentially enhanced fronto-temporal mechanisms. While not many studies analyze the inversed MMN amplitudes at TP9 and TP10, it has been reported in SCZ that TP MMN amplitudes do not experience the reductions observed at frontal sites (see review:(Näätänen et al., 2012) and (Baldeweg et al., 2002, 2004; Sato et al., 2003)). As participants of the current study are all healthy individuals, it was safe to expect normal MMN measures in general and specifically at frontal electrodes, while it was assumed that temporal electrodes would also show normal inverted MMN measures

without a clear idea of what the active treatment might elicit. Our findings illustrate a differential response to treatment at frontal vs. temporal cortical regions in LG healthy participants. While statistical examination of this frontal-temporal difference is beyond the scope of this study, it informs us on the importance of separately evaluating the response of these generators. Primarily this evaluation will give us a deeper insight on the modulation of the temporal generator responsible for pre-perceptual detection of sound change (which is believed to trigger the frontal MMN generator), this is especially valuable to pursue as the three subgroups expressed significantly different temporal deviance detection levels at baseline. Furthermore, temporal examination of MMN amplitudes signals the importance of multi-site topographical assessment and source localization approaches for detecting treatment-responsive cortical regions for future electrophysiological studies investigating novel pharmacotherapies for sensory/cognitive processing deficits.

Employing speech stimuli within the "oddball" MMN paradigm permitted the examination of the combined CDP-choline/galantamine treatment on deviance detection of more realistic, real-world input (in comparison to computerized tones/sounds). While the specific interaction of nACh deficits with AVHs and their relation to MMN processing have not been extensively studied, low- and high-level speech processing impairments are inherent to SCZ symptomatology and have been linked to thought disorders and AVHs (Brown & Kuperberg, 2015). Modulation of MMN amplitudes to variations in linguistic features has been extensively studied in language-related disorders and has been suggested for the investigation of neurological diseases with associated language and speech deficits such as SCZ (Pakarinen et al., 2009, 2014). MMN amplitudes have been evidenced to show speech-related hemispheric lateralization with larger amplitudes recorded from the left (vs. right) frontal hemisphere (Shtyrov et al., 1998). At

frontal sites, our speech MMNs were larger at the right frontal electrode F4 (vs. the left F3) for frequency and duration deviants, which is in line with previous reports in studies employing computerized tones(Paavilainen et al., 1991). At temporal-parietal sites, vowel and consonant deviants demonstrated left hemisphere lateralization under both treatment conditions for vowel deviants while only under the CDP-choline/galantamine condition for consonant deviants. Most recently, a study employing phoneme stimuli revealed that early SCZ individuals did not show smaller MMN amplitudes in comparison to healthy controls at frontal sites. However, significantly smaller MMN amplitudes were recorded for chronic SCZ individuals in comparison to healthy controls and early SCZ (Fisher et al., 2019). This study did not report findings in parietal regions and did not find hemispheric lateralization of MMN amplitudes at frontal electrodes. Examining speech MMNs in healthy and SCZ populations and their response to CDP-choline and other nAChR agonists and PAMs may help better our understanding of speech-related mechanism impairments and their potential for amelioration with nAChR stimulation.

In contrast with recent studies employing speech MMN and showing no significant latency shifts associated with either ketamine administration (de La Salle et al., 2019b) or SCZ spectrum disorder (Fisher et al., 2019), our results of significant latency differences for consonant, frequency, and duration deviants leave important elements to consider for future experiments employing speech stimuli. For consonant deviants, HG individuals (vs. LG) demonstrated longer latencies indicative of potentially a longer detection time required for the subtle variation from the standard stimulus. While LG individuals benefited from a CDP-choline/galantamine mediated MMN amplitude increase for consonant deviants, latencies where not affected by the active treatment. However, the acute CDP-choline/galantamine administration did produce significantly longer latencies for LG individuals at frontal and

temporal-parietal electrode sites following duration deviants. While under placebo conditions the latency mean difference between LG and HG is over 24 ms shorter for the LG, peak latency lengthens to a level comparable to that of the HG with CDP-choline/galantamine treatment. In comparison, nicotine shortened latencies in healthy individuals to frequency deviants (Inami et al., 2005), and in participants with SCZ following intensity deviants (Fisher, Grant, et al., 2012) contradicting reports of no nicotine mediated latency changes (Dulude et al., 2010; Martin et al., 2009). While these studies with nicotine don't examine inter-individual differences, our findings potentially reveal that for the LG this optimized treatment impacts both speed and strength duration deviant detection.

4.7.1 Limitations

The study design employed double-blind and randomized treatment administration, and a cross-over repeated measures design. The assessment of female and male smokers and non-smokers in the ratios observed in the SCZ population permit the generalizability of the data and results to SCZ. Despite these strengths, certain limiting factors need to be considered and include a relatively small sample size in the stratified amplitude groups that could have limited the statistical power.

The CDP-choline/galantamine active treatment was administered to healthy participants in a single dose for the purpose of this pilot study. Our findings support the examination of this treatment in different dosages that will also help in better defining the dose-response curve of CDP-choline and galantamine separately and in combination. Also, considering receptor desensitization, a longer administration period will help in evaluating the long-term efficacy and benefits of this combined strategy. In favour of the long-term use of this approach, a recent study revealed additive improvements of cognitive performance in patients with Alzheimer's Disease

administered an acetylcholine esterase inhibitor in combination with CDP-choline (vs. an AChEI alone, i.e. donepezil, rivastigmine, or galantamine) (Gareri et al., 2017).

Many studies examining treatments targeting nAChRs exclude smokers to avoid the potential confounding effect of withdrawal symptoms and the possible alleviation of these symptoms with nicotinic treatment administration. However, including smokers increases the translatability of these findings to the realistic population that experiences cognitive impairments. Furthermore, our analyses comparing smokers to non-smokers revealed no significant differences amongst these two groups for MMN amplitudes and latencies, or adverse events scores. While smoking status has been previously suggested to modulate MMN via a7 nAChRs specifically (Dulude et al., 2010; Martin et al., 2009), it was lastly reported that nicotine smoking differentially impacts modulation of MMN latency depending on clinical status. Smokers with SCZ were shown to be sensitive to nicotine modulation of MMN, while non-smokers with SCZ failed to show this effect. In comparison to healthy non-clinical subjects, nicotine decreased MMN latency regardless of smoking status (Inami & Kirino, 2019).

Future experiments examining this optimized treatment strategy should incorporate an additional preliminary baseline testing session to serve for stratification into low, medium and high amplitude groups. The placebo data was used for group stratification in our study design, and this data was also subsequently used for statistical analyses, which is considered a limitation especially as this strategy may be confounded with some participants potentially regressing to the mean without the influence of the active treatment. However, no significant differences were observed when analyses were conducted using treatment sessions (i.e., not placebo) stratification which was analyzed in order to verify that results are not arbitrary and not caused by a regression to the mean, a possible benefit of employing a counterbalanced design. These findings highlight

to future pharmacotherapeutic studies the value of targeting individuals who show a baseline deviance detection deficit stratified by an early baseline testing session. Thus, individuals who express optimal levels of deviance detection will not experience the possible hampering effect of the active treatment, furthermore active treatments targeting the cholinergic system might have a better outcome result in general. In line with this theory, our findings might help explain failure to find cognitive improvement in recent examinations of AVL-3288 (a selective α7 type 1 PAM) in SCZ patients which were selected with a relatively higher baseline cognitive performance level (Gee et al., 2017; Kantrowitz et al., 2020). Furthermore, our findings instigate future studies examining the effect of this treatment exclusively in individuals with relatively lower deviance detection levels allowing for a better efficacy measure of this active treatment.

4.8 Conclusion

Larger temporal MMN amplitudes for frequency, intensity, duration, and vowel deviants were recorded following an acute dose of the optimized CDP-choline/galantamine treatment in a SCZ (MMN) surrogate group of healthy individuals expressing relatively lower amplitudes at baseline. Our findings implicate α7 nAChRs in MMN sensory memory/deviance detection/error-prediction processing, and further supports the examination of this treatment in SCZ. In addition, our results further support the use of MMN as a biomarker in early phase trials for parcelling individual differences that are sensitive to the potential pro-cognitive benefits induced by nAChR stimulation.

Chapter 5

Effects of CDP-Choline and Galantamine on MMN Deviance Detection in Individuals with Schizophrenia

5.1 Preface

Overview

CDP-choline and galantamine were examined in this pilot study on deviance detection indexed in MMN measures in twenty-four patients with SCZ stratified into low, medium, and high groups based on their baseline MMN amplitude.

Statement of author contribution

This study was designed by Dr. Verner Knott, with contributing input from Joelle Choueiry. The study setup was done by Joelle Choueiry and Dhrasti Shah. Paradigm programming with auditory speech stimuli was done by Joelle Choueiry, Derek Fisher, and Dylan Smith. Participant recruitment and screening were done by Joelle Choueiry and Crystal Blais. Recruited participants were clinically interviewed by Dr. Alain Labelle. Administration of study tasks and ERP recording were done by Joelle Choueiry and Crystal Blais. ERP processing and analyses, statistical analyses, tables and figures and manuscript writing were done by Joelle Choueiry. The final manuscript was reviewed by all authors.

5.2 Title page

An α7 nAChR approach for the baseline-dependent modulation of deviance detection in schizophrenia: A pilot study assessing the combined effect of CDP-choline and galantamine

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Declaration of interest: All authors declare not conflict of interest.

5.3 Abstract

Background

Cognitive operations including pre-attentive sensory processing are markedly impaired in patients with schizophrenia (SCZ) but evidence significant interindividual heterogeneity, which moderates treatment response with nicotinic acetylcholine receptor (nAChR) agonists. Previous studies in healthy volunteers have shown baseline-dependency effects of the □7 nAChR agonist CDP-choline administered alone and in combination with a nicotinic allosteric modulator (galantamine) on auditory deviance detection measured with the mismatch negativity (MMN) event-related potential (ERP).

Aim

The objective of this pilot study was to assess the acute effect of this combined □7 nAChR-targeted treatment (CDP-choline/galantamine) on speech MMN in patients with SCZ (N = 24) stratified by baseline MMN responses into low, medium, and high baseline auditory deviance detection subgroups.

Methods

Patients with a stable diagnosis of SCZ attended 2 randomized, double-blind, placebo-controlled and counter-balanced testing sessions where they received a placebo or a CDP-choline (500 mg) and galantamine (16 mg) treatment. MMN ERPs were recorded during the presentation of a fast multi-feature speech MMN paradigm including 5 speech deviants. Clinical measures were acquired before and after treatment administration.

Results

While no main treatment effect was observed, CDP-choline/galantamine significantly increased MMN amplitudes to frequency, duration, and vowel speech deviants in low group individuals.

Individuals with higher PANSS negative, general, and total scores expressed the greatest MMN amplitude improvement following CDP-choline/galantamine.

Conclusions

These baseline-dependent nicotinic effects on early auditory information processing warrant different dosage and repeated administration assessments in patients with low baseline deviance detection levels.

5.4 Introduction

5.4.1 The cholinergic system: a sensory/cognition target in schizophrenia

Sensory dysfunction in schizophrenia (SCZ) is directly associated with patients' functional disability and has proven to be non-responsive to neuroleptics targeting dopamine receptors, despite these treatments' effectiveness in alleviating positive clinical symptoms (Javitt and Freedman, 2015). Evidence associating pathophysiology of the cholinergic system, precisely α7 nicotinic acetylcholine receptors (nAChR), with sensory and cognitive dysfunction in SCZ, further validates this receptor's designation as a top pharmacological target by the Measure and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) (Azzopardi et al., 2013; Braff, 2011; Jones et al., 2016; Mackowick et al., 2014). However, a gap remains in finding an effective cholinergic treatment and given increasing evidence that early "bottom-up" pre-attentive processes contribute to clinical, cognitive and functional symptoms in SCZ, (Dondé et al., 2019a,b; Koshiyama et al., 2021; Thomas et al., 2017) sensory processes are considered a viable target in α7 drug development and treatment (Hashimoto, 2015; Olincy and Stevens, 2007; Smucny and Tregellas, 2017). Therefore, the general objective of this study was to examine the effect of a combined treatment, targeting the α7 nicotinic acetylcholine receptor, on measures of early auditory information processing in individuals with SCZ.

SCZ is a multigenic neurodevelopmental disorder with reported impairments in brain regions essential for sensory and cognitive functioning (Court et al., 1999; Freedman et al., 1995; Guan et al., 2000; Leonard and Freedman, 2006). The α7 nAChR and its coding gene (CHRNA7) have been associated with cognitive processing in learning, memory, and attention, and with pre-attentive sensory gating and deviance processing (Bertelsen et al., 2015; D'Souza and Markou, 2012; Leonard and Freedman, 2006; Mackowick et al., 2014; Ochoa and Lasalde-Dominicci, 2007; Sinkus et al., 2015; Young and Geyer, 2013). Despite the early success in

preclinical trials and in early phase 1 and phase 2 clinical trials, adjunctive treatment in SCZ with novel α7 nAChR agonists have been unsuccessful in larger phase 3 trials (Recio-Barbero et al., 2021). Contributing factors suggested to contribute to this lack of success include amongst others, a failure to: a) focus on low agonist concentrations in order to offset the rapid desensitization of α7 nAChRs in response to high dose ligand binding (Tregellas and Wylie, 2019) and b) exclude patients with relatively "normal" cognitive/sensory performance who are likely not to benefit from a pro-cognitive agent (Lewis et al., 2017; Terry and Callahan, 2020).

In parallel, positive allosteric modulators (PAMs) have been considered as an alternative approach increasing nAChR activity via orthosteric binding sites (Wallace and Bertrand, 2015). Hence, a synergistic strategy administering a selective α7 nAChR agonist, cytidine 5'-diphosphocholine (CDP-choline; a precursor and metabolite of acetylcholine), with a nAChR PAM, galantamine, was initially examined over 10 years ago (Deutsch et al., 2013; Deutsch, Rosse, et al., 2008; Deutsch, Schwartz, et al., 2008) and recently with a novel electrophysiological biomarker-based baseline stratification approach which showed improved measures of auditory sensory gating, and auditory deviance detection deficits indexed in electroencephalography (EEG) derived P50 and mismatch negativity (MMN) event-related potentials (ERPs), respectively (Choueiry et al., 2019a,b; Choueiry et al., 2020).

The MMN is typically elicited during the presentation of an "oddball" paradigm where a series of standard auditory stimuli (tones) are interrupted by a novel stimulus distinguished by a variation in tonal physical features, including frequency, intensity, duration, location or even the omission of the sound. Auditory deviance detection measured with the MMN is thought to reflect early, pre-attentive processing, indexing the integrity of sensory "echoic" memory traces of the sound environment and prediction-error signalling mechanisms generating the MMN

response (El Karoui et al., 2015; Javitt, 1996, 2000; Rosburg et al., 2005). This mature ERP is recognized as a biomarker and genomic endophenotype in SCZ following numerous replicability studies ascertaining robust attenuation of the MMN in SCZ (Näätänen and Kähkönen, 2009), and associations of lower MMN amplitudes with the severity of clinical features (i.e. hallucinations) and cognitive and social dysfunction in first-episode, and both medicated and non-medicated chronic SCZ (Näätänen et al., 2016). It has also been shown to predict conversion into psychosis in children at high-risk (Bodatsch et al., 2011; Perez et al., 2014). And most recently, treatment-related improvement in MMN measures was shown to be associated with improvements in clinical features (hallucinations; (Francis et al., 2020)) and attention and memory processing (Javitt et al., 2018). Thus, further reinforcing the implication of MMN as a translatable neural biomarker aiding in the development of novel therapeutic methods and pharmaceuticals in SCZ (Butler et al., 2012; Green et al., 2009; Nagai et al., 2013; Tada et al., 2019; Todd et al., 2013).

5.4.2 MMN modulation in schizophrenia

The MMN is thought to represent trial-by-trial encoding of prediction errors (i.e., where 'deviant' does not match preceding 'standard' template) which is likely dependent on N-methyl-D-aspertate receptor (NMDAR)-dependent plasticity at glutamatergic synapses (Harris et al., 1984; Wigström and Gustafsson, 1984). The NMDAR antagonist ketamine robustly reduces MMN amplitude across different deviant types including speech in humans (de La Salle et al., 2019; Rosburg and Kreitschmann-Andermahr, 2016). This effect is replicable in rats (Ehrlichman et al., 2008) and mice (Javitt, 1996) and in genetic models of NMDAR hypofunction (Light and Braff, 2005; Umbricht and Krljesb, 2005). Although the NMDA-targeted approach continues to evolve with the objective of finding an effective cognitive enhancement compound, recent evidence also suggests that nAChRs have the potential to

modulate NMDA receptors and glutamatergic signalling in the CA1 hippocampal region (Bali et al., 2017, 2019).

The modulatory effect of the prototypical nAChR agonist nicotine on measures of MMN in earlier studies (Baldeweg et al., 2006; Dulude et al., 2010; Fisher, Grant, et al., 2012; Inami et al., 2005; Kohlhaas et al., 2015; Martin et al., 2009; Mathalon et al., 2014) was followed by CDP-choline-enhanced MMN amplitudes in healthy volunteers and SCZ patients with marked reductions in MMN amplitudes (Aidelbaum et al., 2021; Knott et al., 2015a). Galantamine alone has not yet been examined on sensory/sensorimotor functioning in SCZ. However, this PAM improved impaired cognitive functioning (Buchanan et al., 2008) and its combination with memantine (an NMDA receptor antagonist) was proposed to accentuate memantine's improvement of sensorimotor gating in SCZ (Koola, 2018; Swerdlow et al., 2016).

5.4.3 Baseline dependency effects

Significant clinical and cognitive heterogeneity in SCZ (Joyce and Roiser, 2007; Seaton et al., 1999) and a highly variable response in the treatment of SCZ (Stroup, 2007) have demonstrated the need for a meaningful subtyping schema (Ahmed et al., 2018), including sample stratification approaches (Takahashi, 2013) and the use of endophenotypes (Albus, 2012) to characterize subgroups of SCZ for more personalized intervention strategies (Malhotra, 2015). At the basic sensory level, findings of interindividual differences in early auditory processing indexed by the tone-matching task (TMT) were reflected by a bi-modal distribution of early auditory processing deficits, with SCZ patients exhibiting markedly impaired performance showing poorer cognitive performance and functional capacity (Dondé et al., 2017; Dondé et al., 2019a) and as well greater cognitive benefits from auditory-training (Medalia et al., 2019) compared to patients with intact (TMT) performance. Interindividual differences in cognitive response to nAChR agonists

are in part due to differences in baseline performance levels (Perkins, 1999) and parsing nicotinic effects on the basis of baseline levels of behavioural and electrophysiological markers has revealed subpopulations of responders and nonresponders with regards to nicotine and CDP-choline effects on sensory gating (Knott et al., 2013, 2014a), MMN (Knott et al., 2015a, 2014b), P300 (Hyde et al., 2016), and cognition (Knott et al., 2015b) in healthy individuals and SCZ (Aidelbaum et al., 2021); antipsychotic treatment effects on sensory gating (Adler et al., 2004, 2005); and combined CDP-choline/galantamine treatment effects on sensory gating in healthy and SCZ participants (Choueiry et al., 2019a,b) and deviance detection in healthy low-baseline amplitude groups (Choueiry et al., 2020).

5.4.4 Objectives and hypothesis

With respect to these recent findings, the specific objective of this preliminary pilot study was to assess the acute effect of a combined CDP-choline/galantamine treatment on auditory deviance detection assessed in patients with SCZ segregated by baseline MMN amplitude into low, medium, and high deviance detection subgroups. Although typically assessed in response to simple (tone) stimuli, MMNs will be examined in response to speech stimuli in an attempt to assess nicotinic-sensory processing relationships in a more clinically meaningful context, particularly in light of the impairments in speech and language functions observed in SCZ (Carrión et al., 2015; Revheim et al., 2014).

Relative to placebo, the combined acute administration of CDP-choline and galantamine was expected to improve speech deviance detection (increased MMN amplitudes) in SCZ individuals who express lower baseline detection (smaller MMN amplitudes). This corresponds to our previous outcomes in which showed improvements in deviance detection (larger MMNs)

during a dose-response study of CDP-choline in more impaired SCZ (Aidelbaum et al., 2021) and healthy individuals (Knott et al., 2015a).

Clinical measures of positive, negative, and general symptoms were analyzed as an exploratory secondary objective as previous studies have shown an association between MMN measures and SCZ clinical ratings (Fisher et al., 2011; Fisher, Labelle, et al., 2012; Ghajar et al., 2018).

5.5 Materials and methods

5.5.1 Study participants

Twenty-six chronic SCZ patients were recruited from the Schizophrenia Outpatient Program at The Royal Ottawa Mental Health Centre. Eligible participants had a DSM-IV SCZ diagnosis with a clinically stable status for a minimum of ninety days prior to study recruitment, assessed with the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987). Recruited patients with SCZ were on a stable neuroleptic regimen for at least four weeks consisting of a one- or a combination of these treatments: aripiprazole, risperidone, flupentixol, haloperidol, paliperidone, levomepromazine, olanzapine, perphenazine, quetiapine, trifluoperazine, ziprasidone. Individuals taking clozapine were not selected to participate. Mixed findings have been previously reported for this treatment's effect on cognition and electrophysiological measures of sensory gating (P50) and deviance detection (Sanchez-Morla et al., 2009; Su et al., 2012). Study exclusion factors included other DSM-IV disorders, medical illness, a recent (< 6 months) head injury with loss of consciousness, and hearing impairment (as measured audiometrically). Individuals who participated in this study were assessed and showed normal laboratory and drug screen tests, normal weight, and normal hearing. All study procedures and participant recruitment, assessment, and testing, were in compliance with the Research Ethics Boards of The Royal Ottawa Mental Health Care Group and the University of Ottawa.

Participants signed an informed consent form prior to undertaking any study procedure and received $100 following study completion. The final study sample of 24 participants consisted of 7 females and 17 males, with 8 non-smokers and 16 smokers, and a mean age of 44.5 years, SE ± 2.06. One participant dropped out before study completion, and another participant's data was discarded due to significant EEG recording artifacts. Non-smoking status relied on participant attestation that they had consumed less than one hundred cigarettes in their lifetime and had not used any tobacco products within the past year prior to study recruitment. Smokers had been smoking for an average of M = 24.3, SE ±2.0 years, consuming on average M = 16.6, SE ±1.9 cigarettes per day. Participants' medications were all evaluated for anticholinergic impact. Each participant was allocated an anticholinergic cognitive burden score (Chew et al., 2008; Salahudeen et al., 2015) that was later examined for its relationship with CDP-choline/galantamine effects and for comparing subgroup differences amongst LG, MG, and HG scores. First, each medication the participant is prescribed was given a score from 1-3 based on the anticholinergic cognitive burden score table which assigns a value of 1 – 3 to medications that exert a mild, moderate, and severe anticholinergic effect (Table 1 in (Boustani et al., 2008); drugs that do not exert an anticholinergic effect were valued at 0). Second, the anticholinergic scores of the different drugs taken by the participant were added together to give the total anticholinergic cognitive burden score for each participant.

5.5.2 Experimental design

A randomized, double-blinded, and counterbalanced design was employed to assess study volunteers during both a placebo treatment session and an active treatment (CDP-choline +

galantamine) session. An equal number of participants started with the placebo as with the treatment session.

To examine the active CDP-choline/galantamine treatment effect within our stratification approach, for each deviant type separately, MMN amplitude measures from the baseline (placebo) treatment condition were used to sub-group the total sample of SCZ participants into low (LG), medium (MG), and high (HG) amplitude individuals. MMN amplitudes at midline frontal (Fz) were used to rank participants' deviance detection with the first 8 participants with the lowest MMN values comprising the LG, the next 8 participants comprised the MG, and the 8 remaining participants exhibiting the highest MMN amplitudes comprised the HG.

5.5.3 Treatment administration

Non-active placebo capsules (250 mg of cellulose) matched the active treatment capsules (2 x 250 mg capsules of CDP-choline and 1 x 250 mg capsule containing 16 mg of galantamine + 234 mg of cellulose) in shape, size, and colour. Participants ingested two (cellulose or CDP-choline-filled capsules) at study time 0 minutes and a single capsule (filled with cellulose or galantamine) sixty minutes later.

5.5.4 Experimental procedure

The two testing sessions started between 8:00 am and 11:30 am (starting time was maintained consistent for both sessions for each participant). Upon arrival at the laboratory, participants verbally confirmed abstinence from food, drugs (neuroleptics for treating SCZ were taken as usual), alcohol, caffeine, and tobacco. Smoking abstinence was further verified with a measurement of exhaled carbon monoxide (CO) that had to be lower than 3 p.p.m. for non-smokers and less than the exhaled CO level at the screening session for smokers. Participants were then asked to orally consume two capsules consisting of either the placebo or active (CDP-choline) treatment (time 0 minutes). Participants were asked to remain seated and relaxed in a

sound-attenuated chamber where they watched an emotionally neutral movie of their choice during the treatment absorption period. Sixty minutes later, the second placebo or active (galantamine) treatment was administered, and the absorption period continued for an additional sixty minutes. MMN paradigm presentation and recording began at peak CDP-choline/galantamine absorption time (120 minutes).

5.5.5 MMN paradigm

During the presentation of the fast multi-feature speech MMN paradigm, participants remained seated as they watched a silent video (The Blue Planet by BC, 2001).

5.5.5.1 Stimuli

Finnish-language consonant-vowel /te:/ and /pi:/ (F0: 101 Hz, syllable duration: 170 ms, and intensity: 70 dB (SPL); (Pakarinen et al., 2009)) stimuli were projected binaurally through noise-cancelling headphones. Deviant stimuli differed from the standard in syllable frequency (FRE), intensity (INT), vowel duration (DUR), and a change of consonant (CON) or vowel (VOW). An 8% increase or decrease in intensity was applied to FRE deviants (F0 ±8%, 93/109 Hz, with an equal distribution between the higher and lower presentations). In comparison to standard stimuli, INT deviants varied in ± 6 dB with an equal number of presentation of both quieter and louder deviants). DUR deviants were 70 ms shorter than the standard stimuli. The MMN paradigm was presented in four blocks. Two blocks used /te/ standard stimuli and presented /pe/ syllables as CONS deviants and /ti/ syllables as VOW deviants. The other two blocks used /pi/ standard stimuli and presented /ti/ syllables as CONS deviants and /pe/ syllables as VOW deviants.

5.5.5.2 Presentation

In accordance with the Optimum-1 MMN paradigm (Näätänen et al., 2004) presentation sequence recommendation, each of the four 5-minute MMN blocks included 465 syllables (1860

stimuli in total) where every other syllable was a standard (p = 0.5), with one of the 5 deviant syllables (p = 0.1, for each deviant type) in between. Each block was initiated with five standard syllables. Syllable presentation was pseudo-randomized to ensure that every deviant type appeared once within the presentation of ten successive stimuli and ensuring that the same deviant was not to repeated consecutively after the standard following it. The presentation order of the standard /te:/ and /pi:/ sequence blocks were randomized amongst participants.

5.5.6 ERP recording and processing

Brain Vision Quickamp® (Brain Products, Gmbh, Munich, Germany) amplifier and Brain Vision Recorder® software were used to record EEG signals. The amplifier bandpass filter was set at 0.1 to 70 Hz with a 500 Hz continuous digitization. Based on the 10/10 international system (Jurcak et al., 2007), thirty Ag^{+}/Ag^{+} Cl^{-} electrodes were positioned at scalp sites: Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T7, T8, P7, P8, Fz, Cz, Pz, Oz, FC1, FC2, CP1, CP2, FC5, FC6, CP5, CP6, TP9, and TP10. Electrode impedance was kept below 5 kΩ throughout the recording session using a reference electrode placed on the nose and a ground electrode placed at the AFz site. Vertical (VEOG) and horizontal (HEOG) electro-oculographic activity were measured using electrodes placed on the supra- and sub-orbital ridges of the right eye and on the external canthus of both eyes, respectively.

Brain Vision Analyzer® (Brain Products, Gmbh, Munich, Germany) software was used for offline processing and analysis of EEG signals. Raw signals were processed in the following order using a 24 dB/octave digital filter initially with a low-high cutoff window of 1 – 20 Hz, followed with ocular-correction (Gratton et al., 1983), segmentation into 500 ms epochs (starting at 100 ms pre-stimulus onset), an automatic artifact rejection eliminating epochs showing voltages surpassing ± 75 µV, and using the 100 ms pre-stimulus electrical activity a baseline-correction was applied. Epochs for each deviant and standard stimulus were averaged separately,

and difference waveforms were derived by digital point-by-point subtraction of the standard waveform voltage values from the deviance waveform values.

The greatest negative peak occurring between 100-250 ms post-stimulus-onset was used to quantify MMN peak amplitude and latency at frontal (F_z, F_3, and F_4) (Näätänen et al., 2004).

5.5.7 Clinical Measures

The severity of positive symptoms (e.g. delusions, hallucinations, score ranges from 7 – 49) and negative symptoms (e.g. blunted affect, emotional withdrawal, ranging from 7 – 49) are highlighted by the positive and negative subscale scores, respectively. The general psychopathology subscale includes symptoms of anxiety, tension, and depression (ranging from 16 – 112), and the sum of all three subscales makes up the PANSS Total score (M = 62.25, SE ±2.8) (Kay et al., 1987).

5.5.8 Adverse events

At the end of each testing session, participants were asked to rate the severity of symptoms experienced following treatment administration on a scale from 1 (no symptom at all) to 5 (severe symptom) on a checklist of physical and psychological adverse events associated with nicotinic cholinergic stimulation.

5.5.9 Vital signs

Participants' heart rate, systolic and diastolic blood pressure were measured before treatment administration (at time 0 minutes, before the administration of the first treatment) and at peak absorption time (~ 90 minutes) for safety purposes only.

5.5.10 Statistical analysis

Recorded MMN amplitude measures from the frontal (Fz) electrode site were analyzed using the Statistical Package for the Social Sciences software (SPSS, IBM Corporation, New

York, USA). MMN amplitudes to each of the deviant types (FRE, INT, DUR, CON, and VOW) were used separately (each deviant type as an independent measure) in all of the analysis presented.

The overall effect of the active CDP-choline/galantamine treatment on measures of MMN amplitudes for each deviant type (separately) in the full group sample was analyzed using separate repeated-measures analysis of variance (ANOVA) with within-subject factors consisting of treatment (two levels, placebo treatment vs. CDP-choline/galantamine treatment) at electrode scalp position Fz. Bonferroni-adjusted planned comparisons were followed-up for significant effects ($p < 0.05$), and Greenhouse-Geisser corrected.

The group stratification of LG, MG, and HG, was used as a between-subjects factor (three levels) in repeated measures ANOVAs for each deviant type separately with treatment (two levels: placebo, CDP-choline/galantamine) as within-subjects repeated measures factors. Significant Greenhouse-Geisser corrected effects ($p < 0.05$) were followed up with Bonferroni-adjusted planned comparisons. As any group differences in treatment response may reflect a 'regression to the mean' effect, similar ANOVAs were conducted with participants stratification using active treatment (i.e., not placebo) MMN scores.

Chlorpromazine equivalent (CPZ; mg/day) was assessed separately for each MMN deviant type (separately) using one-way ANOVAs to verify any LG, MG, and HG participants differences with respect to their current neuroleptic treatment and hence eliminate a potential association of deviance detection subgroup differences with current neuroleptic treatment differences.

Potential between-group differences were assessed using Fisher's Exact Test analysis for gender (female/male) and smoking status (non-smoker/smoker), and oneway ANOVAs to assess

age, PANSS scores, anticholinergic load (Chew et al., 2008; Salahudeen et al., 2015), and chlorpromazine equivalent score (Leucht et al., 2016). Spearman's correlations were employed to examine relationships between treatment-induced MMN change (indexed by difference scores [CDP-choline/galantamine MMN amplitude minus placebo MMN amplitude]) and positive, negative, general, and total PANSS scores.

5.6 Results

5.6.1 Demographic and clinical measures

Twenty-four participants with SCZ were part of the final sample included in this study (M_{age} = 44.5 years, SE ± 2.06) and consisted of 7 females and 17 males, 8 non-smokers and 16 smokers. Demographic data for baseline low (LG), medium (MG), and high (HG) amplitude responder subgroups for each deviant type are presented in Table 5.1. LG, MG, and HG subgroups were not statistically distinguished based on age, gender, or smoking status following one-way ANOVAs (for age) and Fisher's test (for gender and smoking status) analysis. Also, ANOVAs and post-hoc analyses confirmed that LG, MG, and HG individuals did not score differently on PANSS (see Table 5.2).

Table 5.1 Demographics for LG (N=8), MG (N=8), and HG (N=8) amplitude subgroups for each MMN deviant type separately. LG, MG, and HG were not significantly different for each demographic measure

	Frequency			
	LG	MG	HG	Group analysis
Age (mean ± SE)	44.5 (2.77)	47.4 (3.87)	41.6 (4.12)	F(2,23) = 0.626, p = .545
Sex (F/M)	2/6	4/4	1/7	FET = 2.607, p = .402
Smoking status (NS/S)	3/5	3/5	2/6	FET = 0.523, p = 1.0
	Intensity			
	LG	MG	HG	Group analysis
Age (mean ± SE)	42.1 (3.65)	48 (3.34)	43.4 (3.84)	F(2,23) = 0.732, p = .493
Sex (F/M)	2/6	3/5	2/6	FET = 0.547, p = 1.00
Smoking status (NS/S)	3/5	2/6	3/5	FET = 0.523, p = 1.0
	Duration			
	LG	MG	HG	Group analysis
Age (mean ± SE)	46.6 (1.98)	46.6 (3.95)	40.2 (4.32)	F(2,23) = 1.066, p = .362
Sex (F/M)	3/5	3/5	1/7	FET = 1.667, p = .619
Smoking status (NS/S)	3/5	3/5	2/6	FET = 0.523, p = 1.0
	Consonant			
	LG	MG	HG	Group analysis
Age (mean ± SE)	47.1 (2.85)	39.5 (2.46)	46.9 (4.74)	F(2,23) = 1.537, p = .238
Sex (F/M)	2/6	0/8	5/3	FET = 7.212, p = .031
Smoking status (NS/S)	2/6	3/5	3/5	FET = 0.523, p = 1.0
	Vowel			
	LG	MG	HG	Group analysis
Age (mean ± SE)	44.4 (2.39)	43.5 (3.49)	45.6 (4.88)	F(2,23) = 0.082, p = .921
Sex (F/M)	1/7	2/6	4/4	FET = 2.607, p = .402
Smoking status (NS/S)	3/5	1/7	4/4	FET = 2.582, p = 0.418

F/M: female/male; NS/S: non-smokers/smokers; FET: Fisher's Exact Test score;

Table 5.2 Mean (±SE) anti-cholinergic load, chlorpromazine equivalent (mg/day), and psychometric scores for LG (N=8), MG (N=8), and HG (N=8) amplitude subgroups for each MMN deviant type separately

	Frequency LG	MG	HG	Group analysis
Anticholinergic load score	3.50 (0.54)	5.75 (1.25)	4.38 (1.19)	F(2,23) = 1.179, p = 0.051
CPZ equivalent (mg/day)	669 (149)	728 (171)	711 (188)	F(2,23) = 0.320, p = 0.969
PANSS Total	67.13 (4.28)	55.5 (3.78)	64.13 (5.85)	F(2,23) = 1.634, p = 0.219
PANSS Positive	16.88 (1.47)	15.38 (1.07)	16 (1.07)	F(2,23) = 0.383, p = 0.686
PANSS Negative	17.5 (1.64)	13.5 (1.94)	18.13 (1.46)	F(2,23) = 2.209, p = 0.135
PANSS General	33.38 (2.16)	26.5 (2.29)	30 (4.58)	F(2,23) = 1.149, p = 0.336
	Intensity LG	MG	HG	Group analysis
Anticholinergic load score	4.38 (0.653)	6.25 (1.21)	3.00 (1.00)	F(2,23) = 2.771, p = 0.086
CPZ equivalent (mg/day)	681 (134)	952 (203)	476 (108)	F(2,23) = 2.399, p = 0.115
PANSS Total	62 (6.87)	64.75 (4.07)	60 (3.45)	F(2,23) = 0.225, p = 0.8
PANSS Positive	16.88 (1.39)	17.13 (1.17)	14.25 (0.75)	F(2,23) = 1.961, p = 0.166
PANSS Negative	16.88 (1.83)	15.13 (1.59)	17.13 (2.04)	F(2,23) = 0.356, p = 0.705
PANSS General	28.88 (4.84)	32.38 (2.63)	28.63 (1.64)	F(2,23) = 0.4, p = 0.675
	Duration LG	MG	HG	Group analysis
Anticholinergic load score	4.50 (1.27)	4.13 (0.83)	5.00 (1.13)	F(2,23) = 0.161, p = 0.852
CPZ equivalent (mg/day)	606 (159)	757 (152)	746 (192)	F(2,23) = 0.247, p = 0.783
PANSS Total	59.5 (3.61)	66.38 (4.83)	60.88 (6.10)	F(2,23) = 0.54, p = 0.591
PANSS Positive	15.38 (1.0)	18.13 (1.29)	14.75 (1.01)	F(2,23) = 2.626, p = 0.096
PANSS Negative	15.25 (1.52)	16.25 (2.04)	17.63 (1.86)	F(2,23) = 0.429, p = 0.657
PANSS General	29.5 (2.10)	32 (2.62)	28.38 (4.69)	F(2,23) = 0.311, p = 0.736
	Consonant LG	MG	HG	Group analysis
Anticholinergic load score	3.88 (0.95)	4.88 (0.97)	4.88 (1.30)	F(2,23) = 0.282, p = 0.757
CPZ equivalent (mg/day)	570 (111)	834 (196)	705 (178)	F(2,23) = 0.635, p = 0.540
PANSS Total	65.75 (3.92)	61.88 (5.04)	59.13 (5.78)	F(2,23) = 0.448, p = 0.645
PANSS Positive	17 (0.96)	15.25 (1.48)	16 (1.12)	F(2,23) = 0.527, p = 0.598
PANSS Negative	16.38 (2.01)	16.63 (1.77)	16.13 (1.78)	F(2,23) = 0.018, p = 0.982
PANSS General	32.25 (2.03)	30.63 (3.28)	27 (4.16)	F(2,23) = 0.674, p = 0.52
	Vowel LG	MG	HG	Group analysis

Anticholinergic load score	3.25 (0.56)	4.50 (1.13)	5.88 (1.25)	F(2,23) = 1.642, p = 0.217
CPZ equivalent (mg/day)	670 (144)	728 (208)	711 (151)	F(2,23) = 0.030, p = 0.971
PANSS Total	70.63 (3.59)	64.88 (3.18)	51.25 (5.10)	F(2,23) = 6.062, p = 0.008
PANSS Positive	17.5 (1.22)	15.63 (1.34)	15.13 (0.93)	F(2,23) = 1.132, p = 0.341
PANSS Negative	18.75 (1.73)	16.75 (1.51)	13.63 (1.78)	F(2,23) = 2.37, p = 0.118
PANSS General	35 (1.64)	32.38 (2.29)	22.5 (3.73)	F(2,23) = 5.973, p = 0.009

Anticholinergic load score based on neuroleptics that are known to interact (i.e., congentin, risperidone, haloperidol, olanzapine, perphenazine, quetiapine, procyclidine, dimenhydrinate, bupropion, stelazine, ranitidine, hydrochlorothiazide, trihexyphenidyl, oxybutynin) with the cholinergic system (Chew et al., 2008; Salahudeen et al., 2015). *Chlorpromazine equivalents (CPZ; mg/day) were calculated according to* (Leucht et al., 2016). *The positive, negative, and general scales are subscales from the Positive and Negative Symptom Scale (PANSS).*

5.6.2 MMN amplitude measures

5.6.2.1 Total Group

No main drug effect was observed in the total group sample for any of the MMN deviants. Grand averaged difference (deviant minus placebo) waveforms for each deviant type during placebo and CDP-choline/galantamine treatment conditions are shown in Figure 5.1.

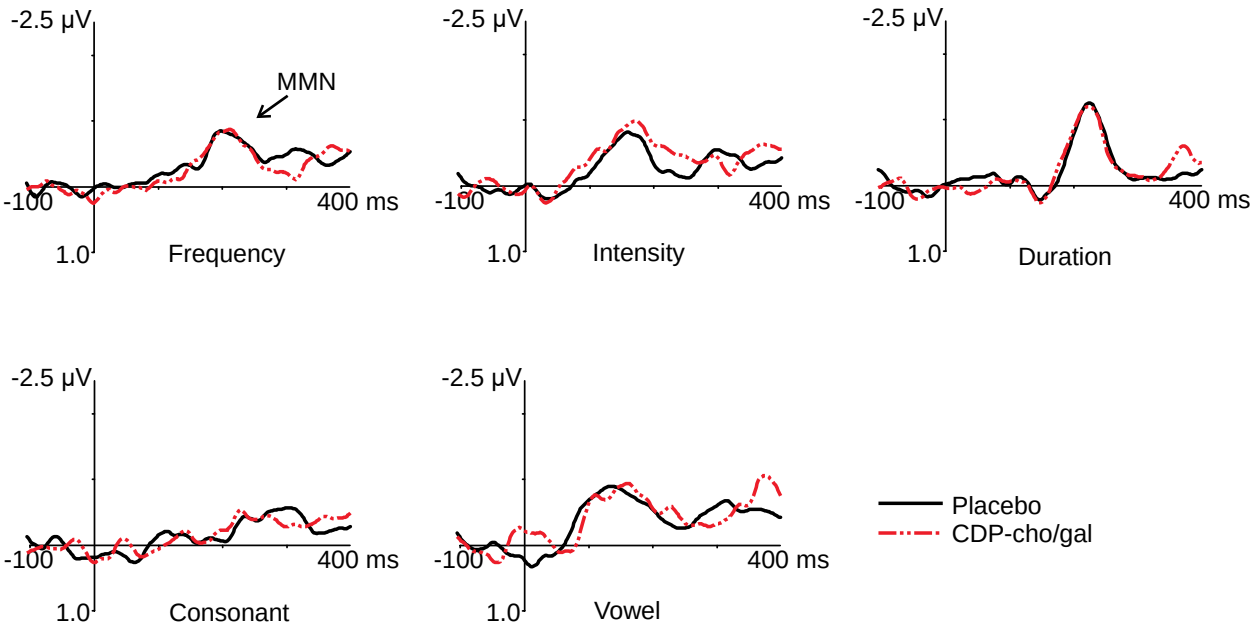

Figure 5.1 Frontal (Fz) ERP grand averaged difference waveforms (deviant minus standard) for the 5 deviants during placebo and CDP-choline/galantamine (CDP-cho/gal) conditions

5.6.2.2 Group comparisons

No main drug effect was observed for any of the MMN deviants.

As expected, based on the study design, main group effects were observed for all deviant types portraying significant amplitude differences amongst LG, MG, and HG (Figure 5.2). Follow-up analyses revealed significantly smaller amplitudes for LG in comparison to HG for all deviants and significantly smaller amplitudes for LG in comparison to MG for INT and VOW deviants.

Significant treatment x group interactions were observed for FRE ($F(2,21) = 9.72$, $p = 0.001$, $\eta_p^2 = .481$), DUR ($F(2,21) = 11.19$, $p < 0.001$, $\eta_p^2 = .516$), CON ($F(2,21) = 6.30$, $p = 0.07$, $\eta_p^2 = .375$), and VOW ($F(2,21) = 10.24$, $p = .001$, $\eta_p^2 = .494$) deviants only (Figure 5.3).

Follow-up comparisons for FRE, DUR, and VOW deviants revealed that CDP-choline/galantamine (vs. placebo) significantly increased MMN amplitudes in LG ($p_{FRE} = 0.005$, $\eta_p^2 = .325$; $p_{DUR} = 0.003$, $\eta_p^2 = .344$; $p_{VOW} = 0.004$, $\eta_p^2 = .327$). The opposite effect was observed for HG with CDP-choline/galantamine for FRE, DUR, CON, and VOW showing smaller amplitudes in comparison to placebo ($p_{FRE} = 0.007$, $\eta_p^2 = .297$; $p_{DUR} = 0.004$, $\eta_p^2 = .329$; $p_{CON} = 0.010$, $\eta_p^2 = .277$; $p_{VOW} = 0.006$, $\eta_p^2 = .310$). No treatment effect was observed for MG for both these deviants.

Also, for FRE, DUR, CON, and VOW deviants, significant group differences were observed only under the placebo condition where significant smaller MMN amplitudes were recorded for the LG in comparison to MG ($p_{FRE} < .001$, $\eta_p^2 = .852$; $p_{DUR} < 0.001$, $\eta_p^2 = .815$; $p_{CON} = 0.012$, $\eta_p^2 = .786$; $p_{VOW} < .001$, $\eta_p^2 = .844$) and HG ($p_{FRE} < 0.001$, $\eta_p^2 = .852$; $p_{DUR} = 0.001$, $\eta_p^2 = .815$; $p_{CON} < 0.001$, $\eta_p^2 = .786$; $p_{VOW} < .001$, $\eta_p^2 = .844$), and for the MG in comparison to the HG

($p_{FRE} < .001$, $\eta_p^2 = .852$; $p_{DUR} = 0.001$, $\eta_p^2 = .815$; $p_{CON} < 0.001$, $\eta_p^2 = .786$; $p_{VOW} < .001$, $\eta_p^2 = .844$).

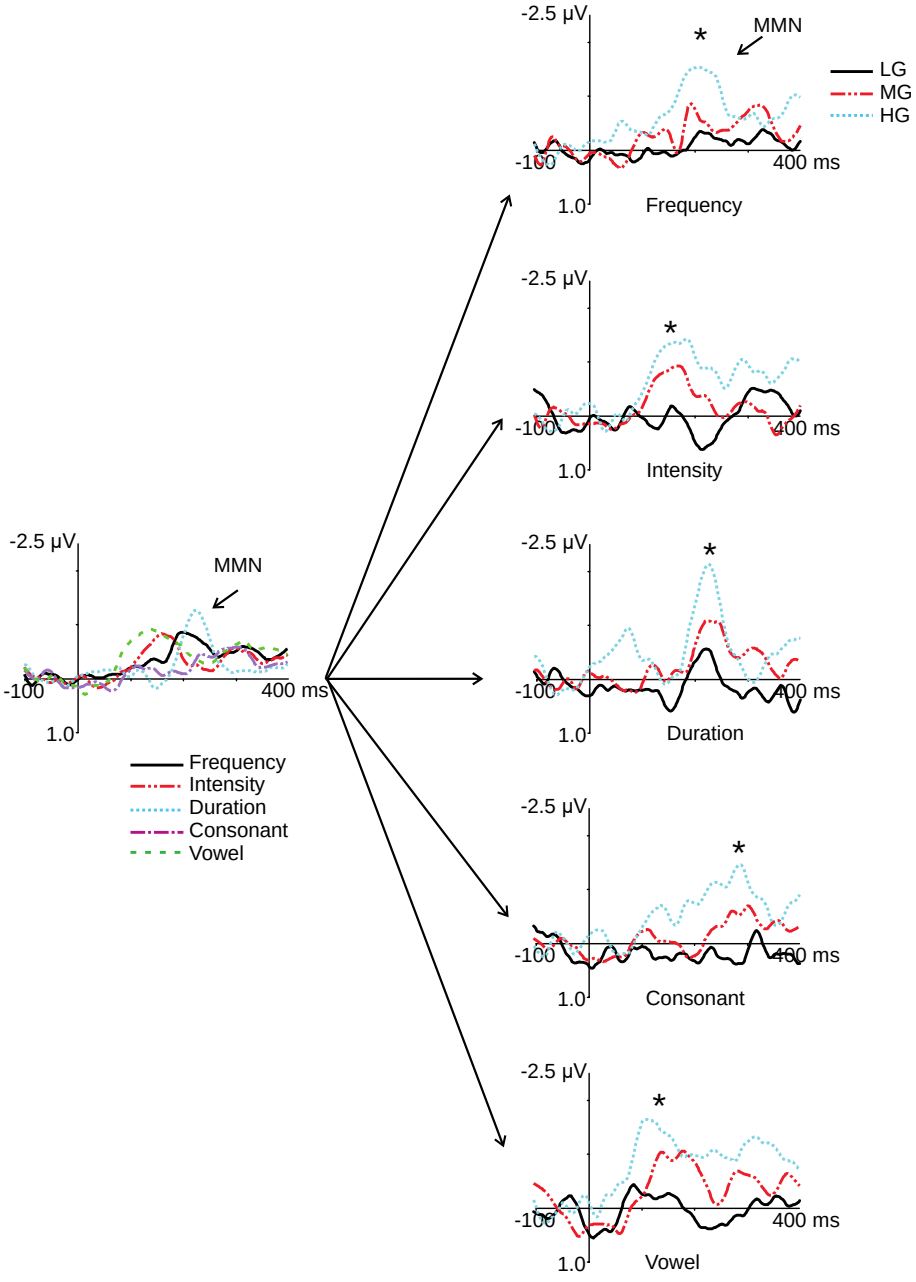

Figure 5.2 Baseline (placebo) grand averaged frontal (Fz) difference waveforms (deviant minus standard) for the 5 deviants in the total sample and in LG (low), MG (medium), and HG (high) amplitude MMN subgroups. (* $p \leq 0.01$)

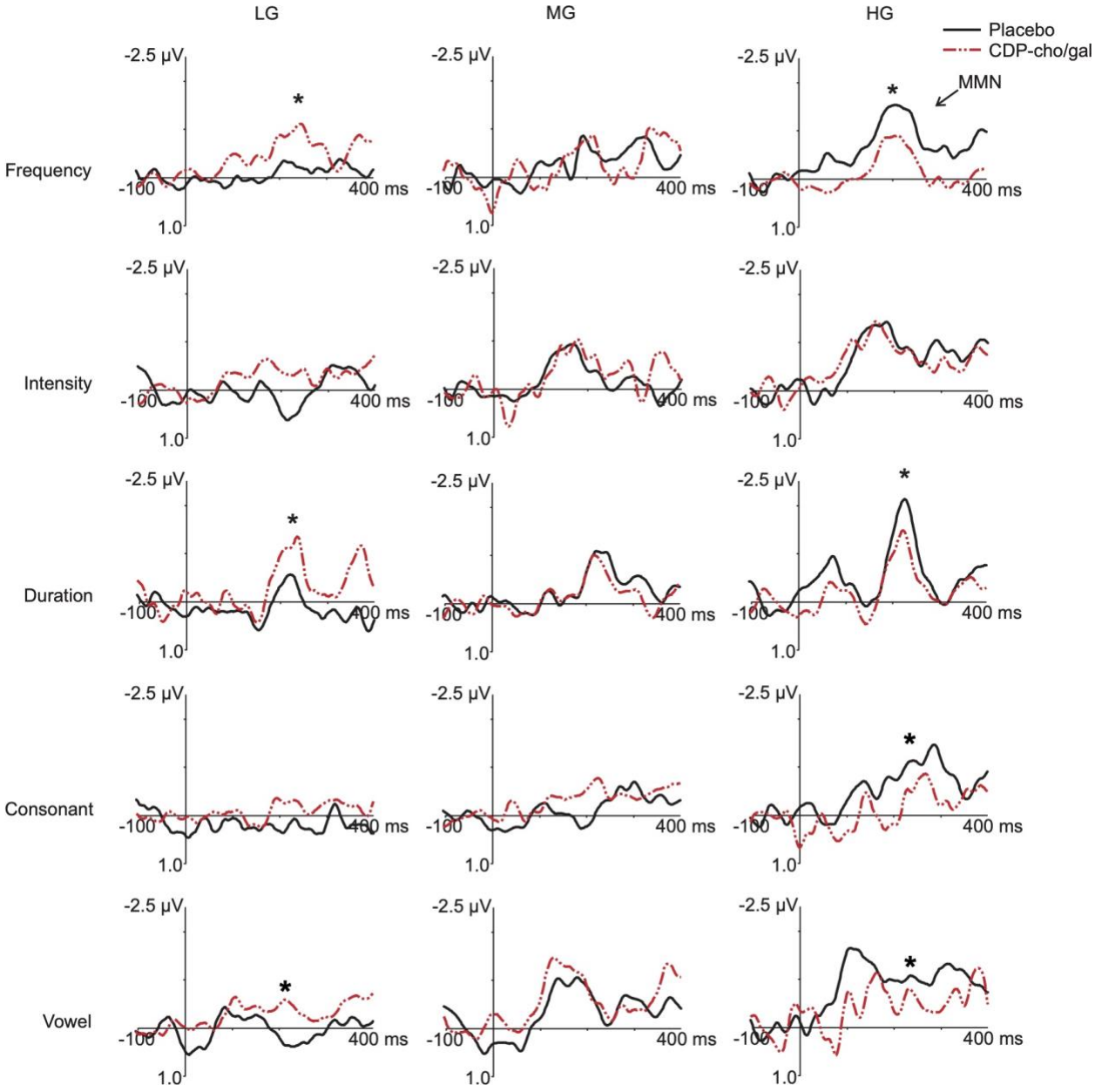

Figure 5.3 Frontal (Fz) grand averaged difference waveforms (deviant minus standard) for the 5 deviants in LG (low), MG (medium), and HG (high) participants during placebo and CDP-choline/galantamine (CDP-cho/gal) conditions. (* p < 0.05)

5.6.3 CDP-choline/galantamine based subgrouping

There were no significant findings when subgrouping was based on amplitude scores from the active CDP-choline/galantamine session (vs. placebo).

5.6.4 CDP-choline/galantamine treatment effect correlations

Treatment-induced amplitude changes were negatively correlated with placebo amplitudes at Fz and for all MMN deviants, indicating that greater CDP-choline/galantamine-mediated amplitude increases were observed in individuals with lower MMN generation at baseline (placebo). The opposite effect was observed in individuals with higher MMN generation at baseline.

5.6.5 PANSS – speech-related MMN relationships

CON amplitude treatment change scores correlated with PANSS total score (Spearman's rho = -.447, p = 0.028), and PANSS total negative subscale score (Spearman's rho = -.414, p = 0.044). VOW amplitude treatment change scores negatively correlated with PANSS total score (Spearman's rho = -.522, p = 0.009), and with PANSS general subscale score (Spearman's rho = -.475, p = 0.019). These CDP-choline/galantamine-related improvements of MMN amplitudes to CON and VOW deviants indicate that greater amplitude increases were observed in individuals who expressed higher PANSS negative, general, and total scores (Figure 5.4).

5.6.6 Adverse events

Participants' self-reports of adverse events on a checklist of symptoms experienced were not significantly different during CDP-choline/galantamine treatment sessions in comparison to placebo. There were no reports of severe symptoms throughout the study.

5.6.7 Vital signs

Measures of systolic and diastolic blood pressure were not statistically different during the CDP-choline/galantamine treatment sessions in comparison to placebo. On that same note, heart rate measures taken pre- and post-treatment administration were also not significantly different during CDP-choline/galantamine treatment sessions in comparison to placebo.

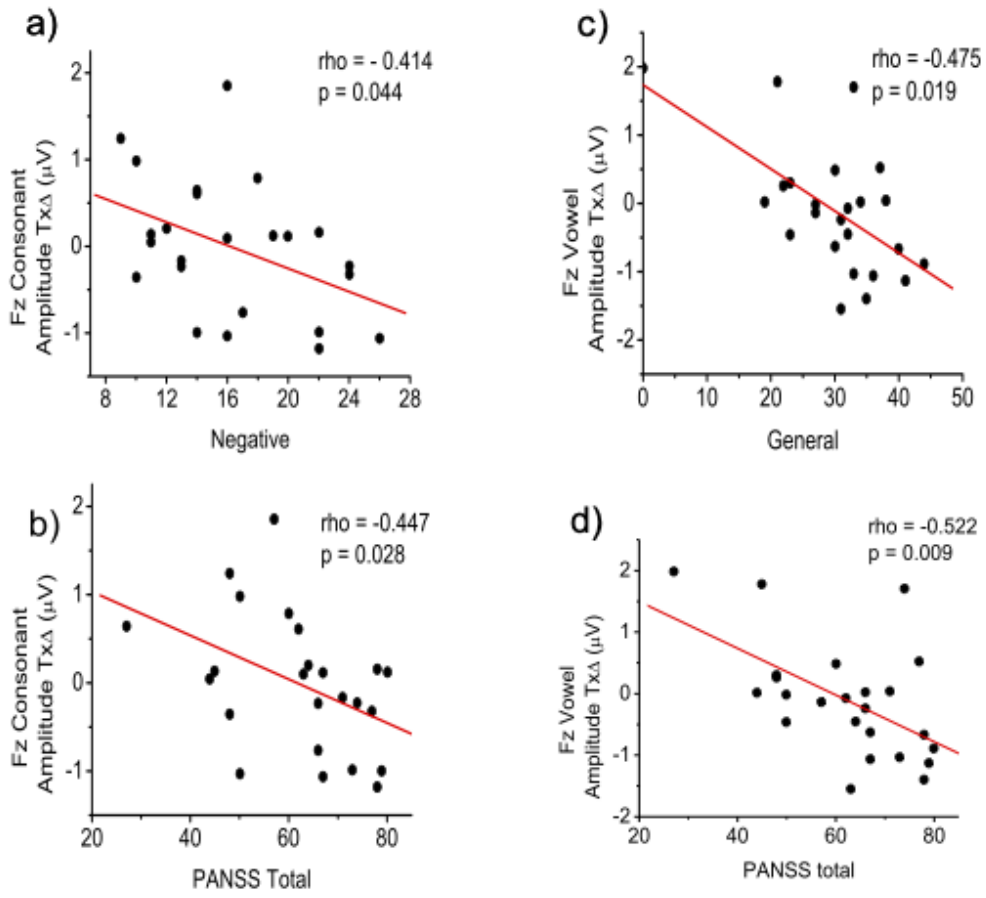

Figure 5.4 Scattergrams of treatment effect (TxΔ) amplitudes (treatment – placebo) for CON at Fz (a, b), and VOW at Fz (c, d) correlation with PANSS total, negative, and general scores

5.7 Discussion

5.7.1 Summary of findings

This is the first examination of the acute and combined treatment of CDP-choline/galantamine on measures of deviance detection in patients with SCZ. The treatment did not show any effects in the full sample group while individuals demonstrating low deviance detection levels at baseline best responded to the treatment with significant enhancement of MMN amplitudes to FRE, DUR, and VOW deviants. These promising preliminary findings in patients with SCZ suggest that modulation of the nicotinic cholinergic system, the α7 nAChR

specifically, differentially impacts early auditory processing in SCZ and may have the potential to benefit selectively those with impaired measures of deviance detection.

5.7.2 CDP-choline/galantamine mediated modulation of deviance detection in schizophrenia

CDP-choline/galantamine treatment significantly increased deviance detection in LG individuals following FRE, DUR, and VOW deviants. However, in HG individuals, this active treatment diminished deviance detection following FRE, DUR, CON, and VOW deviants.

In general, the differential (baseline-dependent) effect of this combined CDP-choline/galantamine treatment is in line with our pilot study in healthy participants where increased amplitudes were observed to VOW deviants (Choueiry et al., 2020). In comparison, 2000 mg of CDP-choline alone induced larger MMN amplitude to DUR deviants (Aidelabum et al., 2021), while our results demonstrated an increase with 500 mg of CDP-choline in combination with galantamine (16 mg). Considering these findings it would be reasonable to suggest that the α7 nicotinic system in chronic SCZ is not permanently disabled due to the neurodevelopmental impact of the illness.

Furthermore, improved Quality of life and cognitive status were associated with long-term (2 years) treatment with CDP-choline in ischemic stroke patients (Alvarez-Sabín et al., 2016) and the combination of nicotine and galantamine was recently shown to benefit working memory in healthy individuals (Hahn et al., 2019). Hence, these latest findings urge the need to evaluate the sensory/cognitive effects of this CDP-choline/galantamine treatment strategy and their relationship to functional outcome indicators. Given that these present findings were obtained with speech MMN, this latter thrust is important as phonological language processing affects educational and occupational function (Carrión et al., 2015; Dondé et al., 2019a; Friedman et al., 2012; Revheim et al., 2006, 2014). Additional studies with this combined

treatment should examine effects on more subtle linguistic deviants (e.g., variations in emotional or attitudinal prosody) that are linked to psychosocial functioning impairments that are often prognostic in SCZ (Javitt and Sweet, 2015; Revheim et al., 2014).

Recent findings bring forth the implication of nAChRs in MMN generation, in addition to its well documented moderation by glutamate and NMDA receptors (Javitt, 1996; Kantrowitz et al., 2018; Swerdlow et al., 2016; Tikhonravov et al., 2008), and highlighting the involvement of α7 nAChRs specifically in the CA1 hippocampal region (known for its role in learning and memory) where α7 nAChRs exerted modulatory effects on NMDA receptors (Askew and Metherate, 2016; Bali et al., 2017, 2019) and learning mechanisms (Broide and Leslie, 1999; Kantrowitz, 2018). These findings suggest a potential role for both these receptor systems in alleviating sensory/cognitive impairments in SCZ and other mental health disorders (Yang et al., 2017).

5.7.3 Relationship to patient symptoms

MMN change scores (CDP-choline/galantamine – placebo) for CON, and VOW deviants differentially correlated with PANSS total, negative, and general scores, revealing that individuals expressing higher PANSS scores showed greater improvements in deviance detection. This is in line with previous correlations of positive, general psychosis, and the hallucinating item of the PANSS with smaller DUR deviant amplitudes at frontal sites in SCZ (Fisher et al., 2011), while DUR deviant latency measures correlated with PANSS negative and general scores (Fisher, Labelle, et al., 2012). Also, an 8-week CDP-choline add-on treatment to risperidone resulted in improved negative symptoms (PANSS) in patients with SCZ (Ghajar et al., 2018). These findings indicate that improvement in deviance detection measures by synergistic cholinergic stimulation, is significant for individuals with severe clinical ratings.

5.7.4 Baseline-dependent treatment effects

Improved deviance detection in LG and worsening in HG SCZ individuals following CDP-choline/galantamine replicate our findings in healthy participants (Choueiry et al., 2020), and extend previous reports of enhanced deviance detection in LG individuals with CDP-choline alone in healthy (Knott et al., 2015a) and SCZ (Aidelbaum et al., 2021) and with nicotine (Knott et al., 2014b; Smith et al., 2015). Full group effects have been reported with nicotine in healthy (Dulude et al., 2010; Inami et al., 2005), Ketamine-induced SCZ model (Mathalon et al., 2014), and psychiatric populations (Baldeweg et al., 2006; Fisher, Grant, et al., 2012; Martin et al., 2009). Interindividual differences observed in response to pharmacological treatments may be the results of several factors, including genetic mutations (SCZ is recognized as a multigenic disease), the use of certain neuroleptics (which have been associated with cognitive modulation), and smoking status (Gilbert and Gilbert, 1995; Kupferschmidt et al., 2010; Li et al., 2009; Perkins, 1995, 2009; Poltavski and Petros, 2005). However, our analyses indicate that LG, MG, and HG individuals did not statistically differ on the basis of medications affecting the cholinergic system (i.e., anticholinergic load) or on the chlorpromazine equivalent. Baseline deviance detection level should be considered when conducting future pilot pharmacological studies as these findings suggest that treatment change scores (treatment – placebo) portrayed an inverted-U-type treatment response. Targeted neural therapy in combination with the targeting of individual patients (expected to benefit and respond to the given treatment/therapy) was recently highlighted as a possible synergistic method toward the achievement of personalized therapy (Fisher and Salisbury, 2019).

5.7.5 Limitations

Multiple strengths characterize this study, including the double-blind and randomized treatment administration, counterbalanced, and a crossover repeated measures design. Also, the assessment

of female and male smokers and non-smokers is reflective of the SCZ population and permits the scientific validity and generalizability of our findings. Our analyses comparing smokers to non-smokers revealed no significant smoking-group differences for MMN amplitudes and latencies, deviating from previous reports showing that α7 agonists have evidenced precognitive effects in studies assessing only non-smoking participants, while negative results are typically shown when the study sample includes only smokers or a mixture of smokers and non-smokers (Tregellas and Wylie, 2019).

The relatively small sample size in the stratified amplitude groups could have limited the statistical power. Furthermore, the baseline stratification was conducted using the placebo session, which was later used for statistical analyses. Our blinded crossover counterbalanced design (with half of the group starting with placebo, while the other half with the active treatment) might have reduced potential regression to the mean effect. However, it would be best to employ a separate baseline session in future studies to eliminate this problem when segregating the full sample into low, medium, and high groups. In addition, it's important to highlight that MMN is a mature and stable ERP and the protocol design accounts for any elements that may contribute to mean regressions or potential flukes in ERP recording. Participants were asked to abstain from consuming any substances that may impact their performance (i.e., stimulants and illicit drugs), testing sessions were scheduled at the same time of day, and the examiner, protocol and steps were the same for each session. An initial baseline session will allow for the predesignation of lower sensory processing baseline individuals most likely to benefit from this treatment approach and will prevent treatment administration to individuals with higher sensory processing levels. Patients with lower baseline deviance detection should also be prioritized as the inclusion of patients with more efficient or intact

deviance processing might underpower the results (Cotter et al., 2019). Furthermore, our stratification strategy may help explain the failure for AVL-3288 (a selective α7 type 1 PAM, previously shown to ameliorate cognition) to enhance cognitive measures in SCZ, as this study selected individuals with higher cognitive processing levels at baseline (Gee et al., 2017; Kantrowitz et al., 2020).

This was a pilot study employing a single dose level of CDP-choline/galantamine to SCZ. The positive findings support further examinations that assess different combination dose levels in order to define a dose-response curve. Also, a recent assessment of long-term cognitive enhancement therapies in patients with Alzheimer's Disease reported time-mediated increasing effect only when acetylcholine esterase inhibitor (donepezil, rivastigmine, or galantamine) was combined with CDP-choline (vs. exclusive acetylcholine esterase inhibitor administration) (Gareri et al., 2017). While PAMs marketed for use in humans are limited, galantamine may be criticized in the context of this study as it is not selective to α7 nAChRs. However, CDP-choline activates several neurotransmitter systems via α7 nAChR downstream signalling and following CDP-choline metabolism into cytidine and choline, which then can produce betaine which in turn activates S-adenosyl-L-methionine production, which is a serotonin precursor (Adibhatla et al., 2001). The CDP-choline/galantamine treatment results in complex pharmacodynamics benefiting several neurotransmitter systems despite the selective nature of CDP-choline, and while this is discussed as a limiting factor for the specificity of the treatment, the most successful neuroleptics today have the ability to modulate several receptor systems (Bertrand and Terry, 2018).

5.8 Conclusion

Measures of auditory deviance detection were improved following the administration of an acute dose of CDP-choline/galantamine in a subpopulation of patients with SCZ expressing lower deviance detection levels at baseline. The effectiveness of this combined cholinergic treatment needs to be further examined in the broad spectrum of the SCZ disorder (including neuroleptic-naïve patients). Furthermore, before progressing to larger scale clinical trial, additional dosage trials for each and combined treatment need to be conducted in SCZ to determine the optimal dose ranges, and these studies need to examine relationships between MMN improvement and changes in behavioural measures of early auditory (e.g., TMT) and cognitive (e.g., MATRICS battery) processes.

Chapter 6

General Discussion

6.1 Summary of findings

The primary objective of this thesis was to assess the acute effect of a combined low dose CDP-choline/galantamine α7 nicotinic treatment on EAIP, specifically using speech P50 and speech MMN ERP biomarkers to examine auditory sensory gating (SG) and deviance detection, respectively, in individuals that are healthy and in people with SCZ. Because SCZ is heterogeneous in its clinical and cognitive/sensory presentation and presumably in its underlying pathophysiology, it was hypothesized that stratifying and analyzing patients' response according to the degree of sensory impairment at baseline (placebo) would help to prospectively identify α7 treatment-sensitive patient subgroups.

6.1.1 P50 findings

There were no main drug effects on P50 in both the healthy participants and patients with SCZ full group analyses.

In healthy high P50 suppressors (optimal gating scores), rP50 and dP50 gating indices were not modulated by CDP-choline/galantamine. However, S_2P50 amplitudes were increased (indicative of reduced inhibition) during the active treatment in comparison to placebo although it did not translate to significant reductions in gating measured by dP50 and rP50 indices. In low P50 suppressors (sub-optimal gating scores), CDP-choline/galantamine (in comparison to placebo) increased SG as measured by the rP50 and dP50 gating indices and decreased S_2P50 amplitudes (indicative of enhanced inhibition).

In high P50 suppressors with SCZ, CDP-choline/galantamine (vs. placebo) reduced SG as measured by rP50 and dP50 gating indices and significantly decreased S_1P50 amplitudes. In low P50 suppressors with SCZ, CDP-choline/galantamine improved SG as shown by rP50 and dP50 gating indices and significantly decreased S_2P50 amplitudes (increased inhibition).

6.1.2 MMN findings

With MMN measured at the frontal (Fz) site in healthy volunteers, CDP-choline/galantamine treatment (vs. placebo) increased vowel MMNs in low baseline amplitude individuals and reduced vowel MMNs and consonant MMNs in high baseline amplitude individuals. Measured at temporal sites, CDP-choline/galantamine treatment increased frequency MMNs, intensity MMNs, duration MMNs, and vowel MMNs in healthy low baseline amplitude individuals. CDP-choline/galantamine did not alter MMNs in high baseline amplitude individuals at temporal sites.

Measured only at the frontal sites, MMN amplitudes in low baseline amplitude individuals with SCZ were increased for frequency, duration, and vowel deviants during the CDP-choline/galantamine treatment (vs. placebo). The opposite effect was observed on high baseline amplitude individuals with SCZ, with frequency MMN, duration MMN, consonant MMN and vowel MMN being reduced with CDP-choline/galantamine compared to placebo.

6.2 Possible mechanisms

Based on previous studies demonstrating baseline-dependent effects of nicotine and choline along an inverted-U treatment response curve, we had hypothesized that individuals (healthy participants and patients with SCZ) that express relatively poorer baseline auditory sensory processing (i.e., higher rP50 scores; lower MMN amplitudes) would exhibit a positive treatment response (i.e., lowering of rP50 scores; increased MMN amplitudes) while individuals who express optimal or superior baseline sensory processing would show no response or decreased auditory sensory processing in response to CDP-choline/galantamine. In line with our hypotheses and expectations, our results demonstrated a baseline-dependent treatment response to a single combined dose of CDP-choline/galantamine, with observations of enhanced responsivity in

relatively poorer sensory processing individuals being similar to findings previously reported for nicotine and CDP-choline administered alone.

Findings of baseline-dependent P50 SG modulation by the acute administration of CDP-choline and galantamine replicate the effects of a single administration of CDP-choline alone in low suppressor healthy participants (Knott, Smith, et al., 2014) and low suppressor patients with SCZ (Aidelbaum et al., 2018), and also replicate the effects of acute nicotine on SG nicotine in healthy low and high suppressors (de La Salle et al., 2013; Knott et al., 2010, 2013; Thomas et al., 2017). Although the baseline-dependent effects of CDP-choline/galantamine on SG cannot be directly linked to variation in α7 nAChR genotype, current findings parallel previous genotype-dependent P50 gating response outcomes to perinatal choline supplementation where CHRNA7 rs3087454 C/C homozygous neonates (associated with SCZ) previously exposed to a placebo choline supplement during gestation expressed the weakest P50 suppression levels while the C/C neonates who were exposed to choline supplementation during gestation demonstrated the largest P50 suppression levels (vs. A/A and C/A) (Ross et al., 2013). This genotype-dependent response to choline was also evidenced at the pre-clinical level in mice, where *Chrna7* null homozygotic (-/-) and heterozygotic (+/-) mutant (a mouse model in which there are no [-/-] or very low [+/-] α7 nAChR in the hippocampus in comparison to +/+ mice who show 50% reduction of α7 receptors in comparison to the wild-type) DBA/2 mice showed no response to perinatal choline supplementation in comparison to DBA/2 +/+ mice (who show reduced (Stevens et al., 2014). Given that previous human research has shown that poor (vs. efficient) P50 suppressors exclusively express a CHRNA7 promoter variant (Leonard et al., 2002), studies with large samples that allow for the parsing of genotype sub-groups are needed to assess the

relationship of genetic differences in α7 nAChR expression and individual differences in gating response to CDP-choline/galantamine and other α7 agonists.

In addition to GABA, α7 nAChRs modulate the release of multiple neurotransmitters, including dopamine (Schilström et al., 1998), cortical levels of which show an inverted U-shaped relationship with cognitive performance (Goldman-Rakic et al., 2000; Monte-Silva et al., 2009; Williams-Gray et al., 2007) and as such, may contribute to the differential gating response to CDP-choline/galantamine in low and high P50 suppressors. Catechol-O-methyltransferase (COMT) is a key enzyme in prefrontal cortical metabolism and, although not seen in all studies (Lu et al., 2007; Shaikh et al., 2011), COMT genotypes have been shown to differ in SG and its response to nicotinic stimulation in a baseline-dependent manner (de La Salle et al., 2013). In healthy, low baseline P50 suppressors who were also Val/Val genotypes (associated with greater enzyme activity and lower cortical dopamine levels), gating was inferior to low baseline P50 suppressors who were also Met/Met genotypes (associated with lower enzyme activity and higher cortical dopamine levels). Additionally, gating in Val/Val low baseline P50 suppressors was enhanced with acute nicotine (vs. decreased in Met/Met genotypes who were either low or high baseline P50 suppressors). The enhanced gating response was presumably related to the well-known dopamine releasing effect of nicotine (Wang et al., 2014), which is also released with CDP-choline (Fioravanti and Buckley, 2006), and hence may contribute to the pro-gating effects observed in healthy volunteers and patients with SCZ exhibiting low baseline P50 suppression. The dopamine-modulating effects of CDP-choline may well be potentiated by the PAM galantamine as it also increases dopaminergic neurotransmission through its allosteric potentiation of nAChRs, which is blocked by α7 antagonist treatment (Schilström et al., 2006).

How CDP-choline/galantamine or other nicotinic modulators of the nAChR may impact mechanisms underlying auditory P50 SG is not well understood in humans, but evidence from mouse models (i.e., DBA/2) and cellular research highlights the role of the hippocampus as the central moderator of response inhibition in concert with cholinergic modulation of the prefrontal and temporal cortices (Boutros et al., 1999, 2013; Freedman et al., 1991; Javitt and Freedman, 2015). In simplified terms, following the activation of pyramidal neurons in response to the conditioning S1 auditory stimulus, the response suppression was evidenced to be mainly driven by hippocampal interneuronal α7 nAChR activation (as shown with BMXB-A, a selective agonist for α7) triggered by the initial S1, which increases GABA release and therefore inhibition of pyramidal cells and hence, an attenuated response to S_2 (Daskalakis et al., 2007; Frazier et al., 1998; Freedman et al., 2000; Hershman et al., 1995; Miller and Freedman, 1995). Recordings from whole-cell or populations of neurons have shown that choline can affect the inhibitory tone of the hippocampus, an effect that is blocked by $GABA_B$ receptor antagonists and drastically reduced with the administration of α-bungarotoxin, a selective α7 nAChR antagonist (Mielke et al., 2011).

The study designs did not include a comparison of the separate effects of CDP-choline and the nAChR PAM galantamine, and although it is possible that enhanced gating in low P50 suppressors may be attributed solely to choline, it is also likely that galantamine may have contributed to gating enhancement but understanding whether this occurred in an incremental, additive or synergistic manner requires direct comparison of these drugs administered separately and in combination. PAMs have been demonstrated to potentiate many types of α7-mediated responses. For example, spontaneous and choline- or ACh-induced increases in GABAergic inhibitory post-synaptic currents were shown to be enhanced by PAMs (Arnaiz-Cot et al., 2008;

de Filippi et al., 2010; Hurst et al., 2005; Malysz et al., 2009; Mok and Kew, 2006). SG also involves top-down modulation of frontal areas (Kurthen et al., 2007), which is of interest as CDP-choline increases frontal lobe levels of high-energy phosphate metabolites, constituents of membrane synthesis – an effect that is of greater magnitude with lower (500 mg) than higher (2000 mg) doses (Silveri et al., 2008).

The combined CDP-choline/galantamine treatment improved not only the 'gating-out' of irrelevant sensory information as evidenced with P50 SG measures but also the 'gating-in' of relevant sensory input as indexed by MMN enhancement both in healthy volunteers and patients with SCZ displaying low baseline MMN amplitudes. According to the "sensory-memory" hypothesis of MMN generation, the elicitation of the MMN ERP in response to the automatic detection of an auditory change in any acoustic physical (i.e., intensity, frequency, duration) or abstract (i.e., pattern change) feature relies on the cross-communication of various regions including fronto-temporal regions orchestrating an initial pre-perceptual registration of repetitive (standard) sound features in the primary auditory cortex, followed by feature trace comparisons stored in echoic memory, where discordance between the novel trace and previous sound feature traces triggers a frontal-cortical process implicated in the MMN generation (Szycik et al., 2013). The glutamatergic system is widespread throughout these subcortical and cortical brain regions, and deficits in MMN generation in SCZ have been most consistently linked to impairments in NMDAR activity. NMDAR antagonists such as ketamine induce symptoms and sensory/cognitive deficits in healthy individuals that closely resemble those of SCZ. Thus, implicating NMDAR hypofunction in the pathogenesis of SCZ (Coyle & Tsai, 2003; Javitt & Zukin, 1991). Such models have been supported by findings of reduced markers of glutamatergic neuronal integrity (Tsai et al., 1995) and reduced plasma or cerebral spinal fluid levels of amino

acids such as glycine (Sumiyoshi et al., 2005) and D-serine (Neeman et al., 2005). Also affecting glutamate neurotransmission and NMDAR function are SCZ susceptibility genes, including neuregulin, ERBB4, dysbindin or D-amino acid oxidase (Harrison and West, 2006). Dietary alterations, such as reduced glutathione levels (Steullet et al., 2001), increased kynurenic acid (Nilsson et al., 2005), or increased homocysteine levels (Neeman et al., 2005), also impact NMDARs. NMDAR antagonists produce SCZ-like dopaminergic dysregulation in humans (Kegeles et al., 2000) and suggest that the observed disturbances in dopaminergic function in SCZ may be secondary to underlying glutamatergic dysfunction (Javitt et al., 2008). Ketamine has been shown to block MMN generation in humans and various animal models (Rosburg and Kreitschmann-Andermahr, 2016), but MMN has not been shown to be responsive to dopaminergic and serotonergic systems (Bickel & Javitt, 2009; Kantrowitz & Javitt, 2010).

MMN deficits have not been systematically studied in relation to the involvement of cholinergic mechanisms. CDP-choline has been previously shown to increase MMN in individuals with low baseline amplitudes (Knott, Impey, et al., 2015), presumably due to its agonist action at α7 receptors, which can directly increase glutamate neurotransmission (Gioanni et al., 1999). As suggested previously in relation to SG, individual differences in baseline deviance detection measured with MMN, which is highly heritable (Hall et al., 2006), may reflect genetic influences. For example, MMN is influenced by the 22q 11.2 deletion syndrome, the strongest known molecular risk factor for SCZ (Francisco et al., 2020). The role of galantamine in MMN augmentation in low baseline amplitude individuals is not clear as it was not administered separately. However, galantamine, administered as a moderate dose concurrently with a low dose of CDP-choline in the current studies, is known to sensitize nAChRs to activation by low, but not high agonist concentrations and has been shown to

potentiate hippocampal glutamate release triggered by ACh (Santos et al., 2002). Furthermore, it was recently shown that NMDA and ACh co-administration exerts a superadditive effect on the firing rate of CA1 neurons in anesthetized rats where glutamatergic signalling was shown to be potentiated by α7 nAChRs (Bali et al., 2017).

Although they have no intrinsic channel activation properties, PAMs have the net effect of enhancing agonist binding to the resting state receptor, increasing potency. Galantamine, a putative nAChR PAM, is non-selective for α7 nAChRs and as such, the current findings observed with CDP-choline/galantamine may, in part, be due to the increased activation efficacy of ACh on non-α7 nicotinic receptors. Development of α7-selective PAMs and comparison of their effects with galantamine would be helpful in delineating the specific pharmacological mechanisms underlying pro-sensory benefits observed with combined CDP-choline/galantamine treatment.

Galantamine is also considered a type I PAM and differs from type II PAMs (e.g., PNU-120596) on the basis of a difference in their effects on receptor desensitization. While type I PAMs predominantly increase peak current with little impact on receptor desensitization kinetics, type II PAMs increase peak current, recruit endogenous choline and produce a persistent α7 receptor activation and efficaciously reactivate desensitized α7 nAChRs (Uteshev, 2014). Although not yet commercially available, the investigation of α7 type II PAMs conjointly with CDP-choline may provide a more targeted α7 approach for addressing sensory/cognitive deficits in SCZ.

Galantamine is also an AChE inhibitor, and it is possible that increases in ACh levels associated with galantamine administration may have participated in nAChR activation to yield improvements in auditory SG and deviance detection. This effect, however, may have been

negated by CDP-choline, which acts to increase hippocampal AChE levels (Plataras et al., 2003). CDP-choline may also result in enhanced sensory processing via increases in phospholipids, which participate in the repair of neuronal membrane structure, function and signalling (Secades, 2019).

6.3 Treatment implications

Basic sensory functions – including auditory-level functions, are impaired in SCZ and contribute substantially to symptoms and overall impairments in psychosocial functioning. A patient's sensory perception of the surrounding world may differ considerably from others' perception, and a person's ability to understand and interact effectively with the surrounding world ultimately depends upon underlying sensory experiences of it (Javitt and Freedman, 2015). P50 suppression and MMN endophenotypes are considered intermediaries between molecular/cellular mechanisms and clinical symptoms in SCZ. These ERP biomarkers reflect the outcome of a screening process located primarily in the auditory cortex that constantly monitors the environment for redundant and for relevant events in the background auditory stimulation, even when such events occur outside the focus of conscious attention (Javitt and Sweet, 2015). In SCZ, these processes are impaired, leading to increased (lower P50 suppression) or reduced (lower MMN) sensitivity to ongoing environmental (auditory) events, both of which are highly interrelated to impaired functional outcome in SCZ, including impairments in reading (Revheim et al., 2014) and educational achievement (Carrión et al., 2015).

Both P50 and MMN ERPs have been used as translational biomarkers in animal and human studies to guide future intervention approaches, but at present, there are no approved treatments that specifically target sensory or cognitive impairments in SCZ. Although self-medication by smoke-inhaled nicotine has not provided consistent pro-sensory/cognitive benefits

for patients with SCZ (Sagud et al., 2019), the implied attempt to activate low-(nicotine) α7 nAChR by heavy smoking, in combination with a large body of supportive evidence (from genetics, receptor desensitization and function, and animal models) the emergence of the α7 receptors as a potential therapeutic target. However, despite promising findings in preclinical and early phase I and phase II clinical trials, no drug targeting nicotinic systems has yet succeeded in larger phase III trials (Tregellas and Wylie, 2019).

One promising success story is the potential use of choline, an endogenous α7 ligand which is critical during fetal development, with maternal choline intake and plasma levels being associated with cognition in newborns and young children (Boeke et al., 2013; Wu et al., 2012). In animal models of SCZ, perinatal choline supplementation improved P50 SG deficits and increased hippocampal α7 nAChRs (Stevens et al., 2008). In humans, dietary supplementation of choline during pregnancy improved P50 SG in newborns with a CHRNA7 genotype associated with SCZ (Ross et al., 2013) and in a follow-up, longitudinal study, maternal choline supplementation improved behavioural measures of attention and social withdrawal in offspring (Ross et al., 2016).

These results suggest that it may be possible to decrease or prevent sensory/cognitive dysfunction in SCZ through interventions that increase choline early in development. To date, apart from the studies within this laboratory, choline has not been investigated as a possible targeted treatment for sensory processing deficits in SCZ. Future studies in this direction will need to include randomized controlled intervention trials conducted in laboratories that target patient subgroups at different stages of the disease (prodrome, first-episode, chronic) and include dosing regiments of choline, PAMs, and their combinations to determine the most optimal pharmacological administration. Also needed are large observational studies examining

relationships between dietary choline intake in patients with SCZ and measures of sensory, cognitive and psychosocial functioning. Given that choline is a relatively safe micronutrient with few significant adverse effects, these latter studies may be complemented by investigations manipulating choline by changes in natural diet or by dietary choline supplementation.

6.4 Speech stimuli in P50 and MMN

This study is the first P50 ERP study to examine speech-related inhibitory mechanisms in SCZ. PANSS scores and PSYRATS total score were not significantly associated with treatment-induced changes (CDP-choline/galantamine minus placebo) for speech P50 SG (rP50, dP50) and amplitudes (S_1P50, S_2P50). However, treatment-induced changes for dP50 SG and S_1P50 amplitudes showed a positive correlation with PSYRATS distress scores. And, treatment-induced changes in rP50 SG and S_2P50 amplitudes negatively correlated with PSYRATS controllability scores. Speech P50 SG has previously been examined in a magnetoencephalography (MEG) study, which evidenced greater speech P50m impairments in patients with SCZ expressing severe AVH ratings (Hirano et al., 2010). These findings parallel previous AVHs associations observed with the clicks P50 paradigm (Faugere et al., 2016; Smith et al., 2013; Thoma et al., 2017).

The modulation of speech SG by CDP-choline/galantamine and the moderation of the response to this treatment by AVH distress and controllability suggests that the nicotinic cholinergic system may be implicated in AVH and low-/high-order processing of speech and emotional processes (Boutros et al., 2013; de Leede-Smith and Barkus, 2013; Wallace and Bertrand, 2015). Despite stemming from a small sample group, this may be useful in informing interventions that may be more impactful in the management of AVHs. For example, individuals expressing lower controllability scores may better benefit from cognitive behavioural therapy

aiming to improve the patient's distinction between and response to salient external vs. internal speech sounds and vocal tones, as these individuals showed weak/impaired rP50 gating to redundant speech stimuli.

Speech MMN amplitudes did not correlate specifically with PSYRATS scores, however, treatment-induced changes for consonant and vowel MMN amplitudes negatively correlated with PANSS total, positive and negative scores (i.e., patients with higher AVHs scores expressed larger treatment-induced MMN amplitudes [MMN amplitudes are negative in polarity]). These findings are in line with expectations that patients with SCZ who express smaller MMN amplitudes at baseline were expected to show the largest CDP-choline/galantamine treatment effect and in line with previous findings of higher PANSS ratings correlating with smaller MMN amplitude scores (Fisher, Labelle, et al., 2012). Given that lower speech MMN amplitudes were reported in a surrogate SCZ model in healthy participants under ketamine, an NMDA receptor antagonist (de La Salle et al., 2019b), PANSS moderation of speech MMN changes induced by CDP-choline/galantamine may reflect interactions between nicotinic and glutamatergic systems.

Frontotemporal cortical activity and structural abnormalities in the left planum temporal have been associated with change/deviance detection in speech sounds, suggesting multi-level language-related dysfunctions in SCZ evidenced at early lower-level phoneme processing in addition to higher-order semantic processing (Kasai, 2004; Kasai et al., 2002). Furthermore, smaller speech MMN amplitudes following duration deviants were associated with lower verbal memory scores (Kawakubo et al., 2006), while greater speech deviance detection was associated with improvements in social skills scores in patients with SCZ (Kawakubo et al., 2007). Hence, this study, the first to examine the modulating impact of CDP-choline/galantamine treatment on measures of speech MMN in association with AVHs in SCZ, added supporting evidence that

suggests a role for the cholinergic system in concert with the NMDAR system in speech deviance detection. Accordingly, nicotinic modulation of salient speech deviants may potentially benefit processes associated with verbal memory and social skills in patients showing higher AVH scores.

6.5 Conclusion

Despite their limitations, it can be concluded that these investigations, supporting previous basic and clinical evidence pointing to α7 nAChR as a viable target for drug development in SCZ, found evidence for the effectiveness of CDP-choline/galantamine as an add-on combination α7 treatment for EAIP deficits in SCZ. What is needed to provide a more accurate picture of the actual effects of such treatment are adequately powered clinical trials varying dose and frequency (intermittent vs. chronic) administration schedules in ERP (P50, MMN) – and/or genotype (CHRNA7) – defined patient subgroups for better targeting of patients that are most likely to benefit from this intervention.

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Annex 1 Supplemental material for Chapter 2

Supplementary treatment-related information

CDP-choline (Citicoline) can be administered orally or through intravenous routes where both administration routes show similar bioavailability (> 90%) and initial peak plasma time at ~2-3 hours after drug administration. Exogenous CDP-choline is a water-soluble compound that is well tolerated with a daily dose ranging from 500 and up to 4000 mg/day. CDP-choline's metabolites cross the blood-brain barrier and can be detected in brain tissue in less than thirty minutes after administration. Although CDP-choline has been extensively associated with increases in phospholipid biosynthesis, and thus neuronal membrane repair, the presence of its metabolites (such as cytidine, choline, and methionine) are indicative of its role in modulating cholinergic receptors and neurotransmitters (Galletti et al., 1991; Gareri et al., 2015; Sarkar et al., 2012; Secades, 2011).

Galantamine, administered orally, has a maximum plasma concentration-time range between 0.5 to 2 hours in healthy participants. Cytochrome P450 isoenzymes rapidly metabolize galantamine in the liver, and its bioavailability ranges between 85 to 100%. The metabolites exert a dual action, primarily as a reversible and competitive acetylcholine esterase inhibitor and also as an allosteric modulator of nicotinic receptor's α subunits (Jann et al., 2002; Scott & Goa, 2000).

Annex 2 Supplemental material for Chapter 3

Table 6.1 List of all neuroleptics and chlorpromazine (CPZ) equivalents for all participants in mg/day.

Participant ID	Suppressor group	Aripiprazole	Flupentixol	Haloperidol	Levomepromazine	Olanzapine	Paliperidone	Perphenazine	Quetiapine	Risperidone	Trifluoperazine	Ziprasidone	CPZ equivalent
SSO02	low		5		10	20				4			1100
SSO03	low						6						300
SSO04	high		1.43			30							971.5
SSO05	high									5			300
SSO06	high					30			800				1500
SSO07	high		3				6						450
SSO08	high								500				375
SSO09	high						12	4	300				865
SSO10	high									6			360
SSO11	high					5							150
SSO12	low							4		3			220
SSO13	high					27						120	1260
SSO14	high	30							50				637.5
SSO15	high	30				10				5			1200
SSO16	low									11.36			681.6
SSO17	low		4.28			30						200	1864.5
SSO18	low	5				5							250
SSO19	high					30							900
SSO20	low			5						5.36			509.1
SSO21	high								900		8		795
SSO22	low									4			240
SSO23	high					20				5.36			921.6
SSO24	low						6		800				900
SSO26	low	30							400				900

Table 6.2 Mean (±SE) Chlorpromazine equivalent oral dose for high and low suppressor groups.

	Suppressor group	N	Mean (± SE)
CPZ equivalent oral dose	High	14	763.2 (107.3)
	Low	10	696.5 (164.6)

Following the analysis of independent samples t-test for equality of means, results revealed that the mean CPZ equivalent oral dose for high suppressors is not significantly different from that of low suppressors, $t(22) = .355$; $p = .726$.

CPZ equivalent doses were calculated using an antipsychotic dose conversion calculator/table by Dr. Leucht (Leucht et al., 2016).