Genes Brain Behav. Author manuscript; available in PMC 2015 July 24.

Published in final edited form as:

Genes Brain Behav. 2015 July ; 14(6): 466–476. doi:10.1111/gbb.12226.

COMT polymorphism modulates the resting-state EEG alpha oscillatory response to acute nicotine in male non-smokers

H. Bowers[†], **D. Smith**[‡], **S. de la Salle**[§], **J. Choueiry**[‡], **D. Impey**[§], **T. Philippe**[¶], **H. Dort**[¶], **A. Millar**[‡,**], **M. Daigle**[**], **P. R. Albert**[‡,**], **A. Beaudoin**[¶], and **V. Knott**[‡,§,¶,*]

[†]Department of Psychology, University of Guelph, Guelph, ON, Canada

[‡]Department of Cellular and Molecular Medicine, University of Ottawa, Ottawa, ON, Canada

[§]School of Psychology, University of Ottawa, Ottawa, ON, Canada

[¶]University of Ottawa Institute of Mental Health Research, Royal Ottawa Mental Health Care Centre, Ottawa, ON, Canada

[**]Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada

Abstract

Performance improvements in cognitive tasks requiring executive functions are evident with nicotinic acetylcholine receptor (nAChR) agonists, and activation of the underlying neural circuitry supporting these cognitive effects is thought to involve dopamine neurotransmission. As individual difference in response to nicotine may be related to a functional polymorphism in the gene encoding catechol-O-methyltransferase (COMT), an enzyme that strongly influences cortical dopamine metabolism, this study examined the modulatory effects of the COMT Val158Met polymorphism on the neural response to acute nicotine as measured with resting-state electroencephalographic (EEG) oscillations. In a sample of 62 healthy non-smoking adult males, a single dose (6 mg) of nicotine gum administered in a randomized, double-blind, placebo-controlled design was shown to affect α oscillatory activity, increasing power of upper α oscillations in frontocentral regions of Met/Met homozygotes and in parietal/occipital regions of Val/Met heterozygotes. Peak α frequency was also found to be faster with nicotine (vs. placebo) treatment in Val/Met heterozygotes, who exhibited a slower α frequency compared to Val/Val homozygotes. The data tentatively suggest that interindividual differences in brain α oscillations and their response to nicotinic agonist treatment are influenced by genetic mechanisms involving COMT.

Keywords

Alpha; catechol-O-methyltransferase; cognition; dopamine; electroencephalography; genotype; nicotine; oscillations; polymorphism; resting state

[*]Corresponding author: V. Knott, University of Ottawa Institute of Mental Health Research, Royal Ottawa Mental Health Care Centre, 1145 Carling Avenue, Ottawa, ON K1Z 7K4, Canada. Verner.Knott@theroyal.ca.

The cognitive enhancement properties of nicotinic acetylcholinergic receptor (nAChR) agonists such as nicotine (Heishman *et al.* 2010) are associated with their moderating effects on the dopamine (DA) pathway connecting the ventral tegmental area (VTA) with cortical regions, including the prefrontal cortex (PFC). Agonists effect this enhancement by binding to nAChRs on VTA DA projection neurons, increasing dopamine signaling and processing in cortical networks (Jasinska *et al.* 2013; Livingstone & Wonnacott 2009; Mansvelder *et al.* 2006). A range of evidence has further shown that nicotinic stimulation increases dopamine concentrations in the PFC, where stimulation of presynaptic nAChRs elevates dopamine levels and influences cognitive processes (Wallace & Bertrand 2013).

Studies of cognitive performance (Newhouse *et al.* 2004; Perkins 1999) and patterns of activation of task-specific neural networks (Bentley *et al.* 2011; Newhouse *et al.* 2011) show considerable intersubject response variability to nicotine and nicotinic agonists, often resembling an 'inverted-U' shaped function (persons exhibiting suboptimal performance *prior* to drug challenge tend to show performance benefits and normalized neural activity with nicotine, while those performing at optimal level or exhibiting task-related neural efficiency tend to show nil or diminished cognitive and neural response to nicotine). While the neurobiological causes underlying this heterogeneity are not well understood, there is an increasing trend to use molecular genetic approaches to assay individual differences in cognitive functions (Greenwood & Parasuraman 2003) and response to pharmacological treatments (Apud & Weinberger 2006; Goldstein *et al.* 2007), including nicotine (Herman & Sofuoglu 2010). Such approaches focus on allelic variations in the pharmacodynamic and pharmacokinetic properties of neurotransmitter genes involved in the different aspects of cognition (Parasuraman 2009). Of the likely candidate genes influencing response heterogeneity to nicotine, those regulating DA neurotransmission show promise as pharmacological studies in animals (Grannon *et al.* 2000) and humans (Kimberg *et al.* 1997; Mattay *et al.* 2000; Mehta *et al.* 2000) indicate that the effects of amphetamine and other dopamimetic drugs are baseline dependent. Relatively poor performers on prefrontal cognitive tasks have improved with treatment, whereas high performers have shown no response or response deterioration.

Catabolic flux of synaptic dopamine in the cortex is controlled primarily by the enzyme catechol-O-methyltransferase (COMT) (Huotari *et al.* 2002). The COMT gene contains a single nucleotide polymorphism that produces a valine-to-methionine (Val/Met) substitution at position 158 (Val158Met), producing a trimodal distribution of enzyme activity (Floderus *et al.* 1981; Lachman *et al.* 1996). Met158 homozygotes biotransform dopamine less than Val carriers, showing one third less COMT enzymatic activity in brain. Hence, there are higher extracellular dopamine levels with Met homozygotes (Chen *et al.* 2004). Val/Met heterozygotes exhibit intermediate levels of COMT activity (Weinshilboum *et al.* 1999).

Thus, COMT is an excellent candidate gene for modulating dopamine levels and function in the cortex and for determining where on the inverted-U shaped curve of dopamine function an individual lies (Tunbridge *et al.* 2006). However, inconsistent behavioral data and performance meta-analyses support only a weak association between COMT polymorphisms and individual differences in PFC function (Barnett *et al.* 2007; Munafo *et al.* 2005). Nevertheless, investigations of individual differences with intermediate brain-based

phenotypes, more sensitive for detecting gene effects on the brain (Green *et al.* 2008; Parasuraman & Jiang 2012), have found greater cortical processing efficiency in Met158 homozygotes compared to Val158 homozygotes, with heterozygotes displaying intermediate activation levels (Egan *et al.* 2001; Heinz & Smolka 2006). Acute dosing with amphetamine, which elevates synaptic dopamine levels, increased PFC task-evoked cortical efficiency in individuals with the Val/Val genotype, who have presumed low prefrontal synaptic dopamine, and reduced PFC processing efficiency compared to low-activity Met/Met genotypes (Mattay *et al.* 2003).

The limited functional magnetic resonance imaging (fMRI) investigations of the COMT polymorphism's effects on the cerebrovascular activational response to nicotine in smokers have shown mixed results. For example, Val/Val smokers were more prone to cognitive impairment and reduced prefrontal activation during smoking abstinence (Loughead *et al.* 2009) but another study showed Met/Met smokers with significant activation reduction of frontal executive control regions during cessation (Ashare *et al.* 2013). Val/Val genotypes experienced more severe withdrawal symptoms following cessation, with greater subjective effects from acute intravenous nicotine (Herman *et al.* 2013; Lee *et al.* 2013). Because these studies in chronic smokers may simply reflect a 'remediation' of a cortical deficiency during nicotine withdrawal (Ashare *et al.* 2014; Beaver *et al.* 2011; Cole *et al.* 2010), a clearer picture of COMT-mediated response differences to nicotine may be obtained using nicotine-naïve volunteers examined with electrophysiological probes that permit direct, instantaneous detection of neuronal activity.

Electroencephalographic (EEG) studies have linked neuronal oscillations at low and high frequency ranges with specific cognitive functions (Lopes da Silva 2013; Uhlhaas *et al.* 2009; Wang 2010). These oscillations are key to sculpting temporal coordination of neural networks governing cognitive functions such as perception, attention and working memory (Cantero & Atienza 2005; Kaiser & Lutzenberger 2003; Lisman & Buzsaki 2008). The basic building blocks defining these oscillations can be probed with the spectral profiling of EEG recordings during a resting state (Narayanan *et al.* 2014), and have shown that distinct changes in oscillatory activity in low and high frequencies are associated with different drug classes (Knott 2000; Saletu *et al.* 2002), including cognitive-enhancing drugs (Ahnaou *et al.* 2014; Leiser *et al.* 2011) and nicotine (Knott 1990).

In acute smoking, EEG studies have shown a characteristic, stimulant-like pharmaco-EEG profile – accelerating the dominant (α) oscillatory frequency (PAF), increasing power of α_2, β, decreasing power of δ, θ, α_1 (Knott 2001; Knott & Venables 1977). Similar patterns are observed in smokers using nicotine replacement products (Knott *et al.* 1999; Lindgren *et al.* 1999; Pickworth *et al.* 1986, 1988; Teter *et al.* 2002). Individual differences in these profiles are reported, with power variations in accord with performances on frontal lobe tasks (Knott *et al.* 1995), presmoking arousal level (Shikata *et al.* 1995), hemisphere dominance (Domino *et al.* 1995a) and personality (Tatsuno 1995). In non-smokers, oscillatory changes due to acute nicotine administration are limited primarily to α rhythms, with increases observed in both PAF (Foulds *et al.* 1994; Harkrider *et al.* 2001) and frontal upper frequency α_2 power (Fisher *et al.* 2012a) during resting states, and increases in anterior α_2 during working memory tasks (Fisher *et al.* 2012b, 2013). Nicotine-induced oscillatory response differences

between smokers and non-smokers may reflect genetic factors, including COMT (Beuten *et al.* 2006; Colilla *et al.* 2005; Guo *et al.* 2007), involved in smoking initiation and progression to dependence (Kendler *et al.* 1999; Maes *et al.* 2004) or individual differences in EEG. Little is known about the genetics underlying EEG traits or pharmacologically modulated EEG, but twin studies show that heritability of resting EEG oscillations is substantial (Stassen *et al.* 1987), particularly for PAF (Posthuma *et al.* 2001; Smit *et al.* 2005, 2006) and α-band oscillations with 80–90% heritability estimates (Van Beijsterveldt & van Baal 2002; Van Beijsterveldt *et al.* 1996). The COMT polymorphism contributes to individual differences in brain α oscillations, with Val homozygotes exhibiting reduced $\alpha 2$ and PAF compared to Met/Met carriers (Bodenmann *et al.* 2009a; Enoch *et al.* 2003), who exhibited greater delta, theta and beta (Solis-Ortiz *et al.* 2015).

We have examined the COMT polymorphism's moderating effects on the EEG oscillatory response to acute nicotine administration in non-smokers with upper alpha (α_2) and PAF as primary endpoints. Assuming that DA neuro-transmission innervates the α oscillatory component of the nicotine-modulated EEG response, and that COMT impacts prefrontal cortical DA signaling, we hypothesized that a single dose of nicotine to non-smokers would act as a pharmacologic probe of dopaminergic tone, enhancing α_2 and accelerating PAF, with the strongest effects in Met/Met individuals with higher levels of cortical dopamine and the weakest effects in Val/Val individuals. These same oscillatory changes should also differentiate COMT polymorphisms *per se*, with Met/Met homozygotes registering greater α_2 power and a higher PAF than Val/Val homozygotes that exhibit higher COMT activity. Secondary study endpoints included low frequency (δ, θ, α_1) and β oscillations as they are consistently modulated by smoking/nicotine (Knott 2001). Given the increasing attention of cortical oscillatory synchrony in the γ frequency range and its association with cognitive processes (Basar 2013; Herrmann *et al.* 2010; Merker 2013), we studied, for the first time in humans, resting-state γ oscillation response to nicotine and its moderation by the COMT polymorphism.

Methods

Study participants

The sample of volunteers consisted of 62 right-handed, healthy, non-smoking males between 18 and 34 years of age (mean age = 22.4 years) who were recruited primarily from local universities. Male, and not female, volunteers were chosen to avoid any potential confounding effects of menstrually related hormonal changes on nicotine response. All were screened for medical history, personal psychiatric history using the structured Clinical Interview, Non-Patient version for DSM-IV (SCID-NP; First *et al.* 2002) and family psychiatric history (first-degree biological relatives) with the Family Interview for Genetic Studies (FIGS; Maxwell 1992). Volunteers were included in the study if they were Caucasian, reported no personal or family psychiatric history including substance/alcohol abuse or dependence and had no significant medical issues and were medication free. Non-smokers were defined as those who had consumed no more than 100 cigarettes in their lifetime and had not smoked a cigarette over the past year. Non-smoking status was confirmed by expired carbon monoxide levels, which were <3 parts per million, a level

consistent with that of non-smokers (Cropsey *et al.* 2006). All volunteers signed a consent form prior to participation in the study, which was approved by the Research Ethics Board of the Royal Ottawa Health Care Group. Each participant received $60 CAD for his involvement in the study.

Experimental design

Each participant was assessed in two test sessions within a randomized, double-blind, placebo-controlled design. The two test sessions, involving nicotine or placebo treatment, were counterbalanced so that half of the participants received nicotine in their first session and placebo in their second session, while the remaining half received treatments in the reverse order. A minimum 2-day interval separated tested sessions.

Testing procedures

Testing was carried out between 0900 and 1630 h, with participants being required to abstain from caffeine, alcohol, drugs and medication and food for a minimum of 8 h prior to their scheduled testing, and abstain from liquids (with the exception of water) for 2 h prior in order to avoid interference with nicotine absorption. Sessions were carried out in a dimly lit, sound-attenuated chamber situated adjacent to the control room housing the monitoring and testing computers. Nicotine/placebo was administered concurrently with EEG electrode hook-up while participants were seated in a large semi-reclining chair. Electroencephalogram was recorded 30 min after nicotine/placebo administration, the time for nicotine to reach peak level in the blood. Vital signs and adverse events were assessed before and after nicotine administration.

Nicotine administration

Oral administration of nicotine was in the form of two pieces (4 mg + 2 mg) of cinnamon-flavored Nicorette® gum (Johnson & Johnson Inc., Markham, Ontario, Canada). Administering a 6 mg dose was intended to result in a similar 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 are achieved approximately 30 min after the beginning of the gum chewing, and the elimination half-life of nicotine is ~120 min. Gum chewing was in accordance with the manufacturer's guidelines, which specified a chewing time of 25 min, biting twice every minute (as cued by an audio recoding) and 'parking' the gum between teeth and cheeks between bites. Placebo gum pieces were cinnamon-flavored and were similar in size, color and texture. Participants were blindfolded and wore nose plugs throughout the gum administration in order to reduce any possible sensory differences between nicotine and placebo. Prior to removing the nose plug after the chewing period, participants chewed a mint-flavored gum for 1–2 min in order to remove any lingering taste differences.

Electroencephalographic acquisition

Electroencephalograms were recorded during a vigilance-controlled, 3-min eyes-closed resting-state condition. Electrical activity was sampled from an electrode cap (Electro-Cap International, Eaton, OH, USA) that positioned Ag^{+}/Ag^{+} CI^{-} electrodes at eight scalp sites;

frontal midline (Fz), left (F3) and right (F4); central midline (Pz), left (C3) and right (C4); midline parietal (Pz) and midline occipital (Oz). An electrode on the nose served as a reference, and an electrode positioned anterior to the Fz site was the ground. Additional electrodes were placed on the supraorbital and suborbital ridges of the right eye, and on the external canthus of both eyes to monitor vertical (VEOG) and horizontal (HEOG) electro-oculographic activity. Electrode impedances were kept below 5 kΩ. Electroencephalograms were acquired (500 Hz sampling rate) with the eight-channel BrainVision V-Amp® amplifier (bandpass filters set at 0.1–120 Hz) and BrainVision Recorder® software (v1.1, Brain Products, Gilching, Germany). Digital recordings were stored for later off-line analysis.

Electroencephalographic processing

Electroencephalographic analysis was carried out with BrainVision Analyzer® software (Brain Products). This included bandpass filtering (0.1–70 Hz; 24 dB/octave roll-off), epoch segmentation (2000 ms), ocular correction (Gratton *et al.* 1983) and artifact rejection (excluding ocular-corrected EEG epochs with voltages exceeding ±100 μV). For each test session, a minimum of 45 2-second artifact-free epochs were subjected to a fast fourier transform (FFT) algorithm (with a high-pass, autoregressive filter, weighted by a 5% cosine taper) for computation of absolute amplitude (μV) at each scalp site for: δ (0.5–5.5 Hz), θ (6–8 Hz), α_1 (8.5–10 Hz), α_2 (10.5–12 Hz), α total (8.5–12 Hz), β_1 (12.5–18 Hz), β_2 (18.5–20.5 Hz), β_3 (21–30 Hz) and γ (40–60 Hz) frequency bands. Relative amplitude (%) was also computed for each band by expressing amplitude in each band as a percent of total amplitude across all bands. As with Bodenmann *et al.* (2009b), PAF was determined visually from each individual's average spectra and was defined as the frequency bin (0.5 Hz resolution) in the α range with the maximal power (0.5 Hz resolution).

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 blinded to the results and provided by an external lab (Dr Paul Albert, Ottawa Hospital 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× Taqman Drug Metabolism Genotyping Assay Kit (Applied Biosystems, USA, Assay ID# C_25746809_50) and template DNA with 1× 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, 40 cycles of denaturation (15 seconds at 92°C) and annealing/extension (90 seconds at 60°C).

Statistical analysis

Statistical analysis of the data was carried out with the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA). Mixed analysis of variance (ANOVA) was used to analyze each band, with separate ANOVAs for log-transformed absolute and relative power in each band consisting of two within-subject factors – treatment (two levels: nicotine and placebo) and scalp region (eight levels: Fz, F3, F4, Cz, C3, C4, Pz and Oz), and one between-subject factor, genotype (three levels: Val/Val, Val/Met and Met/Met curriers). Similar ANOVAs were run for PAF but as peak spectral frequency was less apparent at

lateral hemisphere recordings, the site factor in the ANOVA contained only four levels (Fz, Cz, Pz and Oz). Regardless of ANOVA significance for α-band measures, planned comparison testing (correlated t-tests) study hypotheses were carried out and were mainly limited to placebo–nicotine contrasts within each genotype, as well as genotype contrasts in the placebo condition. For non-α-band measures, significant main or interaction effects ($P < 0.05$) were followed up with Bonferroni-corrected pairwise comparisons. Significant region effects were not examined in any of these comparisons unless they interacted with treatment and/or genotype.

Results

Allelic distribution

Catechol-O-methyltransferase genotyping resulted in the following distribution within the study sample: Met/Met = 24.19% ($N = 15$); Val/Met = 48.38% ($N = 30$) and Val/Val = 27.42% ($N = 17$). As evident with χ^2 statistics, no significant deviation from Hardy–Weinberg equilibrium was shown in the sample ($\chi^2 = 3.76$, $P = 0.05$). No significant age differences were observed between genotypes.

Alpha oscillations

Analysis of absolute amplitude in total α ($F = 183.16$, df = 7/413, $P < 0.0001$) and α_1 bands ($F = 121.12$, df = 7/413, $P < 0.0001$) yielded significant effects for region but not for treatment, genotype or their interaction. Upper alpha (α_2) analysis resulted in significant treatment ($F = 6.75$, df = 1/2, $P < 0.015$), region ($F = 160.15$, df = 7/413, $P < 0.0001$) and treatment × region × genotype interaction effects ($F = 2.93$, df = 14/143, $P < 0.020$). Genotypes did not differ with respect to absolute α_2 amplitude during the placebo session but treatment comparisons within each genotype group (Fig. 1) found increases in absolute α_2 amplitude with nicotine (vs. placebo) in Met/Met carriers at left (F3: $P < 0.05$), right (F4: $P < 0.03$) and mid-frontal (Fz: $P < 0.015$) regions as well as at left (C3: $P < 0.03$), right (C4: $P < 0.03$) and mid-central (Cz: $P < 0.02$) regions. In carriers of the Val/Met allele, nicotine-induced absolute α_2 amplitude increases were limited to mid-parietal (Pz: $P < 0.01$) and mid-occipital (Oz: $P < 0.003$) recording regions.

Relative amplitude analysis for total ($F = 66.23$, df = 7/413, $P < 0.0001$) and lower (α_1) alpha ($F = 42.34$, df = 7/413, $P < 0.0001$) showed only significant region effects, whereas relative upper alpha (α_2) amplitude was significantly affected by treatment ($F = 3.86$, df = 1/2, $P < 0.05$), region ($F = 68.95$, df = 7/413, $P < 0.0001$) and a treatment × region × genotype interaction ($F = 2.44$, df = 14/413, $P < 0.05$). Similar to the effects shown with absolute amplitude, no significant genotype differences were observed in the placebo session but in the Met/Met carriers, nicotine increased amplitude in all frontal (F3: $P < 0.03$; F4: $P < 0.04$; Fz: $P < 0.02$) and central scalp regions (C3: $P < 0.02$; C4: $P < 0.03$; Cz: $P < 0.03$) but not at posterior regions.

The PAF analysis resulted in significant treatment ($F = 5.92$, df = 1/2, $P < 0.02$), region ($F = 18.59$, df = 73/197, $P < 0.0001$) and treatment × genotype ($F = 3.41$, df = 2/59, $P < 0.04$) interaction effects. The PAF was shown to be progressively higher from frontal to posterior

regions and in the placebo session, Val/Met carriers displayed the slowest PAF at Fz, which was significantly different from PAF of Val/Val ($P < 0.04$) but not Met/Met carriers (Fig. 2). Treatment comparisons within genotypes found significant PAF acceleration in the Val/Met carriers with nicotine (vs. placebo) at frontal (Fz: $P < 0.01$), central (Cz: $P < 0.02$) and occipital (Oz: $P < 0.01$) regions, and at the parietal (Pz: $P < 0.05$) region in Met/Met carriers (Fig. 3).

Non-alpha oscillations

Absolute amplitude analysis yielded significant region effects for δ ($F = 80.56$, df = 7/413, $P < 0.0001$), θ ($F = 43.54$, df = 7/413, $P < 0.0001$), β_1 ($F = 55.51$, df = 7/413, $P < 0.0001$), β_2 ($F = 15.72$, df = 7/413, $P < 0.0001$), β_3 ($F = 12.72$, df = 7/413, $P < 0.0001$) and γ ($F = 6.29$, df = 7/413, $P < 0.0001$) but no treatment, genotype or interaction effects were observed.

Similar region effects were found for relative amplitude in δ ($F = 9.36$, df = 7/413, $P < 0.0001$), θ ($F = 10.92$, df = 7/413, $P < 0.0001$), β_1 ($F = 5.53$, df = 7/413, $P < 0.0001$), β_2 ($F = 6.12$, df = 7/413, $P < 0.0001$), β_3 ($F = 69.68$, df = 7/413, $P < 0.0001$) and δ ($F = 63.76$, df = 7/413, $P < 0.0001$) bands, which were not affected by treatment, genotype or their interaction.

Discussion

Our results indicate that the COMT Val158Met polymorphism contributes to individual differences in resting-state EEG oscillations and their response to acute nicotine. This points to a heritable dopaminergic mechanism in electrocerebral rhythmic activities that may reflect the cognitive response variability to nicotinic agonists. Earlier EEG research showed that in non-smokers only resting- and task-associated oscillations in the α band varied with COMT polymorphism (Bodenmann *et al.* 2009a) and were sensitive to nicotine (Fisher *et al.* 2012a, 2012b, 2013; Foulds *et al.* 1994; Harkrider *et al.* 2001). Our EEG findings were limited to PAF and α_2 oscillations, thus linking dopamine signaling and COMT variation with α-mediated oscillatory functions, possibly supporting cognitive enhancement associated with nicotine. Although cognitive processing was not directly assessed in this study, the case that resting neural changes affected by COMT polymorphism and nicotine interaction may meaningfully influence cognition is based on studies showing significant correlations between EEG during rest (pretask baseline) and behavioral performance. With respect to alpha, resting oscillatory activity in this band has detected both trait and state differences in cognitive functioning (Angelakis *et al.* 2004a,2004b) and interindividual differences in resting-state PAF and alpha power have been shown to be linearly associated with behavioral performance in healthy (Zhou *et al.* 2012; Zunini *et al.* 2013) and pathological populations (Dubbelink *et al.* 2013; Dubovik *et al.* 2012, 2013; Velikova *et al.* 2011).

Nicotine effects on EEG oscillations were evident only in the α-frequency range and, consistent with our study hypothesis and previous non-smoker studies, PAF was accelerated and amplitude in α_2 was enhanced with single-dose treatment. A sizable body of research on the functional roles of brain oscillations has implicated α in sensory processing and cognition (Basar 2012; Basar & Guntekin 2012), and during working memory (Roux & Uhlhaas 2014), where it may play a role in maintaining information through active inhibition

of task-irrelevant information (Klimesch *et al.* 2007; Sauseng 2009). Acetylcholine is thought to modulate the efficiency of the cortical processing of sensory or associational input (Basar & Guntekin 2012; Sarter *et al.* 2005); damage to the basal forebrain, the main source of acetylcholine, reduces resting EEG α, which also diminishes in a number of cognitive disorders (schizophrenia and Alzheimer's disease) which, as our lab demonstrated, exhibit α increases with smoking (Knott *et al.* 1995) and nicotine (Knott *et al.* 2000).

This is, to our knowledge, the first time that nicotine influences on resting EEG have been shown to be modulated by COMT polymorphism. Because these effects were assessed in non-smokers, they cannot be attributed to a 'remediation' of withdrawal-induced alterations in neural networks observed in smokers during abstinence (Ashare *et al.* 2014; Beaver *et al.* 2011; Cole *et al.* 2010). The Val158Met polymorphism of COMT was shown to modulate the resting-state response to nicotine, with α-band oscillatory changes confirming our hypothesis, namely that such modulations occurred with carriers of the Met allele and not Val/Val. For α_2, nicotine was found to increase oscillatory power in both Met/Met and Val/Met carriers but in different brain regions, with Met/Met in the frontocentral and Val/Met in the posterior cortical region. These COMT polymorphisms also exhibited PAF acceleration following nicotine administration but this time with Met/Met showing PAF increments in the posterior and Met/Val in the frontocentral regions. Because faster PAF and greater upper-α activity are linked to greater cognitive and memory performance (Klimesch 1997, 1999), altered PAF and α_2 oscillatory states induced by nicotine might be expected to preferentially enhance associated cognitive processes, presumably by increasing dopamine signaling in a regionally specific manner.

In line with these resting-state findings, previous fMRI studies on acute nicotine dosing in healthy volunteers (Herman *et al.* 2013), dopamimetics (Hamidovic *et al.* 2010; Mattay *et al.* 2003) and COMT inhibitors (Apud *et al.* 2007; Farrell *et al.* 2012; Giakoumaki *et al.* 2008) generally support the inverted-U model of dopamine function. By enhancing PFC dopamine in the higher COMT activity of homozygotes (Val/Val, positioned left of Met genotypes on the curve) these drugs shifted Val genotypes rightward, closer to the increased subjective responses as well as enhanced cortical efficiency and performance, while reducing cortical processing in Met/Met genotypes, presumably beyond the peak of the inverted-U. The actions of DA in the PFC are concentration- and receptor subtype-dependent, and while a balance is assumed between D1 and D2 dopamine receptor activation during resting states, working and memory tasks produce low to moderate increases in dopamine (Phillips *et al.* 2004) and D1 dopamine receptor activation (thought to enhance PFC glutamatergic and GABAergic currents) (Seamans *et al.* 1998). This is in contrast to high phasic dopamine levels, which are thought to activate D2 receptors and reduce these currents (Seamans & Yang 2004). Interestingly, in our study with smokers, smoking-induced β_2 increases appear to be mediated by D2 receptor activation as they are blocked by haloperidol, a D2 receptor antagonist (Walker *et al.* 2001).

COMT studies involving fMRI have typically assessed Blood-oxygen-level dependent (BOLD) activation during executive (e.g. working memory) task performance. There is increasing evidence, however, that the resting-state activity and deactivation of these neural networks, such as the default mode network (DMN) (regions that are active during non-task

conditions and are suppressed by goal-directed cognitive demands; Raichle *et al.* 2001), determine the ability of task-positive networks to perform tasks, as measured by task-related fMRI (De Luca *et al.* 2006) and vary across individuals to predict behavioral performance (Kelly *et al.* 2008). There are a number of studies of dopaminergic modulation of task-induced changes in the DMN with transient dopamine depletion (Carbonell *et al.* 2014; Nagano-Saito *et al.* 2008), administration of dopamine receptor agonists and antagonists (Cole *et al.* 2013), levodopa (Delaveau *et al.* 2010), apomorphine (Nagano-Saito *et al.* 2009) and with pharmacological blockade (Minzenberg *et al.* 2011) and natural variation in dopamine transporter binding (Tomasi *et al.* 2009). All of these suggest that higher dopamine transmission is associated with augmented task-induced DMN deactivation. The COMT gene variation has similarly affected the fMRI–DMN response (Liu *et al.* 2010) with *intermediate* levels of COMT activity associated with increased medial PFC connectivity, which in turn correlates with increased task-induced DMN deactivation (reduced BOLD) and better performance (Dang *et al.* 2013).

Although there are inconsistencies (Neuner *et al.* 2014), both EEG (Cannon & Baldwin 2012; Chen *et al.* 2008, 2013; Knyazev 2013; Knyazev *et al.* 2011) and simultaneous EEG–fMRI studies (Chang *et al.* 2013; Jann *et al.* 2009; Liu *et al.*, 2014; Mo *et al.* 2013) suggest that alpha and upper α, in particular (Jann *et al.* 2009), positively correlate with the fMRI–DMN. As ongoing oscillatory alpha activity is associated with processing internal stimuli and can determine stimulus detection and attention (Hanslmayr *et al.* 2011; Klimesch 1999, 2012; Klimesch *et al.* 2007), the apparent nicotine-induced enhancement of the EEG–DMN network (evidenced by α_2 increases in frontocentral regions in Met/Met carriers and in parietal/occipital regions in Val/Met carriers) may reflect the differential effects of dopamine neurotransmission on inhibitory and selection processes in anterior and posterior hubs of the DMN. Both of these are sensitive to individual differences (Knyazev *et al.* 2012) but appear to exhibit distinct relationships with dopamine transporter availability (Tomasi *et al.* 2009) and levodopa treatment (Asanuma *et al.* 2006).

Genotype differences in the placebo condition were expressed only with PAF, which, contrary to our hypothesis, was found to be faster in Val homozygotes than heterozygotes. This is in direct contrast to a previous report of a slower PAF in Val/Val (vs. Met/Met) genotype (Bodenmann *et al.* 2009a) and another showing no effect of COMT polymorphism on PAF (Veth *et al.* 2014). Although this may be due to differences in EEG methodology or PAF measurement techniques (Bazanova & Vernon 2014), COMT–PAF relationships require further study as this electrophysiological index is thought to reflect the influence of individual genes on the underlying neural mechanisms generating α activity (Hughes *et al.* 2011; Lopes da Silva 1991; Steriade & Timofev 2003; Steriade *et al.* 1990). The behavioral significance of PAF is not clear but does provide a mechanism for searching and identifying encoded information (Angelakis *et al.* 2007; Bazanova & Aftanas 2006, 2008; Bazanova & Vernon 2014; Bodenmann *et al.* 2009b; Klimesch *et al.* 1993; Zoefel *et al.* 2011). Posterior PAF increases with increasing cognitive demands (Haegens *et al.* 2014) and artificially induced increases in α power above one's PAF have resulted in improved cognitive performance (Hanslmayr *et al.* 2005; Klimesch *et al.* 2003). Interestingly, given the impaired executive performance in Val allele carriers, performance and brain activation are more efficient and emotional (anxiety) disorders less prevalent in this same genetic group

compared to Met allele carriers (Heinz & Smolka 2006; Mier *et al.* 2010). The negative emotionality associated with low COMT activity (high cortical/subcortical tonic dopamine) in the Met allele may be related to the inflexibility of neural networks in processing information related to emotion, which in the Val allele is more flexible due to decreased tonic dopamine cortically and subcortically (Bilder *et al.* 2004). Alpha oscillations are particularly sensitive to the processing of negative emotional stimuli (Guntekin & Basar 2007) and as PAF is reduced in patients with anxiety disorder and increased with treatment (Saunders *et al.* 2015), the faster PAF in the Val carriers may be a neural marker of the dopaminergic regulation of the stability/flexibility of brain networks related to emotional processing.

Limitations

The present findings on COMT–nicotine interactions with EEG need to be interpreted within the limitations of the study, which include the assessment of a relatively small sample and one that was all male and was nicotine naive, thus limiting generalization to smokers – individuals who comprise a proportion of the population with psychiatric disorders (e.g. schizophrenia) and are purported to use smoking/nicotine for their cognitive enhancing properties (Kumari & Postma 2005). Dose- and time-response effects were not examined with nicotine and the neural effects associated with the relatively slow absorption of nicotine via gum may be dissimilar from those obtained with the rapid nicotine delivery associated with cigarette smoking. Blood nicotine levels were not assessed and as α_2 increments with smoking are not observed with blood levels of nicotine below 10 ng/ml (Domino *et al.* 1995b), it is uncertain whether our observed genotype differences reflect different nicotine absorption levels. Our EEG recording montage, containing only eight recording sites, did not allow for a comprehensive assessment of electrocerebral activity and the use of larger electrode arrays in future studies would not only permit the localization of sources contributing to COMT and nicotinic influences on scalp EEG activity but also on inter-regional connectivity, which has been shown to be modulated by COMT polymorphism (Lee *et al.* 2011). Oscillatory measures included power and frequency but not phase characteristics, which, for α rhythms, is associated with unique sensory and cognitive processes (Bazanova & Vernon 2014). Electroencephalogram was assessed only during rest and not during task engagement which, if incorporated in future studies, would allow for clearer understanding of the cognitive implications of the COMT-modulated resting electrocortical response to nicotine.

Conclusion

This study tentatively suggests that COMT polymorphism, nicotine and their interaction affect resting-state electro-cerebral rhythms. That the nicotine-induced electrocortical changes were evident in individuals with the COMT Met allele infers that the acute, nicotine-modulated spontaneous oscillations reflect tonic cortical dopamine level and its potential functional role in cognitive tasks. These spectral EEG findings were observed with respect to α oscillatory activity, which is associated with cognitive processes and therefore may be of relevance to people diagnosed with schizophrenia – a disorder invariably linked with COMT polymorphism (Gupta *et al.* 2011; Lewandowski 2007; Sagud *et al.* 2010;

Williams *et al.* 2007), and is also associated with excessive smoking (Winterer 2010), aberrant dopamine neuro-transmission (Brisch *et al.* 2014), abnormalities in α rhythms (Knott *et al.* 2001; Narayanan *et al.* 2014; Venables *et al.* 2009; Wix-Ramos *et al.* 2014), fMRI– (Whitfield-Gabrieli *et al.* 2009) and electrophysiologic–DMN (Kim *et al.* 2014) and cognition (Nuechterlein *et al.* 2014), with the latter being shown to improve both with smoking and nicotine administration (D'Souza & Markou 2012). Schizophrenia patients have shown increases in α_2 with the smoking of a single cigarette (Knott *et al.* 1995), but the role of COMT in these oscillatory changes is not yet known and the cognitive changes accompanying these cortical rhythms require addressing.

Acknowledgments

This work was supported in part by a grant to V.K. from NSERC (Natural Sciences and Engineering Research Council of Canada – #210572-152799-2001); and a grant to P.R.A from CIHR (Canadian Institutes of Health Research).

References

Ahnaou A, Hysmans H, Jacobs T, Drinkenburg W. Cortical EEG oscillations and network connectivity as efficiency indices for assessing drugs with cognition enhancing potential. Neuropsychopharmacology. 2014; 86:362–377.

Angelakis E, Lubar J, Stathopoulou S, Kounios J. Peak alpha frequency: an electroencephalographic measure of cognitive preparedness. Clin Neurophysiol. 2004a; 115:887–897. [PubMed: 15003770]

Angelakis E, Lubar J, Stathopoulou S. Electroencephalographic peak alpha frequency correlates of cognitive traits. Neurosci Lett. 2004b; 371:60–63. [PubMed: 15500967]

Angelakis E, Stathopoulou S, Frymiare J. EEG neurofeedback: a brief overview and an example of peak alpha frequency training for cognitive enhancement in the elderly. Clin Neurophysiol. 2007; 21:110–129.

Apud J, Weinberger D. Pharmacogenetic tools for the development of target-oriented cognitive-enhancing drugs. J Am Soc Exp Neurother. 2006; 3:106–116.

Apud J, Mattay V, Chen J, Kolachana B, Callicott J, Ragetti R. Toliopone improves cognition and cortical information processing in normal human subjects. Neuropsychopharmacology. 2007; 32:1011–1020. [PubMed: 17063156]

Asanuma K, Tang C, Ma Y, Dhawan V, Mattis P, Edwards C. Network modulation in the treatment of Parkinson's disease. Brain. 2006; 129:2667–2678. [PubMed: 16844713]

Ashare R, Valdez J, Ruparel K, Albelda B, Hopson R, Kiefe J, Loughead J, Lerman C. Association of abstinence-induced alterations in working memory function and COMT genotype in smokers. Psychopharmacology (Berl). 2013; 230:653–662. [PubMed: 23828159]

Ashare R, Falcone M, Lerman S. Cognitive function during nicotine withdrawal: implications for nicotine dependence treatment. Neuropharmacology. 2014; 76:581–591. [PubMed: 23639437]

Barnett J, Heron J, Ring S. Gender-specific effects of the catechol-O-methyltransferase Val 108/158 Met polymorphism on cognitive function on children. Am J Psychiatry. 2007; 164:142–149. [PubMed: 17202556]

Basar E. A review of alpha activity in integrative brain function: fundamental physiology, sensory coding, cognition and pathology. Int J Psychophysiol. 2012; 86:1–24. [PubMed: 22820267]

Basar E. A review of gamma oscillations in healthy subjects and in cognitive impairments. Int J Psychophysiol. 2013; 90:99–117. [PubMed: 23892065]

Basar E, Guntekin B. A short review of alpha activity in cognitive processes and in cognitive impairment. Int J Psychophysiol. 2012; 86:25–38. [PubMed: 22801250]

Bazanova O, Aftanas L. Relationship between learnability and individual indices of EEG alpha activity. Ann Gen Psychiatry. 2006; 5:74–75.

Bazanova O, Aftanas L. Individual measures of electroencephalogram alpha activity and non-verbal creativity. Neurosci Behav Physiol. 2008; 38:227–235. [PubMed: 18264769]

Bazanova O, Vernon D. Interpreting EEG alpha activity. Neurosci Biobehav Rev. 2014; 44:94–110. [PubMed: 23701947]

Beaver J, Long C, Cole D, Durcan M, Bannon L, Michara R, Mathews P. The effects of nicotine replacement on cognitive brain activity during smoking withdrawal studies with simultaneous fMRI/EEG. Neuropsychopharmacology. 2011; 36:1792–1800. [PubMed: 21544072]

Bentley P, Driven J, Dolan R. Cholinergic modulation of cognition: insights from human pharmacological functional neuroimaging. Prog Neurobiol. 2011; 94:360–388. [PubMed: 21708219]

Beuten J, Payne T, Ma J, Li M. Significant association of catechol-O-methyltransferase (COMT) heliotypes with nicotine dependence in male and female smokers of two ethnic populations. Neuropsychopharmacology. 2006; 31:675–684. [PubMed: 16395295]

Bilder R, Volauka J, Lachman H, Grace A. The catechol-O-methyltransferase polymorphism: relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. Neuropsychopharmacology. 2004; 29:1943–1961. [PubMed: 15305167]

Bodenmann S, Rusterholz T, Durr R, Stoll C, Bachmann V, Geissler E, Jaggi-Schwarz K, Landolt HP. The functional Val158Met polymorphism of COMT predicts interindividual differences in brain α oscillations in young men. J Neurosci. 2009a; 29:10858–10862.

Bodenmann S, Yu S, Luhmann U, Arand M, Berger W, Jung H, Landolt H. Pharmacogenetics of Modafinil after sleep loss: catechol-O-methyltransferase genotype modulates waking functions but not recovery sleep. Clin Pharmacol Ther. 2009b; 85:296–304. [PubMed: 19037200]

Brisch R, Saniotis A, Wolf R, Bielau H, Bernstein H, Steiner T, Bogerts B, Braun K, Jankowski Z, Kumaratilake J, Hennenberg M, Gos T. The role of dopamine in schizophrenia from a neurobiological evolutionary perspective: old fashioned, but still in vogue. Front Psychiatry. 2014; 5:47. [PubMed: 24904434]

Cannon R, Baldwin D. EEG current source density and the phenomenology of the default network. Clin EEG Neurosci. 2012; 43:257–267. [PubMed: 23185086]

Cantero J, Atienza M. The role of neural synchronization in the emergence of cognition across the wake-sleep cycle. Rev Neurosci. 2005; 16:69–83. [PubMed: 15810655]

Carbonell F, Nagano-Saito A, Loyton M, Cisek P, Benkelfat C, He Y, Dagher A. Dopamine precursor depletion impairs structure and efficiency of resting state brain functional networks. Neuropharmacology. 2014; 84:90–100. [PubMed: 24412649]

Chang C, Liu Z, Chen M, Liu X, Doyn J. EEG correlates of time-varying BOLD functional connectivity. Neuroimage. 2013; 15:227–236.

Chen J, Lipska B, Halim N, Ma Q, Matsumoto M, Melhem S. Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain. Am J Hum Genet. 2004; 75:807–821. [PubMed: 15457404]

Chen A, Feng W, Zhao H, Yin Y, Wang P. EEG default mode network in the human brain: spectral regional field powers. Neuroimage. 2008; 41:561–574. [PubMed: 18403217]

Chen JL, Ros T, Gruzelier J. Dynamic changes of ICA-derived EEG functional connectivity in the resting state. Hum Brain Mapp. 2013; 34:852–868. [PubMed: 22344782]

Cole D, Bechman C, Long C, Mathews P, Durcan M, Beaver J. Nicotine replacement in abstinent smokers improves cognitive withdrawal symptoms with modulation of resting brain network dynamics. Neuroimage. 2010; 52:590–599. [PubMed: 20441798]

Cole D, Beckman C, Oei N, Both S, van Gerven J, Rombouts S. Differential and distributed effects of dopamine neuro-modulators on resting-state network connectivity. Neuroimage. 2013; 78:59–67. [PubMed: 23603346]

Colilla S, Lerman C, Shields P, Jepson C, Rukstalis M, Berlin J. Association of catechol-O-methyltransferase (COMT): effects on mRNA, protein and enzyme activity in postmortem human brain. Am J Hum Genet. 2005; 75:807–821.

Cropsey K, Eldridge E, Weaver M, Vilalobos F, Stitzer M. Expired carbon monoxide levels in self-reported smokers and non-smokers in prison. Nicotine Tob Res. 2006; 8:653–659. [PubMed: 17008192]

D'Souza M, Markou A. Schizophrenia and tobacco smoking comorbidity: nAChR agonists in the treatment of schizophrenia-associated cognitive deficits. Neuropharmacology. 2012; 62:1564–1573. [PubMed: 21288470]

Dang L, O'Neil J, Jagust W. Genetic effects on behaviour are mediated by neurotransmitters and large-scale neural networks. Neuroimage. 2013; 66:203–214. [PubMed: 23142068]

De Luca M, Beckmann C, De Stafano M, Mathews P, Smith S. fMRI resting state networks define distinct modes of long-distance interactions in the human brain. Neuroimage. 2006; 29:1359–1367. [PubMed: 16260155]

Delaveau P, Salgado-Pineda P, Fossati P, Witjas T, Azulay J, Bliu O. Dopamineric modulation of the default mode network in Parkinson's disease. Eur Neuropsychopharmacol. 2010; 20:784–792. [PubMed: 20674286]

Domino, E., Kadoya, C., Matsuoka, S. Effects of tobacco smoking on the topographic electroencephalogram. In: Domino, E., editor. Brain Imaging of Nicotine and Tobacco Smoking. NPP Books; Ann Arbor, MI: 1995a. p. 253-262.

Domino, E., Matsuoka, S., Kadoya, C. Variable EEG brain localization effects of tobacco smoking in relationship to plasma nicotine levels. In: Domino, E., editor. Brain Imaging of Nicotine and Tobacco Smoking. NPP Books; Ann Arbor, MI: 1995b. p. 263-273.

Dubbelink O, Stoffers D, Deijen J, Twisk J, Stam C, Berendie H. Cognitive decline in Parkinson's disease is associated with slowing of resting-state brain activity: a longitudinal study. Neurobiol Aging. 2013; 34:408–418. [PubMed: 22495052]

Dubovik S, Pignat J, Ptak R, Aboulafia T, Allet L, Gillabert N, Magnin C, Albert F, Momjian-Mayor I, Nahum L, Lascano A, Michel C, Schnider A, Guggisberg A. The behavioral significance of coherent resting-state oscillations after stroke. Neuroimage. 2012; 61:249–257. [PubMed: 22440653]

Dubovik S, Ptak R, Aboulafia T, Magnin C, Gillabert N, Allet L, Pignat J, Schnider A, Gugginberg A. EEG alpha band synchrony predicts cognitive and motor performance in patients with ischemic stroke. Behav Neurol. 2013; 26:187–189. [PubMed: 22713421]

Egan M, Goldberg T, Kioluchang B, Callicott J, Mazzanti C, Straub R. Effect of COMT Val 108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proc Natl Acad Sci USA. 2001; 98:6917–6922. [PubMed: 11381111]

Enoch M, Xu K, Ferro E, Harris C, Goldman D. Genetic origins of anxiety in women: a role for a functional catechol-O-methyltransferase polymorphism. Psychiatr Genet. 2003; 13:33–41. [PubMed: 12605099]

Farrell S, Tunbridge E, Braeutigam S, Harrison P. COMT Val (158) Met genotype determines the direction of cognitive effects produced by catechol-O-methyltransferase inhibition. Biol Psychiatry. 2012; 71:538–544. [PubMed: 22364739]

First, M., Spitzer, R., Gibbon, M., Williams, J. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Non-Patient Version. American Psychiatric Association; Washington, DC: 2002.

Fisher D, Daniels R, Jaworska N, Knobelsdorf A, Knott V. Effects of acute nicotine administration on resting EEG in non-smokers. Exp Clin Psychopharmacol. 2012a; 20:717s.

Fisher D, Daniels R, Jaworska N, Knobelsdorf A, Knott V. Effects of acute nicotine administration on behavioural and neural (EEG) correlates of working memory in non-smokers. Brain Res. 2012b; 1429:72–81. [PubMed: 22079316]

Fisher D, Knobelsdorf A, Jaworska N, Daniels R, Knott V. Effects of nicotine on electroencephalographic (EEG) and behavioural measures of visual working memory in non-smokers during a dual-task paradigm. Pharmacol Biochem Behav. 2013; 103:494–500. [PubMed: 23026057]

Floderus Y, Ross S, Wetterberg L. Erythrocyte catechol-O-methyltransferase activity in a Swedish population. Clin Genet. 1981; 19:389–392. [PubMed: 7296928]

Foulds J, McSorley K, Sneddon J, Feyerabend C, Jarvis M, Russell M. Effect of subcutaneous nicotine injections on EEG alpha frequency in non-smokers: a placebo-controlled pilot study. Psychopharmacology (Berl). 1994; 115:163–166. [PubMed: 7862890]

Giakoumaki S, Roussos P, Bitsios P. Improvement of pre-pulse inhibition and executive function by the COMT inhibitor Tolcapone depends on COMT Val(158)Met polymorphism. Neuropsychopharmacology. 2008; 33:3058–3068. [PubMed: 18536698]

Goldstein D, Need A, Singh R, Sisodiya S. Potential genetic causes of heterogeneity of treatment effects. Am J Med. 2007; 120:S21–S25.

Grannon S, Passetti F, Thomas K, Dalley T, Everitt B, Robbins T. Enhanced and impaired attentional performance after infusion of D1 dopaminergic receptor agents into the rat prefrontal cortex. J Neurosci. 2000; 20:1208–1215. [PubMed: 10648725]

Gratton G, Coles M, Donchin E. A new method for off-line removal of ocular artifact. Electroencephalogr Clin Neurophysiol. 1983; 55:468–484. [PubMed: 6187540]

Green A, Munafo M, DeYoung C, Fossella J, Fan J, Gray J. Using genetic data in cognitive neuroscience: from growing pains to genuine insights. Nat Rev Neurosci. 2008; 9:710–720. [PubMed: 19143051]

Greenwood P, Parasuraman R. Normal genetic variation, cognition and aging. Behav Cogn Neurosci Rev. 2003; 2:278–306. [PubMed: 15006290]

Guntekin B, Basar E. Emotional face expression are differentiated with brain oscillations. Int J Psychophysiol. 2007; 64:91–100. [PubMed: 17156875]

Guo S, Chen D, Zhou D, Sun H, Wu G, Halle C, Kosten T, Zhang X. Association of functional catechol-O-methyltransferase (COMT) Val108Met polymorphism with smoking severity and age of smoking initiation in Chinese male smokers. Psychopharmacology (Berl). 2007; 190:449–456. [PubMed: 17206495]

Gupta M, Kaur H, Jajodia A, Jain S, Satyamoorthy K, Mukerji M, Thirthalli J, Kuhaeti R. Diverse facets of COMT: from a plausible predictive marker to a potential drug target for schizophrenia. Curr Mol Med. 2011; 2:732–743.

Haegens S, Cousin H, Wallis G, Harrison P, Nobre A. Inter- and intra-individual variability in peak alpha frequency. Neuroimage. 2014; 92:46–55. [PubMed: 24508648]

Hamidovic A, Dlugos A, Palmer A, de Wit H. Polymorphisms in dopamine transporter (S2C6A3) are associated with stimulant effects of D-amphetamine: an exploratory pharmacogenetic study using healthy volunteers. Behav Genet. 2010; 40:255–261. [PubMed: 20091113]

Hanslmayr S, Sav Seng P, Doppelmayr M, Schabus M, Klimesch W. Increasing individual upper alpha power by neurofeedback improves cognitive performance in human subjects. Appl Psychophysiol Biofeedback. 2005; 30:1–10. [PubMed: 15889581]

Hanslmayr S, Gross J, Klimesch W, Shapiro K. The role of alpha oscillations in temporal attention. Brain Res Rev. 2011; 67:331–343. [PubMed: 21592583]

Harkrider A, Champlin C, McFadden D. Acute effect of nicotine on non-smokers: III. LLRs and EEGs. Hear Res. 2001; 160:99–110. [PubMed: 11591495]

Heinz A, Smolka M. Effects of catechol-O-methyltransferase genotype on brain activation elicited by affective stimuli and cognitive tasks. Rev Neurosci. 2006; 17:359–367. [PubMed: 16878403]

Heishman S, Kleykamp B, Singleton E. Meta-analysis of the acute effects of nicotine and smoking on human performance. Psychopharmacology (Berl). 2010; 210:453–469. [PubMed: 20414766]

Herman A, Sofuoglu M. Cognitive effects of nicotine: genetic mediators. Addict Biol. 2010; 15:250–265. [PubMed: 20456288]

Herman A, Jatlow P, Gelernter J, Listman J, Sofuoglu M. COMT Val158Met modulates subjective response to intravenous nicotine and cognitive performance in smokers. Pharmacogenomics. 2013; 13:490–497.

Herrmann C, Frund I, Lenz D. Human gamma-band activity: a review on cognitive and behavioural correlates and network models. Neurosci Biobehav Rev. 2010; 34:981–992. [PubMed: 19744515]

Hughes S, Lorincz M, Blethyn K, Kekesi K, Juhas G, Turmaine M, Parnavelas J, Crunello V. Thalamic gap junctions control local neuronal synchrony and influence macroscopic oscillation amplitude during EEG alpha rhythms. Front Psychol. 2011; 2:193. [PubMed: 22007176]

Hukkanen J, Jacob P, Benowitz N. Metabolism and disposition kinetics of nicotine. Pharmacol Rev. 2005; 57:79–115. [PubMed: 15734728]

Huotari M, Gogos J, Karayiorgov M, Koponen O, Forsberg M, Rassmaja A. Brain catecholamine metabolism in catechol-O-methyltransferase (COMT)-deficient mice. Eur J Neurosci. 2002; 15:246–256. [PubMed: 11849292]

Jann K, Dierks T, Boesch C, Kottlow M, Strik W, Koenig T. BOLD correlates of EEG alpha phase-locking and the fMRI default mode network. Neuroimage. 2009; 45:903–916. [PubMed: 19280706]

Jasinska A, Zorick T, Brody A, Stein ET. Dual role of nicotine in addiction and cognition: a review of neuroimaging studies in humans. Neuropharmacology. 2013; 84:111–122. [PubMed: 23474015]

Kaiser J, Lutzenberger W. Induced gamma-band activity and human brain function. Neuroscientist. 2003; 9:475–484. [PubMed: 14678580]

Kelly A, Liddin B, Biswal F, Castellanos M, Milham M. Competition between functional brain networks mediates behavioural variability. Neuroimage. 2008; 39:527–537. [PubMed: 17919929]

Kendler K, Neale M, Sullivan P, Corey L, Gardner C, Prescott C. A population-based twin study in women of smoking initiation and nicotine dependence. Psychol Med. 1999; 29:299–308. [PubMed: 10218922]

Kim J, Shin K, Jung W, Kim S, Kwon J, Chung C. Power spectral aspects of the default mole network in schizophrenia: an MEG study. BMC Neurosci. 2014; 15:104. [PubMed: 25189680]

Kimberg D, D'Esposito M, Farah M. Effects of bromocriptine on human subjects depend on working memory capacity. Neuroreport. 1997; 8:3581–3585. [PubMed: 9427330]

Klimesch W. EEG-alpha rhythms and memory processes. Int J Psychophysiol. 1997; 26:319–340. [PubMed: 9203012]

Klimesch W. EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. Brain Res Rev. 1999; 29:169–195. [PubMed: 10209231]

Klimesch W. Alpha-band oscillations, attention, and controlled access to stored information. Trends Cogn Sci. 2012; 16:606–617. [PubMed: 23141428]

Klimesch W, Schimke H, Pfurtscheller G. Alpha frequency, cognitive load and memory performance. Brain Topogr. 1993; 5:241–251. [PubMed: 8507550]

Klimesch W, Sausang P, Gerloff C. Enhancing cognitive performance with repetitive transcranial magnetic stimulation at human individual alpha frequency. Eur J Neurosci. 2003; 17:1129–1133. [PubMed: 12653991]

Klimesch W, Sauseng P, Hanslmayer S. EEG alpha oscillations: the inhibition–timing hypothesis. Brain Res Rev. 2007; 53:63–88. [PubMed: 16887192]

Knott, V. Neuroelectric approach to the assessment of psychoactivity in comparative substance use. In: Warburton, D., editor. Addiction Controversies. Harwood Academic Publishers; Churchill, UK: 1990. p. 66-89.

Knott V. Quantitative methods and measures in human psychopharmacological research. Hum Psychopharmacol. 2000; 15:479–498. [PubMed: 12404618]

Knott V. Electroencephalographic characterization of cigarette smoking behaviour. Alcohol. 2001; 24:95–97. [PubMed: 11522429]

Knott V, Venables P. EEG alpha correlates of non-smokers, smoking and smoking deprivation. Psychophysiology. 1977; 14:150–156. [PubMed: 847066]

Knott, V., Hooper, C., Lusk-Mikkelsen, S., Kerr, C. Variations in spontaneous brain electric (EEG) topography related to cigarette smoking: acute smoking, drug comparisons, cholinergic transmission, individual differences and psychopathology. In: Domino, E., editor. Brain Imaging of Nicotine and Tobacco Smoking. NPP Books; Ann Arbor, MI: 1995. p. 167-189.

Knott V, Bosman M, Mahoney C, Ilivitsky V, Quirt K. Transdermal nicotine: single dose effects on mood, EEG, performance, and event-related potentials. Pharmacol Biochem Behav. 1999; 63:253–261. [PubMed: 10371654]

Knott V, Engeland C, Mohr E, Mahoney C, Ilivitsky V. Acute nicotine administration in Alzheimer's disease: an exploratory EEG study. Neuropsychobiology. 2000; 41:210–220. [PubMed: 10828731]

Knott V, Labelle A, Jones B, Mahoney C. Quantitative EEG in schizophrenia and in response to acute and chronic clozapine treatment. Schizophr Res. 2001; 50:41–53. [PubMed: 11378313]

Knyazev G. Extraversion and anterior vs. posterior DMN activity during self-referential thoughts. Front Hum Neurosci. 2013; 6:1–10.

Knyazev G, Slobodskoj-Plusnin J, Bocharov A, Pylkova L. The default mode network and EEG alpha oscillations: an independent component analysis. Brain Res. 2011; 1402:67–79. [PubMed: 21683942]

Knyazev G, Savostyanov A, Volf N, Liou M, Bocharov A. EEG correlates of spontaneous self-referential thoughts: a cross-cultural study. Int J Psychophysiol. 2012; 86:173–181. [PubMed: 22985738]

Kumari V, Postma P. Nicotine use in schizophrenia: the self-medication hypothesis. Neurosci Biobehav Rev. 2005; 29:1021–1034. [PubMed: 15964073]

Lachman H, Papoulos D, Saito T, Yu YM, Szumlanski C, Weinshiboum R. Human catechol-O-methyltransferase phamacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. Pharmacogenetics. 1996; 6:243–250. [PubMed: 8807664]

Lee TW, Younger Y, Hong CJ, Tsai SJ, Wu HC, Chen TJ. The effects of catechol-O-methyltransferase polymorphism Val158Met on functional connectivity in healthy young females: a resting EEG study. Brain Res. 2011; 1377:21–31. [PubMed: 21195697]

Lee M, Gallen C, Rois T, Kurup P, Salmeron B, Hodgkinson C, Goldman D, Stein E, Enoch M. A preliminary study suggests that nicotine and prefrontal dopamine affect corticostriatal areas in smokers with performance feedback. Genes Brain Behav. 2013; 12:554–563. [PubMed: 23433232]

Leiser S, Dunlop J, Bowlby M, Devilbiss D. Aligning strategies for using EEG as a surrogate biomarker: a review of pre-clinical and clinical research. Biochem Pharmacol. 2011; 81:1408–1421. [PubMed: 20937262]

Lewandowski K. Relationship of catechol-O-methyltransferase to schizophrenia and its correlates: evidence for associations and complex interactions. Harv Rev Psychiatry. 2007; 15:233–244. [PubMed: 17924258]

Lindgren M, Molander L, Verhaan C, Lunell E, Rosen J. Electroencephalographic effects of intravenous nicotine: a dose-response study. Psychopharmacology (Berl). 1999; 145:342–350. [PubMed: 10494584]

Lisman J, Buzsaki G. A neural coding scheme formed by the combined function of gamma and theta oscillations. Schizophr Bull. 2008; 34:974–980. [PubMed: 18559405]

Liu B, Song M, Li J, Liu Y, Li K, Yu C, Jiang T. Prefrontal-related functional connectivities within the default network are modulated by COMT val158met in healthy young adults. J Neurosci. 2010; 30:64–69. [PubMed: 20053888]

Liu Y, Bengson J, Huang H, Mangun E, Ding M. Top-down modulation of neuronal activity in anticipatory visual attention: control mechanisms revealed by simultaneous EEG-fMRI. Cereb Cortex. 2014 Epub ahead of print 9 September 2014. pii: bhu204.

Livingstone P, Wonnacott S. Nicotinic acetylcholine receptors and the ascending pathways. Biochem Pharmacol. 2009; 78:744–755. [PubMed: 19523928]

Lopes da Silva F. Neural mechanisms underlying brain waves: from neural membranes to networks. Clin Neurophysiol. 1991; 79:81–93.

Lopes da Silva F. EEG and MEG: relevance to neuroscience. Neuron. 2013; 80:1112–1128. [PubMed: 24314724]

Loughead J, Wiley E, Valdez J, Sanborn P, Tang K, Strasser A. Effect of abstinence challenge on brain function and cognition in smokers differs by COMT genotype. Mol Psychiatry. 2009; 14:820–826. [PubMed: 19065145]

Maes H, Sullivan P, Bulik C, Newle M, Prescott C, Eaves L, Kendler K. A twin study of genetic and environmental influences on tobacco initiation, regular tobacco use and nicotine dependence. Psychol Med. 2004; 34:1217–1261.

Mansvelder H, van Aerde K, Covey J, Brussard A. Nicotinic modulation of neuronal networks: from receptors to cognition. Psychopharmacology (Berl). 2006; 184:292–305. [PubMed: 16001117]

Mattay V, Callicott J, Bertolino A, Heaton I, Frank J, Coppola R, Berman K, Goldberg T, Weinberger D. Effects of dextroamphetamine on cognitive performance and cortical activation. Neuroimage. 2000; 12:268–275. [PubMed: 10944409]

Mattay V, Goldberg T, Fera F, Hariri A, Tessitore A, Egan M, Kolachana B, Callicott J, Weinberger D. Catechol-O-methyltransferase val^{158}-met genotype and individual variation in the brain response to amphetamine. Proc Natl Acad Sci USA. 2003; 100:6186–6191. [PubMed: 12716966]

Maxwell, M. Interview for Genetic Studies (FIGS). Manual for FIGS. Clinical Neurogenetics Branch, Intramural Research Program, National Institute of Mental Health; Bethesda, MD: 1992.

Mehta M, Owen A, Sahakian B, Mavaddat N, Pickard J, Robbins T. Methylphenidate enhances working memory by modulating discrete frontal and parietal lobe regions in the human brain. J Neurosci. 2000; 20:RC65. [PubMed: 10704519]

Merker B. Cortical gamma oscillations: the functional key is activation, not cognition. Neurosci Biobehav Rev. 2013; 37:401–417. [PubMed: 23333264]

Mier D, Kirsch P, Meyer-Lindenberg A. Neural substrates of pleiotropic action of genetic variation in COMT: a meta-analysis. Mol Psychiatry. 2010; 15:918–927. [PubMed: 19417742]

Minzenberg M, Yoon J, Carter C. Modafinil modulation of the default mode network. Psychopharmacology (Berl). 2011; 215:23–31. [PubMed: 21153806]

Mo J, Liu Y, Huang H, Ding M. Coupling between visual alpha oscillations and default mode activity. Neuroimage. 2013; 68:112–118. [PubMed: 23228510]

Munafo M, Bowes L, Clark T, Flint J. Lack of association of the COMT (Val 158/108 Met) gene and schizophrenia: a meta-analysis of case control studies. Mol Psychiatry. 2005; 10:765–770. [PubMed: 15824744]

Nagano-Saito A, Leyton M, Monihi O, Goldberg Y, He Y, Dagher A. Dopamine depletion impairs frontostriatal functional connectivity during a sit-shifting task. J Neurosci. 2008; 28:3697–3706. [PubMed: 18385328]

Nagano-Saito A, Liu J, Doyon J, Dagher A. Dopamine modulates default mode network deactivation in elderly individuals during the Tower of London task. Neurosci Lett. 2009; 458:1–5. [PubMed: 19442867]

Narayanan B, O'Neil K, Berwise C, Stevens M, Calhoun V, Clementz B, Tamminga C, Sweeney J, Keshavan M, Pearlson G. Resting state electroencephalogram oscillatory abnormalities in schizophrenia and psychiatric bipolar patients and their relatives from the bipolar and schizophrenia network on intermediate phenotype studies. Biol Psychiatry. 2014; 76:456–465. [PubMed: 24439302]

Neuner I, Arrubla J, Werner C, Hitz K, Boers F, Kawohl W, Shah N. The default mode network and EEG regional spectral power: a simultaneous fMRI-EEG study. PLoS One. 2014; 9:e88214. [PubMed: 24505434]

Newhouse P, Potter A, Singh A. Effects of nicotinic stimulation on cognitive performance. Curr Opin Pharmacol. 2004; 4:36–46. [PubMed: 15018837]

Newhouse P, Potter A, Dumas J, Thiel C. Functional brain imaging of nicotinic effects of higher cognitive processes. Biochem Pharmacol. 2011; 82:943–951. [PubMed: 21684262]

Nuechterlein K, Ventura J, Subotnik K, Bartzokis G. The early longitudinal course of cognitive deficits in schizophrenia. J Clin Psychiatry. 2014; 75(Suppl 2):25–29. [PubMed: 24919168]

Parasuraman R. Assaying individual differences in cognition with molecular genetics: theory and application. Theor Iss Ergon Sci. 2009; 10:399–416.

Parasuraman R, Jiang Y. Individual differences in cognition, affect, and performance: behavioural, neuroimaging, and molecular genetic approaches. Neuroimage. 2012; 59:70–82. [PubMed: 21569853]

Perkins K. Baseline-dependency of nicotine effects: a review. Behav Pharmacol. 1999; 10:597–615. [PubMed: 10780501]

Phillips A, Ahn S, Floresco S. Magnitude of dopamine release in medial prefrontal cortex predicts accuracy of memory on a delayed response task. J Neurosci. 2004; 24:547–553. [PubMed: 14724255]

Pickworth W, Herning R, Henningfield J. Electroencephalographic effects of nicotine chewing gum in humans. Pharmacol Biochem Behav. 1986; 25:879–882. [PubMed: 3786346]

Pickworth W, Herning R, Henningfield J. Mecamylamine reduces some EEG effects of nicotine chewing gum in humans. Pharmacol Biochem Behav. 1988; 30:149–153. [PubMed: 3174738]

Posthuma D, Neale M, Boomsma D, de Geus J. Are smarter brains faster: heritability of alpha peak frequency, IQ and their interrelation. Behav Genet. 2001; 31:567–569. [PubMed: 11838534]

Raichle M, Macleod A, Snyder A, Powers W, Gusnard P, Shulman G. A default mode of brain function. Proc Natl Acad Sci USA. 2001; 98:676–682. [PubMed: 11209064]

Roux F, Uhlhaas P. Working memory and neural oscillations: alpha-gamma versus theta-gamma codes for distinct WM information. Trends Cogn Sci. 2014; 18:16–25. [PubMed: 24268290]

Sagud M, Much-Seler D, Mihaljevic-Peles A, Voksan-Cosa B, Zivkovic M, Jakoviljevic M, Pivac M. Catechol-O-methyltransferase and schizophrenia. Psychiatr Danub. 2010; 22:220–224.

Saletu B, Anderer G, Saletu-Zyhlarz G, Arndol O, Pascual-Marqui R. Classification and evaluation of the pharmacodynamics of psychotropic drugs by single-lead pharmaco-EEG, EEG mapping and tomography (LORETA). Methods Find Exp Clin Pharmacol. 2002; 24:97–120.

Sarter M, Hasselmo M, Bruno J, Givens B. Unravelling the attentional functions of cortical cholinergic inputs, interactions between signal-driven and cognitive modulation of signal detection. Brain Res Rev. 2005; 35:98–111.

Saunders N, Downham R, Turman B, Kropotor J, Clark R, Yumash R, Szatmacy A. Working memory training with TDCS improves behavioural and neurophysiological symptoms in pilot group with post-traumatic stress disorder (PTSD) and with poor working memory. Neurocase. 2015; 21:271–278. [PubMed: 24579831]

Sauseng P. Brain oscillatory substrates of visual short-term memory capacity. Curr Biol. 2009; 29:1846–1852.

Seamans J, Yang C. The principle features and mechanisms of dopamine modulation in the prefrontal cortex. Prog Neurobiol. 2004; 74:1–57. [PubMed: 15381316]

Seamans J, Floresco S, Phillips A. D1 receptor modulation of hippocampal-prefrontal cortical circuits integrating spatial memory with executive function in the rat. J Neurosci. 1998; 18:1613–1621. [PubMed: 9454866]

Shikata, H., Fukai, H., Sakaki, T. Pattern recognition study in topographic EEG changes when smoking a cigarette. In: Domino, E., editor. Brain Imaging of Nicotine and Tobacco Smoking. NPP Books; Ann Arbor, MI: 1995. p. 235-252.

Smit D, Posthuman D, Boomsma D, Geuss E. Heritability of background EEG across the power spectrum. Psychophysiology. 2005; 42:691–697. [PubMed: 16364064]

Smit C, Wright M, Hansel N, Geffen G, Martin N. Genetic variation of individual alpha frequency (IAF) and alpha power in a large adolescent twin sample. Int J Psychophysiol. 2006; 61:235–243. [PubMed: 16338015]

Solis-Ortiz S, Parez-Luque E, Gutieriez-Munoz M. Modulation of the COMT Val^{158}Met polymorphism on resting-state EEG power. Front Hum Neurosci. 2015; 9:118. [PubMed: 25798100]

Stassen H, Bomben G, Propping P. Genetic aspects of the EEG: an investigation into the within-pair similarity of monozygotic and dizygotic twins with a new method of analysis. Electroencephalogr Clin Neurophysiol. 1987; 66:489–501. [PubMed: 2438114]

Steriade M, Timofev I. Neuronal plasticity in thalamocortical networks during sleep and waking oscillations. Neuron. 2003; 37:563–576. [PubMed: 12597855]

Steriade M, Gloor P, Linas R, Lopes da Silva F, Mesulam M. Report of IFCM committee on basic mechanisms. Basic mechanisms of cerebral rhythmic activities. Electroencephalogr Clin Neurophysiol. 1990; 76:481–508. [PubMed: 1701118]

Tatsuno, J. Two dimensional topographic EEG maps of cigarette smoking in healthy medical students. In: Domino, E., editor. Brain Imaging of Nicotine and Tobacco Smoking. NPP Books; Ann Arbor, MI: 1995. p. 235-252.

Teter C, Asfam B, Lisong N, Lutz M, Domino E, Guthrie S. Comparative effects of tobacco smoking and nasal nicotine. Eur J Pharmacol. 2002; 58:309–314.

Tomasi D, Volkow N, Wang R, Telang F, Wang G, Chang L, Ernst T, Fowler J. Dopamine transporters in striatum correlate with deactivation in the default mode network during visuospatial attention. PLoS One. 2009; 4:e6102. [PubMed: 19564918]

Tunbridge E, Harrison P, Weinberger D. Catechol-O-methyltransferase, cognition, and psychosis: Val^{158} Met and beyond. Biol Psychiatry. 2006; 60:141–151. [PubMed: 16476412]

Uhlhaas P, Pipa G, Lima B, Melloni L, Neuenschwander S, Nikolić D, Singer W. Neural synchrony in cortical networks: history, concept and current status. Front Integr Neurosci. 2009; 3:17. [PubMed: 19668703]

Van Beijsterveldt C, van Baal G. Twin and family studies of the human electroencephalogram: a review and a meta-analysis. Biol Psychol. 2002; 61:111–138. [PubMed: 12385672]

Van Beijsterveldt C, Molinaar P, de Geos E, Boomsma D. Heritability of human brain functioning as assessed by electroencephalography. Am J Hum Genet. 1996; 58:562–573. [PubMed: 8644716]

Velikova S, Magnini G, Arcari C, Falautano M, Franceschi M, Comi G, Leocani L. Cognitive impairment and EEG background activity in adults with Down's syndrome: a topographic study. Hum Brain Mapp. 2011; 32:719–729.

Venables N, Bernat E, Sponheim R. Genetic and disorder-specific aspects of resting state EEG abnormalities in schizophrenia. Schizophr Bull. 2009; 35:826–839. [PubMed: 18381357]

Veth C, Arns M, Drinkenburg W, Falloen W, Peeters P, Gordon E, Buitelaar J. Association between COMT Val158Met genotype and EEG alpha peak frequency tested in two independent cohorts. Psychiatry Res. 2014; 219:221–224. [PubMed: 24889847]

Walker D, Mahoney C, Ilivitsky V, Knott V. Effects of haloperidol pretreatment on the smoking-induced EEG/mood activation response profiles. Neuropsychobiology. 2001; 43:102–112. [PubMed: 11174054]

Wallace T, Bertrand D. Importance of the nicotinic acetylcholine receptor system in the prefrontal cortex. Biochem Pharmacol. 2013; 85:1713–1720. [PubMed: 23628449]

Wang XJ. Neurophysiological and computational principles of cortical rhythms in cognition. Physiol Rev. 2010; 90:1195–1268. [PubMed: 20664082]

Weinshilboum R, Otterness D, Szomlanska C. Methylation pharmacogenetics: catechol-O-metyltransferase, theopurine methyltransferase, and histamine N-methyltransferase. Annu Rev Pharmacol Toxicol. 1999; 39:19–52. [PubMed: 10331075]

Whitfield-Gabrieli S, Thermenos H, Milanovic S, Tsvang S, Ming T, Faraone S, McCarley K, Shenton M, Green A, Nieto-Castanon A, LaViolette P, Wojcik J, Gabrieli J, Seidman L. Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. Proc Natl Acad Sci USA. 2009; 106:1279–1284. [PubMed: 19164577]

Williams H, Owen M, O'Donovan M. Is COMT a susceptibility gene for schizophrenia? Schizophr Bull. 2007; 33:635–641. [PubMed: 17412710]

Winterer G. Why do patients with schizophrenia smoke? Curr Opin Psychiatry. 2010; 23:112–119. [PubMed: 20051860]

Wix-Ramos R, Moreno X, Capote E, Gorizaliz G, Uribe E, Ebien-Zaijur A. Drug treated schizophrenia, schizoaffective and bipolar disorder patients evaluated by qEEG absolute spectral power and mean frequency analysis. Clin Psychopharmacol Neurosci. 2014; 12:48–53. [PubMed: 24851121]

Zhou G, Liu P, He J, Dong M, Yang X, Hou B, von Deneen K, Qin W, Tian J. Interindividual reaction time variability is related to resting-state network topography: an electroencephalogram study. Neuroscience. 2012; 202:276–282. [PubMed: 22173012]

Zoefel B, Huster R, Herrmann C. Neurofeedback training and the upper alpha frequency band is REC improves cognitive performance. Neuroimage. 2011; 54:1427–1437. [PubMed: 20850552]

Zunini L, Thivierge J, Kousaie S, Sheppard S, Taler V. Alterations in resting-state activity relate to performance in a verbal recognition task. PLoS One. 2013; 8:e65608. [PubMed: 23785436]

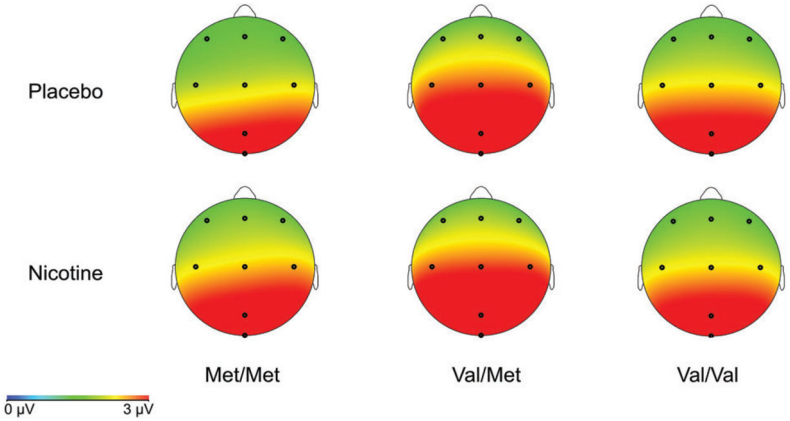

Figure 1.

Grand averaged topographic EEG maps of α_2 during placebo and nicotine treatment in Met/Met (M/M), Val/Met (V/M) and Val/Val (V/V).

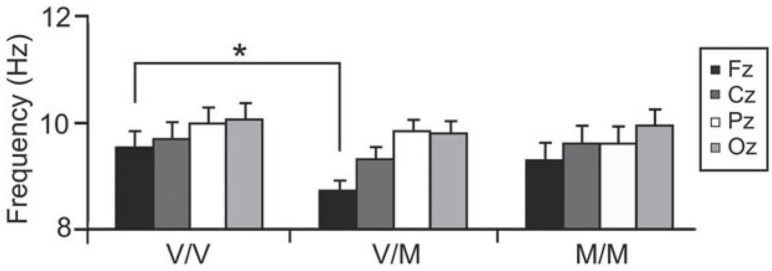

Figure 2.

Mean (±SE) placebo peak alpha frequency in Val/Val (V/V), Val/Met (V/M) and Met/Met (M/M) genotypes at each electrode site.

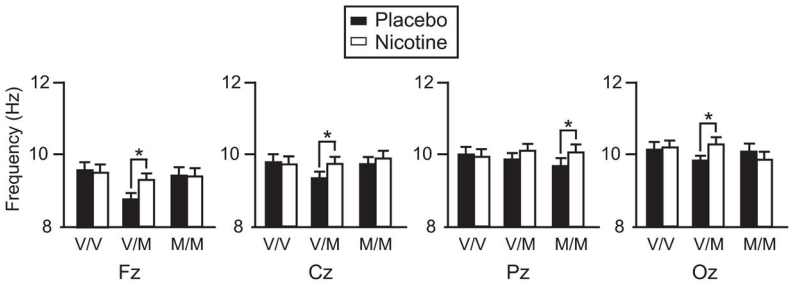

Figure 3.

Mean (±SE) peak alpha frequency of placebo and nicotine in Val/Val (V/V), Val/Met (V/M) and Met/Met (M/M) carriers at each midline electrode site.