EFFECTS OF COMT GENOTYPE ON SENSORY GATING AND ITS MODULATION BY NICOTINE: DIFFERENCES IN LOW AND HIGH P50 SUPPRESSORS

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Abstract

Elevated smoking rates seen in schizophrenia populations may be an attempt to correct neuropathologies associated with deficient nicotinic acetylcholine receptors and/or dopaminergic systems using exogenous nicotine. However, nicotine's effects on cognitive processing and sensory gating have been shown to be baseline-dependent. Evidence of a restorative effect on sensory gating deficits by nicotine-like agonists has been demonstrated, however, its underlying mechanisms in the context of dopamine dysregulation are unclear. Catechol-O-methyltransferase (COMT), a key dopamine regulator in the brain, contains a co-dominant allele in which a valine-to-methionine substitution causes variations in enzymatic activity leading to reduced synaptic dopamine levels in the Val/Val genotype. Using a randomized, double-blind, placebo-controlled design with 57 non-smokers, this study examined the effects of COMT genotype on sensory gating and its modulation by nicotine in low vs. high suppressors. The results were consistent with the hypothesis that increased dopamine resulting from nicotine stimulation or Met allelic activity would benefit gating in low suppressors and impair gating in high suppressors, and that this gating improvement with nicotine would be more evident in Val carriers who were low suppressors, while the gating impairment would be more evident in Met carriers who were high suppressors. These findings reaffirm the importance of baseline-dependency and suggest a subtle relationship between COMT genotype and baseline-stratified levels of sensory gating, which may help to explain the variability of cognitive abilities in schizophrenia populations.

Keywords

schizophrenia; P50 sensory gating; catechol-O-methyltransferase; nicotine; baseline-dependency; non-smokers

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INTRODUCTION

Elevated smoking rates (~55–80%) in the schizophrenia (SZ) population have been interpreted as a form of self-medication (de Leon and Diaz, 2005), believed to improve underlying cognitive deficits (Kumari and Postma, 2005), which are important predictors of functional outcome (Winterer, 2010). Although nicotine's cognitive enhancing actions are seen over a range of cognitive domains (Heishman et al., 2010), individual differences are marked and have been interpreted within an inverted U-shaped relationship between baseline cognitive performance and nicotinic stimulation, whereby similar doses improve performance in individuals with below-optimal baseline levels and impair performance in those with above-optimal baseline levels (Newhouse et al., 2004).

Nicotine's baseline-dependence (Perkins, 1999) has been examined with respect to prepulse inhibition (Vollenweider et al., 2006; Csomor et al., 2008), antisaccade performance (Petrovsky et al., 2012), inhibition and motor planning (Allman et al., 2010), and more recently with respect to sensory gating (Csomor et al., 2008; Knott et al., 2010a), which is impaired in SZ (Patterson et al., 2008). Sensory gating, an established method of assessing individual differences in filtering stimuli, can be measured using the P50 event-related potential (ERP) component. This auditory paradigm involves the presentation of a series of paired clicks (S_1 , S_2) in which S_1 is believed to activate inhibitory mechanisms that diminish the response to S_2 (Brenner et al., 2009). P50 studies consistently show S_2 to be significantly smaller than S_1 in healthy controls, producing a P50 ratio (S_2/S_1) of ~0.40, while in SZ this ratio is ~0.80 (Patterson et al., 2008). Both SZ and P50 gating deficits have been linked to the $\alpha 7$ -nicotinic acetylcholine receptor (nAChR) subunit gene (Freedman et al., 2001), and acute nicotine has been shown to improve gating in SZ and their relatives (Adler et al., 1992, 1993).

Antipsychotics, which are primarily dopamine (DA) antagonists, exert little or no effects on cognitive deficits and gating in SZ (Adler et al., 2004), but individual differences in genotypes (DRD2, DAT1) regulating striatal DA (Knott et al., 2010b; Millar et al., 2011) have been shown to affect baseline and nicotine-modulated gating. The relationship between prefrontal DA and cognitive performance has also been described as a U-shaped curve, whereby an excess or an insufficiency can be detrimental (Goldman-Rakic et al., 2000; Williams-Gray et al., 2007; Monte-Silva et al., 2009). Catechol-O-methyltransferase (COMT), a key enzyme in prefrontal cortex (PFC) DA metabolism, has been extensively investigated in relation to cognition (Egan et al., 2001). A common guanine-to-adenine nucleotide polymorphism causes a valine-to-methionine substitution at codon 158 (Val158Met) leading to a trimodal distribution in which Met/Met has a three- to fourfold lower enzymatic activity compared to Val/Val (Williams et al., 2007). Val homozygotes exhibit suboptimal DA levels, while Met homozygotes exhibit near-optimal DA levels at baseline (Goldberg and Weinberger, 2004). Val homozygotes are shifted into an optimal range with decreased COMT activity or increased PFC DA activity, while these changes have the opposite effect in Met homozygotes (Tunbridge et al., 2006).

COMT-modulated PFC DA effects on cognition have been shown to be task-dependent (Bilder et al., 2004) and the results with gating have been mixed. Lu et al. (2007) reported

that Val homozygotes exhibited greater gating deficits in both SZ patients and controls. Shaikh et al. (2011) found no association between Val158Met and P50 gating in SZ patients, first-degree relatives, and controls. Majic et al. (2011) also reported that P50 gating was not affected by COMT genotype in healthy controls. Cao et al. (2012) showed that nicotine increased P20 (P50 mouse analog) amplitude and latency in COMT-Val transgenic mice. Increased PFC DA may only benefit low (vs. high) baseline gaters, whose gating has been shown to increase with acute nicotine (Knott et al., 2010a) and antipsychotics (Csomor et al., 2008), but has yet to be examined with respect to COMT or its moderating actions on nicotine-modulated gating.

Given the evidence for gating facilitation with nicotine and its dependence on DA gene polymorphisms, this study extended this work by examining COMT genotype effects and their moderating role on nicotine-modulated gating in healthy controls stratified as low and high baseline gaters (S₂ P50 suppressors). We expected increased DA, resulting from nicotine stimulation or Met activity, would benefit gating, in low P50 suppressors (LS) only. In contrast, increased DA in high suppressors (HS) was expected to impair gating. Nicotine-induced gating improvements were predicted to be most evident in Val carriers, i.e. those with low PFC DA, who were LS, while those with high PFC DA, i.e. Met carriers and HS, were expected to exhibit nicotine-induced gating impairments.

EXPERIMENTAL PROCEDURES

Volunteer sample

A sample of 57 right-handed, healthy, non-smoking males between 18 and 40 years of age were recruited via a screening interview, which included a general medical history and the use of Structured Clinical Interview, Non-Patient version (SCID-NP; Williams et al., 1992) for DSM-IV to assess personal psychiatric history, and the Family Interview for Genetic Studies (FIGS; Maxwell, 1992) to assess psychiatric history of first-degree biological relatives. For study inclusion, participants had to report having no prior or current psychiatric or substance abuse/dependence problems or any significant medical illness. They must also have reported no psychiatric disorders among their first-degree biological relatives. Participants were required to be medication-free and to report having normal hearing. Non-smokers were defined as those who had consumed no more than 100 cigarettes in their lifetime and had not smoked a cigarette for over a year. This was confirmed by analysis of a sample of expired air carbon monoxide, levels of which were all below three parts per million. All participants signed a consent form prior to participation in this study, which was approved by the Research Ethics Board of the Royal Ottawa Health Care Group, and they received \$60 for their involvement.

Experimental design

Volunteers were assessed in two test sessions within a randomized, double-blind, placebo-controlled crossover design with parallel genotype groupings (i.e. Val/Val, Val/Met, and Met/Met COMT genotypes), with participants of each group being further separated into low P50 suppressors (LS) and high P50 suppressors (HS). The order of nicotine and placebo sessions (separated by a minimum of 2 days) was counterbalanced so that half of each group

(randomly selected) received nicotine in their first session and placebo in their second session, while the remaining half received their treatments in the reverse order.

Nicotine administration

Nicotine was administered orally in the form of two pieces (4 mg+2 mg) of cinnamon-flavored Nicorette[®] gum (Johnson & Johnson Inc., Markham, Ontario, Canada). The total (6 mg) dose was intended to result in a similar blood nicotine level as achieved by smokers smoking a single cigarette of average nicotine yield, producing a nicotine blood concentration of approximately 15–30 ng/ml (Hukkanen et al., 2005). Peak blood nicotine levels with this dose have been shown at approximately 30 min after the beginning of the gum chewing, and the elimination half-life of nicotine is ~120 min. The gum was chewed in accordance with the manufacturer's guidelines, which specified a chewing time of 25 min, biting twice every minute (as cued by a recording) and "parking" the gum between the teeth and cheeks between bites. Gum pieces used as placebos were similar in size, color, texture, and taste. In addition, the participants were temporarily blindfolded while placing the gum in their mouths and wore nose plugs throughout the chewing process in order to reduce any possible sensory differences between nicotine and placebo. Prior to removing the nose plug following the 25-min chewing period, the participants were given a commercially available mint-flavored gum for 1–2 min in order to remove any lingering taste.

Procedure/recording

Participants arrived at the laboratory at 8:00 AM having been instructed to abstain overnight (beginning at 12:00 AM) from food, nicotine, caffeine, alcohol, drugs, and medications. Volunteers were seated in a sound-attenuated, dimly-lit chamber where nicotine was administered and electrodes were placed on the scalp. Following these procedures, the auditory P50 paired-click paradigm was presented. This involved the presentation of a series of 64 paired clicks (S_1 – S_2) heard binaurally through headphones at 10-s inter-pair intervals. The clicks had a sound pressure level of 85 dB, with 100- μ s click durations and 500-ms inter-click intervals. An eyes-open electroencephalogram (EEG) was recorded with Ag^+/Ag^+Cl^- electrodes from eight scalp sites: frontal midline (Fz), left (F3) and right (F4); central midline (Cz), left (C3) and right (C4); midline parietal (Pz); and midline occipital (Oz), using a common average reference and a ground electrode positioned anterior to the Fz site. Additional electrodes were placed on the supra- and sub-orbital ridges of the right eye and on the external canthus of both eyes to record vertical (VEOG) and horizontal (HEOG) electro-oculographic activity. Electrode impedances were maintained below 5 k Ω . Electrical activities were recorded using a Brain Vision[®] Quickamp amplifier and a Brain Vision Recorder[®] (Brain Products, Germany) with amplifier bandpass filters and sampling rate set to 0.1–120 Hz and 500 Hz, respectively.

ERP processing

The off-line analysis was carried out using Brain Vision Analyzer[®] (Brain Products) software. This included bandpass filtering (10–49 Hz; 24 dB/octave – roll-off), epoch segmentation (150 ms, beginning 50 ms pre-stimulus onset), EOG correction (Gratton et al., 1983), artifact rejection (excluding ocular-corrected EEG epochs with voltages exceeding $\pm 75 \mu$ v), baseline correction, and selective averaging for each (S_1 , S_2) stimulus of the click

pairs. The P50 at Cz scalp site has been shown to be the best discriminator of gating differences between SZ and control groups, as well as for being the site of maximal P50 amplitude (Clementz et al., 1998). From this site, P50 amplitudes were identified semi-automatically using previously outlined criteria (Boutros et al., 2004, 2009; Olincy et al., 2010). P50 was chosen as the second of two positive peaks in a post-stimulus latency range of 15–80 ms, and preceding an earlier positive peak (P_a) in a 15–40 ms range. P50 must also have been present in one other central recording site (C3 or C4) besides Cz. The two P50 peaks (S_1 P50 and S_2 P50) from the Cz site were scored for latency and amplitude. The scoring method involved a peak-to-trough index, i.e. the voltage difference between P50 and the preceding negative peak (N40) at approximately 30–50 ms. Auditory P50 suppression was defined as $S_2/S_1 \times 100$, or the gating ratio “rP50”. It should be noted that reports of questionable test–retest reliability have characterized the ratio index of gating (Fuerst et al., 2007), while the difference score (dP50) index of gating (derived by subtracting S_2 amplitude from S_1 amplitude) has been advocated due to greater reliability (Dalecki et al., 2011). In our study, we conducted the analysis with both rP50- and dP50-defined subgroups and both the genotype and drug effects were found to be similar with both indices. As the rP50 is the most frequently used measure in healthy control and patient studies, only the findings associated with the rP50-defined groups are reported.

COMT genotyping

A sample of each participant’s saliva was collected using Oragene DNA Self-Collection Kits (DNA Genotek Inc., Ottawa, Ontario, Canada). The genetic analysis was provided by an external lab (Dr. Paul Albert, Ottawa Health Research Institute). Extracted genomic DNA was assessed by real-time polymerase chain reaction (PCR) (Rotor-Gene RG-3000) to determine allele frequencies of the COMT Val158Met polymorphism (rs#4680), using $0.1 \times$ Taqman Drug Metabolism Genotyping Assay Kit (Applied Biosystems, USA, Assay ID# C_25746809_50) and template DNA with $1 \times$ Taqman master mix (4304437). The Rotor-gene 3000 (Corbett Research) real-time PCR apparatus was used with PCR cycling parameters, which included an initial 10 min denaturation at 95 °C, 45 cycles of denaturation (15 s at 92 °C), and annealing/extension (60 s at 60 °C).

Statistical analysis

Data were analyzed with two separate sets of analysis of variances (ANOVA), one for the gating index and one for amplitudes. For gating, the ANOVA included genotype (3 levels) and drug (2 levels) as between- and within-subject factors, respectively. Individuals within each genotype were stratified as HS or LS by a median split, as carried out by previous studies (Csomor et al., 2008; Knott et al., 2010a), of their rP50 scores and suppressor group was included as a second between-subject factor (2 levels). Stimulus (2 levels) served as an additional within-subject factor in ANOVAs of P50 amplitudes. Regardless of whether or not Greenhouse–Geisser corrected significance ($p < .05$) was revealed with these ANOVAs, Bonferroni-adjusted planned comparisons (using separate [vs. pooled] error estimates) were carried out with respect to our a priori hypotheses.

RESULTS

Allelic distribution and demographics

The COMT genotyping resulted in a distribution of 22.81% (Met/Met), 49.12% (Val/Met), and 28.07% (Val/Val). Using Chi square statistics, no significant deviation from the Hardy–Weinberg equilibrium was evident in the sample ($\chi^2=3.76$, $p=0.15$). After stratification, there were seven HS and six LS in the Met/Met genotype, 14 HS and 14 LS in the Val/Met genotype, and eight HS and eight LS in the Val/Val genotype. The age range of the sample was 18–34 years, with a mean age of 22.4 years ($\pm .49$), and no significant differences were observed between genotype or suppressor groups.

P50 amplitude

Figs. 1 and 2 display the S_1 and S_2 grand average baseline (placebo) ERP waveforms for the three genotypes and two suppressor groups, respectively. Grand average waveforms recorded during placebo and nicotine sessions for the three genotypes stratified as low and high suppressors are shown in Fig. 3. Analysis of individual S_1 and S_2 amplitudes revealed a main effect of stimulus ($F=85.17$, $df=1$, $p<.001$, partial eta-squared=.625) and stimulus $\times$ suppressor group ($F=7.30$, $df=1$, $p<.009$, partial eta-squared=.125), drug $\times$ stimulus $\times$ suppressor group ($F=20.69$, $df=1$, $p<.001$, partial eta-squared=.289), and drug $\times$ stimulus $\times$ suppressor group $\times$ genotype interactions ($F=3.25$, $df=2$, $p<.047$, partial eta-squared=.113). In both placebo and nicotine sessions, it was found that the S_1 amplitudes were significantly larger than the S_2 amplitudes in both the HS ($p=.001$) and LS ($p=.001$) groups.

LS exhibited significantly ($p=.015$) smaller S_1 amplitudes ($M=2.71$ μV , $SE\pm .32$) compared to HS ($M=3.86$ μV , $SE\pm .33$) as well as significantly ($p=.002$) larger S_2 amplitudes ($M=1.90$ μV , $SE\pm .16$) compared to HS ($M=1.21$ μV , $SE\pm .17$) during baseline (placebo). Larger ($p=.006$) S_2 amplitudes were observed in the Val/Val group ($M=2.00$ μV , $SE\pm .21$) as compared to both the Met/Met ($M=1.10$ μV , $SE\pm .23$) and the Val/Met ($M=1.43$ μV , $SE\pm .16$) genotype ($p=.034$). Additional planned comparisons showed these genotype effects to be dependent on suppressor grouping, with the Val/Val group ($M=1.82$ μV , $SE\pm .30$) exhibiting significantly larger ($p=.027$) S_2 amplitudes as compared to both the Met/Met group ($M=.79$ μV , $SE\pm .34$) and ($p=.006$) the Val/Met group ($M=.76$ μV , $SE\pm .22$), but only in HS. Within the Val/Met genotype, S_2 amplitudes were significantly ($p=.001$) larger in the LS ($M=2.10$ μV , $SE\pm .22$) as compared to the HS ($M=.76$ μV , $SE\pm .22$). Baseline genotype amplitude differences were not seen between the LS genotypes.

Nicotine ($M=1.45$ μV , $SE\pm .19$) significantly ($p=.043$) decreased S_2 amplitudes in LS compared to placebo ($M=1.90$ μV , $SE\pm .16$), however, this was shown to be dependent on genotype. Nicotine ($M=1.35$ μV , $SE\pm .27$) significantly ($p=.016$) decreased S_2 amplitude in the LS Val/Met group as compared to the placebo condition ($M=2.10$ μV , $SE\pm .22$) and similarly, nicotine ($M=1.36$ μV , $SE\pm .35$) reduced ($p=.042$) S_2 amplitude compared to placebo ($M=2.19$ μV , $SE\pm .30$) in the LS Val/Val group.

In contrast to these effects in the LS, nicotine ($M=3.12$ μV , $SE\pm .35$) significantly ($p=.016$) decreased S_1 amplitudes in the HS compared to placebo ($M=3.86$ μV , $SE\pm .33$), while significantly ($p=.050$) increasing S_2 amplitudes ($M=1.58$ μV , $SE\pm .20$) compared to placebo

($M=1.12 \mu V$, $SE \pm .17$). Different drug effects observed among the genotypes were found to vary with suppressor group, as there was a significant ($p=.006$) decrease in S_1 amplitudes in the HS Val/Met group from placebo ($M=4.07 \mu V$, $SE \pm .44$) to nicotine ($M=2.99 \mu V$, $SE \pm .47$), as well as a significant ($p=.004$) increase in S_2 amplitude in the HS Val/Met group from placebo ($M=.76 \mu V$, $SE \pm .22$) to nicotine ($M=1.66 \mu V$, $SE \pm .27$). No significant nicotine-induced amplitude changes were observed in the Met/Met genotype.

P50 gating

Significant drug $\times$ suppressor group ($F=22.48$, $df=1$, $p<.001$, partial eta-squared=.306) and drug $\times$ genotype interactions ($F=4.05$, $df=2$, $p<.023$, partial eta-squared=.137) were observed with the rP50 index. As would be expected, follow-up analyses of the drug $\times$ suppressor group interaction revealed significantly ($p=.001$) lower ratios (increased gating) in the HS ($M=.30$, $SE \pm .07$) vs. LS ($M=.82$, $SE \pm .063$) group in the placebo condition.

Within the baseline (placebo) condition of the drug $\times$ genotype interaction, significantly ($p=.012$) higher ratios were found in the Val/Val ($M=.75$, $SE \pm .081$) vs. Met/Met ($M=.44$, $SE \pm .09$) and ($p=.009$) Val/Met ($M=.48$, $SE \pm .061$) genotypes. Additional planned comparisons showed these genotype effects to be dependent on suppressor grouping, with Val/Val ($M=1.06 \mu V$, $SE \pm .11$) exhibiting significantly higher ratios than both the Val/Met ($M=.77 \mu V$, $SE \pm .09$) genotype ($p=.012$) and the Met/Met ($M=.62 \mu V$, $SE \pm .12$) genotype ($p=.048$), but only in LS individuals.

High ratios observed in the LS groups during placebo were significantly ($p<.001$) reduced (improved gating) with nicotine ($M=.53$, $SE \pm .092$), while ratios in the HS groups during placebo were significantly increased (impaired gating) by nicotine ($M=.75$, $SE \pm .010$). Drug effects in the drug $\times$ genotype interaction were limited to the Met/Met genotype, where, compared to placebo ($M=.44$, $SE \pm .09$), nicotine ($M=.84$, $SE \pm .13$) significantly ($p=.013$) increased ratios (impaired gating).

In addition, planned comparisons revealed significant drug effects in genotypes that varied with suppressor group. In the LS, nicotine ($p=.006$) reduced ratios (improved gating) in Val/Val carriers ($M=.49$, $SE \pm .17$) compared to placebo ($M=1.06$, $SE \pm .11$) as well as ($p=.027$) in the Val/Met carriers ($M=.43$, $SE \pm .13$) compared to placebo ($M=.77$, $SE \pm .09$). Conversely, in the high suppressors, nicotine increased ($p=.002$) ratios (impaired gating) in the Met/Met carriers ($M=.99$, $SE \pm .19$) compared to placebo ($M=.25$, $SE \pm .13$) as well as ($p=.004$) in the Val/Met carriers ($M=.65$, $SE \pm .13$) compared to placebo ($M=.19$, $SE \pm .09$).

DISCUSSION

The main purpose of this study was to examine the effects of acute nicotine administration and COMT genotype on P50 sensory gating in healthy non-smokers stratified for low and high suppression. In this investigation, S_1 amplitudes were significantly larger than S_2 amplitudes across drug conditions and genetic and suppressor groups, thus providing evidence of sensory gating similar to previous studies utilizing the paired stimulus paradigm. LS, as required by stratification, exhibited larger gating ratios (poorer gating) as compared to HS, and, consistent with previous findings, LS also demonstrated smaller S_1 (Knott et al.,

2009, 2010a,b) and larger S_2 amplitudes (Csomor et al., 2008; Knott et al., 2009; Holstein et al., 2011) compared to HS at baseline. Genotype differences in P50 amplitude and gating and their alteration with nicotine were found to vary between suppressor groups and thus supported the notion that molecular and pharmacological variations in DA affecting sensory gating are baseline-dependent. Putative increases in central DA tone associated both with the Met allele and nicotine administration improved gating but only in LS. The use of individual differences in sensory gating among healthy controls thus may be a practical and viable Phase I alternative to investigating novel gene or drug interventions in SZ because it avoids possible clinical and medication confounds associated with patient testing (Light and Braff, 2003).

Baseline-dependent effects of genotype on sensory gating

In general, the Val/Val genotype showed the poorest sensory gating ability at baseline. The average $S_2/S_1\%$ gating ratio of ~75% for the Val/Val genotype at baseline was well within 1 SD (24.3) of the mean gating ratio of 79% observed in SZ patients, whereas the gating scores of ~44% for Met/Met and ~48% for Val/Met genotypes were within 1 SD (15.3) of the mean gating ratio of 39% observed in healthy controls (Patterson et al., 2008). The results of the amplitude analysis were also consistent with these findings, as the Val/Val genotype exhibited the largest S_2 amplitudes, indicating a relative failure in sensory inhibition. In previous work with healthy volunteers, LS exhibited larger S_2 amplitudes as compared to HS (Csomor et al., 2008; Knott et al., 2009; Holstein et al., 2011). Studies involving SZ patients have also found larger S_2 amplitudes (Clementz, 1998). The reduced ability to suppress the second stimulus in LS and Val/Val is consistent with the idea that there is a failure of inhibitory mechanisms (de Wilde et al., 2007), and these findings suggest that poorer levels of sensory gating stemming from failed S_2 inhibition “gating out” deficits, as opposed to a deficiency in responding to stimulus changes, or “gating in” mechanisms (Brenner et al., 2009), is associated with low PFC dopaminergic tone.

Comparison with previous findings

The current results are consistent with the findings of Lu et al.’s (2007) study involving SZ patients ($n=45$) and healthy controls ($n=25$), which found that individuals with the Val/Val genotype showed the greatest P50 deficit. The other two studies involving P50 sensory gating and the COMT Val158Met polymorphism found no association in both a large sample consisting of SZ patients ($n=138$), first-degree relatives ($n=109$) and healthy subjects ($n=204$) (Shaikh et al., 2011) and a sample of healthy controls ($n=282$) (Majic et al., 2011). However, the methodology of these studies varied greatly with regard to the study sample, P50 paradigm and recording, as well as ERP processing. The Lu et al. (2007) study’s participants were primarily males (80.6%), whereas the other studies consisted of approximately half male subjects (Shaikh, 46.6%; Majic, 51.4%). In the present study, males were used in order to avoid confounding issues of gender and hormonal differences in response to nicotine. Gender differences with regards to sensory gating in healthy controls have been shown previously, with weaker P50 gating in females compared to males (Hetrick et al., 1996; Patterson et al., 2008). Studies involving healthy controls have also reported weaker P50 gating ability with increased age (Patterson et al., 2008; Turetsky et al., 2008). The mean age of the participants in the three other COMT/sensory gating studies were 43.5,

42.3 and 41.3 (Lu et al., 2007; Majic et al., 2011; Shaikh et al., 2011), reaching as high as 65 years, whereas the mean age in the present study was approximately 22.4 years. Furthermore, none of these studies controlled for smoker (vs. nonsmoker) status as a potential confounding variable, which has also been shown to moderate P50 inhibition (Crawford et al., 2002; Croft et al., 2004). In smokers, cognitive deficits, withdrawal symptoms, and functional brain activation during brief tobacco abstinence all vary with COMT genotype (Loughead et al., 2009). Additionally, chronic nicotine exposure upregulates nAChRs (Benwell et al., 1988) and alters their sensitivity (Picciotto et al., 2008), while also varying the expression of nAChR and DA genes in the brain (Flatscher-Bader and Wilce, 2009). The P50 paradigm and recording method used in these studies varied as well. While all of the studies' paradigms used an inter-stimulus interval of 500 ms, the inter-pair intervals differed, from 10 s (Lu et al., 2007), 7–11 s (Shaikh et al., 2011), to four fixed pseudorandomized inter-pair intervals (1.5 s, 3 s, 3.8 s, and 4.6 s; mean inter-pair interval: 2.8 s)(Majic et al., 2011). The paradigms differed with regard to stimulus intensity and duration, as well as the participants' task instructions (eyes open vs. eyes closed, eyes fixed on a target or not). The processing methodology of the P50 also varied between the studies (filtering, epoch segmentation, artifact rejection, S₁ and S₂ P50 identification, etc.).

Interpretation through current dopaminergic theories

The results of the present study are consistent with the inverted U-shaped relation between PFC DA and COMT activity, since reduced synaptic DA levels resulting from a more rapid degradation in the Val/Val genotype leads to DAergic hypofunction (Tunbridge et al., 2006). As with the inverted-U theory, Val/Val individuals revealed poorer gating at baseline, while Val/Met and Met/Met individuals exhibited superior gating, presumably as a result of optimal levels of prefrontal DA. Further planned comparisons revealed the baseline-dependency of these COMT gene differences on sensory gating as the greater gating efficiency of the Met/Met and Val/Met (vs. Val/Val) was evident only in LS, thus reaffirming the idea that the gating-enhancing effects of increased cortical DA are dependent on initial gating ability.

These findings may be interpreted and understood through the Dual-State (Durstewitz and Seamans, 2008) and Tonic–Phasic (Grace, 1991) theories of DA transmission. The higher COMT activity present in the Val/Val group (which leads to a decrease in tonic DA transmission, decreases in cortical DA concentrations, and increases in D2 receptor transmission) is thought to be responsible for the increase in neural network flexibility and decrease in neural network stability in these individuals. In contrast, the lower COMT activity present in the Met/Met group (which leads to a rise in tonic DA transmission, increases in cortical DA concentrations, and increases in D1 receptor transmission) is believed to be responsible for an increase in neural network stability and a decrease in neural network flexibility (Bilder et al., 2004). Sensory gating is a fundamental aspect of information processing from external stimuli and is important for the filtering of information in order to avoid an overload of conscious information (Potter et al., 2006), and has also been said to be a protective element for the integrity of higher-order processes (Freedman et al., 1991; Boutros et al., 2004; Wan et al., 2008). It is then reasonable to suppose that adequate sensory gating abilities would be important for an individual's overall neural

stability, though this has not been conclusively established. There is some evidence which suggests that those in the Val/Val group may perform better on tasks requiring greater flexibility rather than stability (Nolan et al., 2004; Colzato et al., 2010), but as of now there is no clear advantage to having the Val/Val genotype (Rosa et al., 2010). However, the Val/Met genotype, with its intermediate levels of prefrontal DA, may represent a balance between the extremes of stability vs. flexibility, which could prove to be advantageous not only for gating but for all cognitive tasks. Since having a Met allele is believed to lead to a higher level of stability, then it may be this attribute that is responsible for the higher level of sensory gating in the Met/Met and Val/Met genotype groups. Similarly, individuals with a Met allele would have a higher energy D1 dominated state, once again favoring neural network stability (Durstewitz and Seamans, 2008).

Baseline-dependent effects of nicotine on sensory gating

Our baseline-dependency hypothesis that increased DA resulting from nicotine stimulation would exhibit a restorative effect on sensory gating in the LS while impairing gating in the HS was confirmed, as nicotine decreased P50 ratios in the LS and increased P50 ratios in the HS. Also as predicted, this increase in gating in the homozygous Val carriers was most evident in LS individuals. The LS Val/Val group significantly improved with nicotine, with a ratio score being reduced from 1.06 to .49, thus improving to levels similar to the Val/Met group at baseline (.48). Analysis of amplitude values confirmed that nicotine mediated this effect by decreasing S_2 amplitude values, leading to a smaller ratio score and thus a higher level of sensory gating. Nicotine effects in Met carriers were also shown to be dependent on initial gating levels, as gating abilities of the LS Val/Met increased, while the abilities of the HS Val/Met and Met/Met genotypes decreased. The mechanisms underlying these divergent baseline dependency effects of nicotine in LS and HS Met carriers also differed as analysis of amplitude values revealed that nicotine diminished gating by reducing S_1 values and increasing S_2 values in the HS Val/Met group, thus producing gating indices which indicate poorer sensory gating (larger ratio score), while nicotine decreased S_2 values in the LS Val/Met group, producing gating indices which indicate more efficient gating (smaller ratio score).

Implications

Overall, our baseline-dependent gating effects with nicotine are consistent with both Newhouse et al.'s (2004) inverted U-shaped curve of nicotine modulation in relation to baseline ability as well as the inverted-U shaped relationship between COMT genotype, DA availability, and cognitive performance. LS Val/Val individuals were shifted from a suboptimal to an optimal range of functioning with an acute administration of nicotine, and conversely, HS Met allele carriers decreased in gating ability with nicotine, passing from an optimal range to a deleterious superoptimal range. These results reaffirm the importance of baseline-dependency and inter-individual differences in sensory gating ability, while illustrating the need for additional psychopharmacological investigations regarding nicotine administration in baseline-stratified groups. These observations have potential implications for the assessment of novel nicotinic and dopaminergic agents in Phase I dose-finding trials with healthy controls who vary in gating ability, as well as in early Phase II trials with patients, a good proportion of whom have gating ratios overlapping with control ratios

(Patterson et al., 2008) and as such may exhibit a distinctly unique gating response to treatment.

Confounds and limitations

There are several confounding factors that should be considered in this study. Samples were relatively small and were limited to non-smokers and as such, the results may not generalize to smokers and/or SZ patients, the majority of whom are heavy smokers. Nicotine was administered as a single dose and measures were assessed at only one time point, so information on dose- and time-response relationships was lacking. Nicotine was administered by gum, which is absorbed slowly and may favor the desensitization of the high-affinity $\alpha 4\beta 2$ nAChRs, but not the low-affinity $\alpha 7$ nAChRs (Dani and De Biasi, 2001), as opposed to smoke-inhaled nicotine, which results in an initial activation of nAChRs. Due to the absence of assessment of plasma nicotine levels, it is also unclear whether response changes or absence of changes were related to “smoking” doses of nicotine that are typically observed with the acute smoking of 1–2 cigarettes. There are also limitations regarding ERPs as they have reduced spatial (anatomical) sensitivity in the brain, and so information regarding brain generators underlying any nicotine/genetic influences remain unresolved. Also controversial is the choice of gating index employed to perform the median split. In the current study, we stratified each measure based on the rP50, a widely used gating index but with low test-retest reliability (Potter et al., 2006). The neuroanatomical and functional substrates of P50 suppression are still unclear (Knott et al., 2009), with each measure potentially reflecting different aspects of gating, and could therefore be differentially expressing the effects of nicotine stimulation. In our most recent study (Knott et al., unpublished observation), each suppressor group segmented with the ratio score, the difference (dP50) score ($S_1 - S_2$), or the gating difference waveform (GDW), showed similar gating responses to nicotine regardless of whether they were stratified by rP50, dP50, or GDW criteria. Future studies may address these issues by comparing smokers and nonsmokers in control and patient samples, by measuring salivaindexed nicotine levels following time-dependent monitoring of multiple administrations, repeated doses of rapid-delivery nicotine systems (e.g. inhalers), by employing source localization procedures to identify target generators of P50 influenced by DA genetics and nicotine, and/or by assessing multiple cognitive and functional domains to isolate specific deficits that may be influenced by the baseline-dependent gating effects of nicotinic and dopaminergic systems.

Acknowledgments

Research was supported in part by grants to V.K. from the Natural Science and Engineering Research Council (NSERC) and the University of Ottawa Medical Research Foundation (UMRF).

Abbreviations

ANOVA	analysis of variances
COMT	catechol-O-methyltransferase
D1	dopamine D1 receptor

D2	dopamine D2 receptor
DA	dopamine
DAT1	gene coding for the dopamine transporter
dP50	P50 difference score index of sensory gating
DRD2	gene encoding for the DAD2 receptor
EEG	electroencephalogram
ERP	event-related potential
GDW	gating difference wave
HS	high suppressors
LS	low suppressors
Met	methionine
nAChR	nicotinic acetylcholine receptor
PFC	prefrontal cortex
PCR	polymerase chain reaction
rP50	P50 ratio index of sensory gating
S₁	first stimulus
S₂	second stimulus
SZ	schizophrenia
Val	valine

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Fig. 1. Grand average baseline (placebo) ERP waveforms at Cz for S₁ (black) and S₂ (gray) stimuli by genotype.

Fig. 2.
Grand average baseline (placebo) ERP waveforms at C_Z for S₁ (black) and S₂ (gray) stimuli by suppressor group.

Fig. 3. Grand average ERP waveforms at Cz during placebo and nicotine sessions for S₁ (black) and S₂ (gray) stimuli for all three genotypes stratified as high (HS) and low (LS) suppressors.