THE MODERATING ROLE OF THE DOPAMINE TRANSPORTER 1 GENE ON P50 SENSORY GATING AND ITS MODULATION BY NICOTINE

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Abstract

Although schizophrenia has been considered primarily a disease of dopaminergic neurotransmission, the role of dopamine in auditory sensory gating deficits in this disorder and their amelioration by smoking/nicotine is unclear. Hypothesizing that individual differences in striatal dopamine levels may moderate auditory gating and its modulation by nicotine, this preliminary study used the mid-latency (P50) auditory event-related potential (ERP) to examine the single dose (6 mg) effects of nicotine (vs. placebo) gum on sensory gating in 24 healthy nonsmokers varying in the genetic expression of the dopamine transporter (DAT). Consistent with an inverted-U relationship between dopamine level and the drug effects, individuals carrying the 9R (lower gene expression) allele, which is related to greater striatal dopamine levels, tended to evidence increased baseline gating compared to 10R (higher gene expression) allele carriers and showed a reduction in gating with acute nicotine. The present results may help to understand the link between excessive smoking and sensory gating deficits in schizophrenia and to explain the potential functional implications of genetic disposition on nicotinic treatment in schizophrenia.

Keywords

schizophrenia; P50; gating; dopamine transporter gene; nicotine; smoking

Early theoretical models of information processing in schizophrenia postulated impairment in the preattentive, automatic processing of sensory input to be a contributing factor in the appearance of psychotic symptoms, perceptual disturbances, and various cognitive deficits that characterize this disorder (Venables, 1964). Meta-analyses and reviews of event-related potential (ERP) studies probing auditory sensory gating in a paired stimulus paradigm (involving the presentation two [S₁, S₂] closely [<1000 ms] separated identical sounds) have

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found that ~90% of patients with schizophrenia as well as ~50% of their first-degree relatives exhibit insufficient inhibitory processing of repetitive, irrelevant acoustic stimuli (Bramon et al., 2004; De Wilde et al., 2007; Patterson et al., 2008). Typically assessed with the amplitude of the early (50 ms) positive ERP component, P50, abnormal auditory sensory gating has been evidenced by a relative inability to suppress P50 to S₂, and is expressed by larger S₂/S₁ ratio (rP50) and/or smaller S₁ minus S₂ difference (dP50) scores.

Smoking and acute nicotine have transiently corrected deficient P50 processing in schizophrenia patients and their relatives, respectively (Adler et al., 1992, 1993). In addition, in a rodent model of schizophrenia-like gating deficiency, studies assessing the P20-N40 ERP, which is an analogue of the human P50, have shown agonists and antagonists of the $\alpha 7$ nicotinic receptor to improve deficient S₂ inhibition and to block normal S₂ inhibition, respectively (Stevens et al., 1998, 1999; Simosky et al., 2001). Other studies reporting gating improvements with nicotine in rodents and humans, however, have found increases in S₁ but not S₂ (Crawford et al., 2002; Cromwell and Woodward, 2007; Metzger et al., 2007; Phillips et al., 2004, 2007; Rudnick et al., 2010). Clozapine, the prototype of the ‘atypical’ antipsychotics, and one of the few medications shown to reverse auditory sensory gating impairment in both schizophrenia and animal models, appears to selectively reduce S₂-P50 responsivity via an $\alpha 7$ nicotinic mechanism (Simosky et al., 2003; Adler et al., 2004; Nagamoto et al., 1996, 1999).

Nicotine influences the release of not only acetylcholine, but also of dopamine (DA) and other neurotransmitters (norepinephrine, serotonin, glutamate, GABA) but it is not clear how these noncholinergic systems participate in gating. Although there is still confusion regarding the temporal sequencing of regionally specific DA changes in schizophrenia (Kellendonck et al., 2006), negative symptoms and cognitive deficits in this disorder have been linked to prefrontal hypodopaminergia while positive symptoms have been associated with striatal hyperdopaminergia (Kapur and Malmö, 2003). Neuropathological and neuroimaging studies in schizophrenia have shown alterations in DA D₂ receptor (D₂R) signaling in the striatum, reflected as an elevation both in presynaptic striatal DA synthesis, and density and occupancy of striatal D₂Rs (Howes and Kapur, 2009), with the latter appearing to be genetically determined in a subpopulation of patients (Allen et al., 2008). Conspicuously, acute challenges with DA augmenting agents have exerted mixed effects on S₁ and S₂ amplitudes and gating (Kenemans and Kähkönen, 2011). Although haloperidol, a D₂R antagonist, has been shown to normalize amphetamine-induced selective gating deficits in rodents (Stevens and Wear, 1997), treatment of schizophrenia with haloperidol and other conventional or ‘typical’ antipsychotics has increased S₁- and S₂-P50 without improving sensory gating (Freedman et al., 1983; Baker et al., 1987; Adler et al., 1986).

DA neurotransmission initiated by presynaptic release is terminated largely by its reuptake by a dopamine transporter (DAT). By rapidly recapturing extracellular dopamine into presynaptic terminals after release, DAT plays a pivotal role in regulating the duration and amplitude of cellular action of dopamine, especially in the striatum, where both DAT (Sesack et al., 1998) and D₂R (Camps et al., 1989) are mostly expressed. The DAT1 gene (SLC6A3) is located on chromosome 5p15.3 (Giros et al., 1992; Vandenbergh et al., 1992);

alleles ranging from 3 to 13 copies of the 40-bp repeats have been described, but alleles with 9 (9R) and 10 repeats (10R) are the most common (Kang et al., 1999; Mitchell et al., 2000).

Single-photon-emission computed tomography has shown relatively increased striatal DAT expression (i.e. availability) in 10R (vs. 9R) allele carriers (Jacobsen et al., 2000; Fuke et al., 2001; Mill et al., 2002; Heinz et al., 2000) who, presumably, would evidence relatively decreased striatal dopamine tone. The SLC6A3/DAT1 genotype has been related to a range of mental processes, including cognitive control/attentional functions (Cornish et al., 2005; Cools, 2008; Cools and D'Esposito, 2006) and reward related processes (Dreher et al., 2009; Colzato et al., 2010), as well as the early sensory and higher order processing of acoustic novelty, as reflected in the N1 and nP3 ERPs, respectively (Garcia-Garcia et al., 2010a,b). Although the majority of data have demonstrated no differences in striatal DAT expression or DAT1 polymorphisms in schizophrenia (vs. controls), striatal DAT availability has been inversely correlated with auditory hallucinations in the acute illness (Schmitt et al., 2006), and DAT1 gene polymorphisms have been shown to play a significant role in response to clozapine (Xu et al., 2010).

To further explore the separate and interacting effects of striatal dopamine and the nicotinic receptor system on gating processes, this preliminary study examined whether: (a) acute nicotine administration and functional allelic differences in the SLC6AS/DAT1 genotype modulate auditory P50 in the paired-stimulus paradigm, and (b) whether nicotine-modulated P50 is moderated by the presence of 9R and 10R alleles. We hypothesized that, relative to the 9R allele, the 10R allele (i.e. reduced DA tone) would be associated with reduced S₁-P50 and P50 gating, and that nicotine would increase S₁-P50 and P50 gating in the presence of the 10R allele. As evidence of nicotine-altered P50/gating in tobacco abstinent smokers may be interpreted as a reversal of withdrawal-induced alterations in sensory processing (Rudnick et al., 2010), and not an absolute affect of nicotine per se, these hypotheses were investigated in nonsmokers.

EXPERIMENTAL PROCEDURES

Volunteer sample

Twenty-four (13 male) healthy volunteers, all right handed, between 18 and 40 years of age and reporting a negative psychiatric, neurological (including seizures and head trauma), and alcohol/substance abuse history were recruited for participation. Given the influence of chronic smoking on P50 suppression (Crawford et al., 2002; Croft et al., 2004; Wan et al., 2006, 2007), participants were all nonsmokers, having smoked less than a lifetime total of 10 cigarettes, and none in the past year. As mid-latency ERPs can be affected by personality (Houston and Stanford, 2001), participants completed the Eysenck Personality (EPQ) Questionnaire (Eysenck and Eysenck, 1975), which was scored for extraversion (E), Neuroticism (N), and Psychoticism (P) dimensions, and the Sensation Seeking Scale (SSS-V; Zuckerman, 1994), the scoring of which was limited to Experience Seeking (ES) and Disinhibition (DIS) factors. All volunteers signed an informed consent prior to participation in the study, which was approved by the Research Ethics Board of the Royal Ottawa Health Care Group.

Research design

Volunteers were assessed in two test sessions within a randomized, double-blind, placebo-controlled crossover design with parallel treatment groups (9R and 10R). Order of nicotine and placebo treatment sessions (separated by a minimum of 2 days) was randomized so that half (randomly selected) of each group received placebo in the first session and nicotine in the second session, while the remaining half of each group received treatments in the reverse order.

Nicotine treatment

Administered in the form of two pieces (4 mg+2 mg) of mint-flavoured Nicorette® gum (Johnson & Johnson, Inc), the total (6 mg) dose of nicotine was expected to produce a nicotine blood concentration of approximately 15–30 ng/ml (Hukkanen et al., 2005), a level similar to that achieved by smokers smoking a single cigarette of average nicotine yield. Gum pieces serving as placebo were similar in size, colour, and texture, and were of mint-flavoured taste, but contained no nicotine (no formal testing was conducted to determine if participants could distinguish active from placebo gum). According to manufacturer's guidelines, gum pieces in both sessions were chewed for 25 min, with participants biting the gum twice per minute and 'parking' the gum between teeth and cheek between bites. During gum administration, participants were blindfolded and wore nose plugs to reduce any potential sensory differences between nicotine and placebo. From the beginning of gum chewing, peak blood nicotine levels are achieved by ~30 min and nicotine half-life is ~120 min. None of the volunteers reported common nicotine side effects such as nausea or dizziness.

Procedure/recording

Participant arrival at 8:00 AM test sessions followed overnight abstinence from medication, drugs, alcohol, caffeine, nicotine, and food. After verbal verification of abstinence, participants sat in a sound-attenuated, dimly lit chamber and were administered gum during electrode hook-up. Following gum chewing, recordings were carried out during eyes-open testing in response to thirty-two 85 dB (SPL) click pairs (previous studies have derived P50 averages with stimulus pairs ranging from 16 to 150) with 100 μ s click durations and 500 ms inter-stimulus intervals, which were presented binaurally through headphones at 10 s inter-pair intervals. Digital sampling (500 Hz) with BrainVision Recorder® software was carried out on amplified (bandpass filters set at 0.1–120 Hz) electrical activity (BrainVision Quickamp®) recorded from 28 scalp electrode ($\text{Ag}^+/\text{Ag}^+\text{Cl}^-$) sites placed according to the extended 10–20 system (FP_1 , FP_2 , F_3 , F_4 , C_3 , C_4 , P_3 , P_4 , O_1 , O_2 , F_7 , F_8 , T_7 , T_8 , P_7 , P_8 , F_z , C_z , P_z , O_z , FC_1 , FC_2 , CP_1 , CP_2 , FC_5 , FC_6 , CP_5 , CP_6) using a common average reference and a ground electrode placed between F_{pz} and F_z sites. Electrodes were also placed on supra- and sub-orbital ridges of the right eye as well as on the external canthus of both eyes to monitor vertical (VEOG) and horizontal (HEOG) electro-oculographic activity. All electrode impedances were kept below 5 $\text{k}\Omega$.

DAT1 genotyping

Using previously described methodology (Vandenberg et al., 1992), genomic DNA was extracted from saliva samples and the 40-bp DAT VNTR was then amplified with 1.25 U Taq DNA polymerase (New England Biolabs) and the oligonucleotide primers: 5' - TGTGGTGTAGGGAACGGCCTGAG - 3' and 5 - CTTC-CTGGAGGTCACGGCTCAAGG - 3'. Primers were designed to yield products of varying sizes, depending on repeat number variation. PCR cycling parameters were as follows: 4 min initial denaturation at 94 °C, 30 cycles of denaturation (30 s at 72 °C), followed by a final 5 min extension at 72 °C. The PCR products were visualized on a 2% agarose gel stained with ethidium bromide, with product size being identified by comparison to a molecular weight standard. The genotype distribution of the DAT1 polymorphism in our sample was 60.86% 10/10 (10R) homozygous subjects and 39.13% nine repeat (9R) carriers. Genotype frequencies were similar to frequencies described in the literature and the allelic distribution of the gene did not significantly deviate from Hardy-Weinberg equilibrium ($P>0.1$).

ERP processing

BrainVision Analyzer® (Brain Products GmbH, Munich, Germany) software was used to process ERPs off-line, which involved re-referencing to linked mastoids, bandpass filtering (10–50 Hz: 24 dB/octave roll-off), epoch segmentation (150 ms, beginning 50 ms prestimulus onset), EOG correction (Gratton et al., 1983), artifact rejection (excluding EEG epochs $>\pm 75 \mu\text{V}$), baseline correction and finally, selective averaging at each electrode site for each (S_1 , S_2) stimulus of the click pairs.

Using the C_z scalp site, which best displays the gating process and best differentiates P50 gating of schizophrenia patients and controls (Clementz et al., 1998), the P50 was identified semi-automatically as described by Boutros et al. (2004) and as used in our previous studies (Knott et al., 2009, 2010a,b). Although frequently measured as the most positive peak between 40 and 80 ms and relative (i.e. trough-to-peak) to the amplitude of the preceding peak negativity (N40) at ~30–50 ms, peak P50 amplitude in our recordings was measured with respect to the average pre- S_1 baseline voltage due to the relative inconsistent appearance of N40 that was frequently obscured by an early positive (P30) component. In addition to the peak amplitude and latency (i.e. time of peak P50 relative to stimulus onset) of S_1 - and S_2 -P50, two auditory gating indexes were derived for each recording: (a) rP50, measured as the amplitude of S_2 -P50 divided by S_1 -P50 amplitude, $\times 100$; (b) dP50, which is the most reliable (relative to rP50) gating index (Fuerst et al., 2007; Rentzsch et al., 2008), was measured as the mathematical difference score derived by subtracting the amplitude of S_2 -P50 from S_1 -P50 amplitude.

Statistical analysis

Each demographic and personality characteristic (age, EPQ, SSS-V) was analyzed with a one-way analysis of variance (ANOVA) comparing the two allele groups. Amplitudes and latencies of the P50 derived from the ERP waveforms were subjected to separate mixed-ANOVAs, with the between-group factor being genotype (two levels) and the within-group factors being drug (two levels) and stimulus (two levels). Both gating indices (rP50, dP50) were analyzed with separate mixed-ANOVAs, with genotype serving as the between-group

factor and drug serving as the within-group factor. Significant Greenhouse-Geisser interactions were followed up with Bonferroni adjusted pairwise *t*-tests. Planned comparisons examining the interaction of between group factors with drug and stimulus were carried out for hypothesis testing.

RESULTS

Mean ($\pm$ SE) demographic and personality characteristics for the DAT1 genotype groups are shown in Table 1. Apart from a significant ($t=2.16$, $df=21$, $P<0.042$) age difference between the two groups, no significant differences were observed for any of the measures.

P50 amplitudes/latencies

Significant stimulus ($F=40.28$, $df=1/21$, $P<0.001$) and drug $\times$ stimulus ($F=4.30$, $df=1/21$, $P<0.05$) effects were observed in the analysis of amplitudes. Mean ($\pm$ SE) amplitudes of S₁-P50 and S₂-P50 were 3.19 μ V ($\pm.29$) and .95 μ V ($\pm.22$), respectively, when collapsed across genotypes, with S₂-P50 being smaller than S₁-P50 for both 9R ($P<0.001$) and 10R allele ($P<0.001$) carriers. Follow-up comparisons of the interaction found similar S₂-P50 amplitude reductions (relative to S₁-P50) in both placebo and nicotine sessions (Fig. 1), and nicotine-treated S₁- and S₂-P50 amplitudes did not differ from placebo-treated S₁- and S₂-P50 amplitudes. No significant differences were observed between allele groups, and allele status did not moderate stimulus or drug effects.

Analysis of P50 latency yielded significant genotype ($F=6.08$, $df=1/21$, $P<0.02$) and genotype $\times$ stimulus ($F=4.97$, $df=1/21$, $P<0.04$) effects. Overall, although latency was shown to be shorter for the 10R ($M=53.61$ ms, $SE\pm.80$) than for the 9R ($M=56.78$ ms, $SE\pm1.00$) allele group, follow-up comparisons found S₂ latency ($M=56.78$ ms, $SE\pm1.80$) of 9R allele participants to be longer ($P<0.02$) than that ($M=50.79$ ms, $SE\pm1.45$) of 10R participants. Further planned comparisons of a nonsignificant genotype $\times$ drugs $\times$ stimulus interaction found that group differences were seen with S₂ latency during nicotine but not placebo administration, with nicotine resulting in a longer ($P<0.02$) S₂-P50 latency in the 9R allele group ($M=57.00$ ms, $SE\pm1.3$) compared to the 10R group ($M=52.43$ ms, $SE\pm1.08$) treated with nicotine.

Gating measures

No significant genotype drug or interaction effects were observed for the ratio (rP50) index of gating. Gating indexed with the difference (dP50) score was found to be affected by genotype ($F=4.97$, $df=1/21$, $P<0.04$), with 9Rs exhibiting greater (i.e. increased gating) scores ($M=2.62$ μ V, $SE\pm.41$) than 10Rs ($M=1.86$ μ V, $SE\pm.38$). A significant drug effect ($F=4.30$, $df=1/21$, $P<0.05$) showed that nicotine resulted in reduced gating ($M=1.87$ μ V, $SE\pm.38$) relative to placebo ($M=2.62$ μ V, $SE\pm.41$). Planned comparisons of a nonsignificant genotype $\times$ drug interaction revealed greater dP50 scores (i.e. increased gating) for the 9R allele group compared to the 10R allele group during placebo ($P<0.06$), and reductions ($P<0.05$) in dP50 scores (i.e. diminished gating) with nicotine relative to placebo were limited to 9R carriers (Fig. 2).

DISCUSSION

To our knowledge, this present study is the first to examine whether the DAT1 gene plays a role in sensory gating and its modulation by acute nicotine. Although P50 amplitudes were not altered by DAT1 polymorphisms, our preliminary findings indicated that P50 suppression, indexed by dP50, tended to be greater in 9R (vs. 10R) individuals during placebo treatment, and was found to be reduced in this same allele group with nicotine (vs. placebo) administration. The notoriously low reliability of the ratio gating (rP50) index may have contributed to its insensitivity to allele type and nicotine, while the relatively higher reliability of dP50 would have maintained suppressor classification across treatment sessions and provided more stability for detecting acute responsiveness to a test dose of nicotine (Rentzsch et al., 2008).

These preliminary findings extend results of previous studies reporting a baseline-dependency of pharmacologically altered neural and cognitive activity that has been ascribed to inter-individual quantitative variations in synaptic dopamine. Observations that dopamine agonists either improve or impair brain processes have been accounted for by using the inverted-U principle, that is, agonists might stimulate the dopamine system to 'optimal' or overdosed levels in individuals with low and high baseline dopamine system functioning, respectively (Cools, 2008; Cools and Robbins, 2004). Initially seen in the context of prefrontal D₁R receptor stimulation, the inverted-U effect has also been extended to the striatal D₂R system (Clatworthy et al., 2009; Cools et al., 2009; Phillips et al., 2004). Studies investigating the moderation of dopamine drug effects on brain activity and performance by variables that might index baseline dopamine levels have made use of the genetic variation associated with Taq1A DRD2 gene polymorphisms, and have observed a baseline-dependency of dopamine drug effects on reward-related processing (Cohen et al., 2007).

With respect to sensory gating, our observation that nicotine disturbs gating in individuals with higher baseline striatal dopamine tone generally parallels findings by Csomor et al. (2007) that haloperidol disrupts P50 gating in those with high baseline gating efficiency, and presumably a different dopamine tone, compared to those with low baseline gating efficiency. Also, individual (baseline) differences in dopaminergic tone reflected in DRD2 Taq1A polymorphisms have been associated with significant variations in S₁-P50 amplitude and gating, with those with reduced striatal D₂R concentration (A1⁺) exhibiting greater S₁-P50 amplitude and gating compared to those with a relatively higher expression (A1⁻) of striatal D₂Rs (Knott et al., 2010b). This genetically driven inter-individual P50/gating variability was explained within a computer model of hippocampal CA3 regulated gating in schizophrenia (Moxon et al., 2003a,b). Accordingly, aberrant deficient P50 responsivity is interpreted as resulting from excessive or diminished dopamine input from the striatum, which functions in part to reduce signal-to-noise (S/N) ratio by impairing the ability of local circuit cells to respond synchronously to sensory events. Putative trait-related imbalances in dopamine neurotransmission (i.e. away from optimal level) reflected in our 9R and 10R allele groups did not alter P50 amplitude, but dP50 gating was influenced by this DAT1 genotype. Specifically, the presence of the 9R (lower gene expression), which is related to greater striatal dopamine availability, tended to be associated with more efficient P50 suppression index compared to that seen in the absence of the 9R (10R). That better gating

can be evidenced both in individuals with relatively low ($A1^{+}$) and high (9R) synaptic dopamine tone in the striatum suggests that the two genetic components (DRD2, DAT1) of dopamine neurotransmission may affect P50 inhibitory proneness through separate neural mechanisms. The observation that S_1 -P50, which is thought to initiate P50 inhibitory processes and is generated primarily in the superior temporal gyri of the primary auditory cortex (Makela et al., 1994; Pelizzone et al., 1987; Reite et al., 1988), is (along with P5-gating) also elevated in $A1^{+}$ (but not 9R) allele carriers may argue that DRD2-related alterations in auditory habituation are primarily innervated via dopaminergic pathways in intrinsic (temporal lobe) brain regions.

Both P50 generation and gating processes also receive contributions from the frontal cortex and require that frontal and temporal lobe mechanisms work in concert to result in optimal P50 suppression (Grunwald et al., 2003; Knight et al., 1999; Weisser et al., 2001; Knott et al., 2009). Although not expressing high levels of DAT, the frontal cortex is connected to the striatum via the corticothalamostriatal loop, and activation of the prefrontal cortex in healthy controls is influenced by variation in the DAT 3' UTR VNTR genotype (Bertolino et al., 2006; Caldú et al., 2007; Yacubian et al., 2007). In schizophrenia patients, who are characterized by elevated striatal dopamine activity, increased prefrontal activation in 9R (vs. 10R patients and 9R/10R controls) allele carriers during executive processing is believed to result from increased local dopamine levels and D_2R stimulation, which inhibits thalamic input into the prefrontal cortex, leading to a marked reduction in S/N ratio and cortical efficiency (Prata et al., 2009). While this baseline-dependent dopaminergic mechanism may play a role in the abnormal P50 gating seen in schizophrenia, it is possible that DAT activity in our healthy control 9R allele carriers may have stimulated striatal D_2Rs to a level that produces a thalamically-mediated optimal prefrontal S/N ratio that benefits a more efficient top-down processing (i.e. suppression) of redundant sensory input in the auditory cortex.

The acute effects of nicotine were manifested by a reduction in dP50-indexed gating and a slowing of S_2 -P50 latency in individuals with relatively higher striatal dopamine levels (9R). As disturbed striatal dopamine neurotransmission is believed to cause psychosis through aberrant salience (Howes and Kapur, 2009), and as the human striatum is necessary for responding to changes in stimulus relevance (Cools and D'Esposito, 2006), the above-optimal level of dopamine stimulated by nicotine in 9R allele carriers may have modified gating activity by altering the salience attributed to S_1 and S_2 (Brenner et al., 2009). Given nicotine's ability to increase dopamine neurotransmission pathways, detrimental effects of nicotinic acetylcholine receptor (nAChR) stimulated dopamine release in 9R allele carriers can be presumed to reflect 'overdosing' of dopamine levels in relatively intact brain structures. Increasing dopamine levels with nicotine may be particularly relevant for 9Rs, as acute nicotine also lowers dopamine transporter activity, impairing the ability to remove dopamine from synapses in a rapid fashion and thus increasing dopamine above an optimal level (Krause et al., 2003). In mutant mice in which dopamine production or the dopamine transporter is inactivated, studies have evidenced a persistent extracellular hyperdopaminergic tone (Jones et al., 1998; Gainetdinov et al., 1999), altered neurocircuitry (Zhang et al., 2010), and hypersensitivity to dopaminergic receptor agonists (Kim et al., 2000). These gating effects stand in contrast to those observed in nicotine naïve rodents, healthy nonsmoking controls, and patients with schizophrenia.

Preclinical investigations showing nicotinic-induced improvements in P50 gating were typically carried out in rodent strains with diminished hippocampal nAChR availability and gating ability (Stevens et al., 1996, 1998, 1999; Stevens and Wear, 1997), a model that mimics both nAChR and gating deficiency in schizophrenic patients, who also show transiently improved gating with nicotine (Adler et al., 1993) and nicotinic agonist treatment (Olinic et al., 2006). As P50 inhibition has been correlated with the number of hippocampal $\alpha 7$ nAChRs (i.e. those with the smallest number of receptors exhibiting the poorest inhibition) (Stevens et al., 1996), it is reasonable to suggest that nicotine's actions on the neural processing of repeated auditory stimuli may only manifest as an improvement in gating when nicotine interacts with aberrant nicotinic and/or dopaminergic systems, the degree of improvement being dependent on the severity of (baseline) receptor dysfunction and the dose and timing of nicotine administration. Of relevance to these interactions is the finding that DAT knock-out mice, who are unable to reuptake dopamine released into the synaptic cleft, exhibit functional alterations of nicotinic neurotransmission, showing increases in $\alpha 4$ and $\alpha 7$ nAChR densities (but a decrease in the $\beta 2$ subunit) and hypersensitivity to nicotinic agonists (Weiss et al., 2007). In 9R allele carriers, who are also characterized by a diminished ability to clear synaptic dopamine, $\alpha 7$ nAChR hypersensitivity resulting from elevated dopamine tone may have contributed to the P50 gating impairment induced by acute nicotine stimulation. Although this nicotinic receptor upregulation in healthy 9R allele carriers may be functionally detrimental in the gating out of redundant acoustic stimuli, it may benefit nAChR deficient schizophrenia patients who carry the 9R allele, and this mechanism may in part underpin gating normalization that is observed with acute nicotine treatment in this disorder.

In light of the attenuated gating seen with nicotine, the slower S₂-P50 latency in 9R (vs. 10R) allele carriers with acute nicotine would suggest that supra-optimal synaptic dopamine levels may alter the temporal dynamics of one or more components of the gating process. This may include the slowing of the speed at which the features of redundant acoustic stimulus are encoded, delaying of the (attentional) disengagement from the S₂ stimulus or retarding the onset of local and distant inhibitory processes. Alternatively, as the DAT1 genotype has been shown to affect the temporal dynamics of the interplay between facilitation and inhibition (Colzato et al., 2010), the above-optimal levels of dopamine stimulated by nicotine in 9R allele carriers may have prolonged S₂-P50 processing by delaying the speed of interplay between prefrontal and striatal inhibitory networks. Neither P50 nor gating in 10R allele carriers were influenced by nicotine. Although one might predict a nicotine-induced gating enhancement in individuals with relatively low striatal dopamine, gating improvements in the healthy intact brain may require a greater nicotine dose than that required for gating disruption in healthy volunteers. Future studies require the implementation of a more systematic dosing regimen that can produce dose-response curves for gating, and will involve not only a range of 'smoking doses' of nicotine but also a range of delivery systems that can mimic smoke-inhaled nicotine, so as to better understand smoking-gating relationships in schizophrenia.

There are several caveats to this preliminary study that require attention. The sample size was relatively small and each of the individual SLC6A3/DAT1 genotypes (9R/9R, 9R/10R, and 10R/10R) was not investigated. Only a single dose of nicotine was used, and this does

not allow clear extrapolation to P50 gating alterations that may occur as a result of nAChR upregulation in chronic heavy cigarette smoking patients. Blood nicotine levels were not assessed to examine relationships to neural responses, and the slow absorption of nicotine gum favours desensitization of nAChRs, which may be markedly different from the central effects of lung-to-brain nicotine delivery (~10 s) resulting from smoke inhalation. Finally, DAT1 primarily modulates dopamine in the striatum, and as P50 gating recruits both prefrontal and midbrain resources, additional studies examining the dopamine underpinnings of P50 may wish to investigate functional polymorphisms that regulate prefrontal synaptic dopamine (e.g. COMT) either alone or in combination with DAT1/DRD2.

CONCLUSION

Although diminished inhibition of the P50 ERP is typically linked to the chromosome 15q14 locus of the $\alpha 7$ nAChR gene (Freedman et al., 2003), our findings tentatively indicate that the human DAT1 gene, and the neuromodular processes depending on it, play a role in sensory gating and its regulation by nicotinic receptor systems. Heritable variation in dopamine neurotransmission associated with DAT1 polymorphisms tended to moderate P50 gating, as evidenced by increased suppression of P50 in the presence of the 9R allele, which is associated with greater synaptic dopamine availability. This genetically driven variation also regulated the manner in which nicotine altered P50 gating, decreasing the strength of gating and the speed of processing of redundant auditory input in 9R allele carriers. These findings have potential clinical implications for the potential use of nicotinic agents in the treatment of gating and cognitive deficits in sub-groups of schizophrenia patients.

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Abbreviations

DA	dopamine
DAT	dopamine transporter
D₂R	DA D ₂ receptor
ERP	event-related potential
nAChR	nicotinic acetylcholine receptor

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Fig. 1.

Grand averaged S1 and S2 waveforms in placebo and nicotine conditions, collapsed across the two (9R, 10R) genotypes. For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

Fig. 2. Mean ($\pm$ SE) dP50 gating values for 9R and 10R allele carriers during placebo and nicotine conditions.

Table 1Means ($\pm$ SE) for group demographic and personality measures

Measure	10R	9R
Age (y)	23.3 (1.07)	27.1 (1.46) *
EPQ scores		
E	15.0 (1.89)	13.9 (1.58)
N	11.71 (1.50)	9.67 (1.44)
P	7.79 (0.66)	7.56 (1.06)
SSS scores		
ES	5.71 (0.40)	6.40 (0.77)
DIS	4.36 (0.70)	3.93 (0.67)

* Indicates significant between-group difference ($P < 0.05$).