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The moderating influence of nicotine and smoking on, resting-state mood and EEG changes in remitted depressed patients during tryptophan depletion

Verner Knott[a,c,d,e,f,*], Jean-Claude Bisserbe[b,e], Dhrasti Shah[c], Andrea Thompson[d], Hayley Bowers[a], Crystal Villeneuve[e], Vadim Ilivitsky[f]

[a] University of Ottawa Institute of Mental Health Research, Ottawa, ON, Canada
[b] Mood Disorders Unit, Royal Ottawa Mental Health Centre, Ottawa, ON, Canada
[c] Department of Psychology, University of Ottawa, Ottawa, ON, Canada
[d] Department of Psychology, Carleton University, Ottawa, ON, Canada
[e] Institute of Cognitive Science, Carleton University, Ottawa, ON, Canada
[f] Department of Psychiatry, University of Ottawa, Ottawa, ON, Canada

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ABSTRACT

Comorbidity between depression and tobacco use may reflect self-medication of serotonergically mediated mood dysregulation, which has been associated with aberrant cortical activation and hemispheric asymmetry in patients with major depressive disorders (MDD). This randomized, double-blind study in 28 remitted MDD patients examined the moderating effects of acute nicotine and smoker vs. nonsmoker status on mood and EEG changes accompanying transient reductions in serotonin induced by acute tryptophan depletion (ATD). In smokers, who exhibited greater posterior high alpha power and increased left frontal low alpha power (signs of deactivation) compared to nonsmokers, ATD increased self-ratings of depressed mood and elevated left frontal and right parietal high alpha power (i.e. further cortical deactivation). Smokers were not affected by nicotine administration. In nonsmokers, ATD did not influence depression ratings, but it reduced vigor ratings and increased frontal and posterior theta power; both of which were blocked by acute nicotine. These findings indicate a role for nicotinic receptors in disordered mood.

1. Introduction

Empirical support associating tobacco smoking with major depressive disorder (MDD) includes such findings as a greater prevalence of smoking in MDD (~50–60%) vs. normal (~20%) population (Anda, Williamson, Escobedo, et al., 1990; Glassman, Helzer, Covey, et al., 1990) and a twofold increase in lifetime prevalence rates of MDD in smokers vs. nonsmokers (Piasecki, 2000). Additionally, a greater likelihood (~2–3 times more likely) of failed attempts to stop smoking in smokers with a MDD history vs. non-MDD history is associated with emergence of depressive symptoms (i.e. a new episode of MDD) during smoking cessation (Covey, Glassman, & Stetner, 1997, 1998; Glassman et al., 1990). Finally, the reduction of depressive symptoms with nicotine treatment has been reported in nonsmoking MDD patients (Salin-Pascual, de la Fuente, Galicia-Polo, et al., 1995).

Co-occurrence of MDD and nicotine dependence disorder may be explained by shared abnormalities in the genetic or neurobiological factors (Kendler, Neale, MacLean, et al., 1993; McCaffery, Niaura, Swan, et al., 2003) that may influence bidirectional causal relationships. Specifically, chronic exposure to nicotine, the primary psychoactive component of tobacco, may induce changes in neurotransmitter systems and neural pathways implicated in mood regulation, acting to exacerbate and/or precipitate depressed mood. On the other hand, depression may cause tobacco dependence by increasing the likelihood that individuals will self-medicate negative affect via nicotine's actions on depression-associated brain networks and neurochemical systems (Markou et al., 1988; Mineur & Picotto, 2009; Rao, Hammen, London, et al., 2009).

Although a complex pattern of dysregulations within and between neurotransmitter systems has been observed in depression (Nikolaus, Hautzel, Heinzel, et al., 2012), converging evidence has specifically associated MDD with reduced and dysregulated activity in serotonin (5-HT)ergic systems and circuits of the brain (Werner & Covenas, 2010). Clinical studies have further clarified the link between serotonin and depression in showing that

* Corresponding author at: University of Ottawa, Institute of Mental Health Research, 1145 Carling Avenue, Ottawa, ON K1Z 7K4, Canada. Tel.: +1 613 722 6521.
E-mail address: Verner.Knott@theroyal.ca (V. Knott).

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acute, transient relapse of depressive symptoms can be produced in remitted patients using the irreversible 5-HT synthesis inhibitor p-chlorophenylalanine (Shopsin, Friedman, & Gershon, 1976; Shopsin, Gershon, Goldstein, et al., 1975). Also resulting in a temporary reduction in central serotonin levels, acute tryptophan depletion (ATD) lowers mood in individuals with a family history of MDD and in euthymic MDD patients, but not in healthy individuals (Ruhé, Mason, & Schene, 2007). Perhaps the strongest evidence for the role of the 5-HT system in MDD is the efficacy of selective serotonin reuptake inhibitors (SSRIs), antidepressants which block the presynaptic 5-HT transporter (SERT) and reuptake into afferent neurons and, thus, increase 5-HT concentrations in the synaptic cleft (Haenisch & Bonisch, 2011).

Acutely abstinent smokers report symptoms similar to those of depression (Covey, Glassman, & Stetner, 1990) and while smoking a cigarette can heighten mood in depressed patients compared to non-depressed volunteers (Kinnunen, Doherty, Milettello, et al., 1996), nicotine patch can reduce depressive symptoms, even in non-smokers (Salin-Pascual et al., 1995). Studies in preclinical rodent models have shown chronic nicotine to elicit antidepressant-like effects in well-established paradigms (Djuric, Dunn, Overstreet, et al., 1999; Semba, Mataki, Yamada, et al., 1998; Tizabi, Overstreet, Rezvani, et al., 1999). Acute nicotine administration increases the discharge rate of 70% of rat dorsal raphé (DRN) 5-HT neurons and elevates the overall mean levels of serotonin (Mihailescu, Guzman-Marin, del Cosem Dominguez, et al., 2002), and while "smoking" concentrations of nicotine increase 5-HT release from striatal synaptosomes (Reuben & Clarke, 2000), high doses of nicotine elevate extracellular frontocortical 5-HT (Ribeiro, Bettiker, Bogdanov, et al., 1993).

Paralleling neuroimaging findings of patients during a depressive episode (Drevets, 2000), diminished glucose metabolism/cerebral blood flow in frontal (orbitofrontal cortex, ventrolateral prefrontal cortex, frontopolar cortex, pregenual and anterior cingulate cortex) as well as in thalamic and caudate brain regions has characterized brain activity following ATD in remitted patients (Bremner, Innis, Salomon, et al., 1997; Morris, Smith, Cowen, et al., 1999). A heightened emotive (i.e. increased depression) and neural response (i.e. reduced frontal activation) to ATD is seen in smokers (vs. nonsmokers) with a history of MDD (Pergadia, Spring, Konopka, et al., 2004; Spring, Hitsman, Pingitore, et al., 2007). Just as brain imaging in depressed patients is associated with hypoperfusion in the left frontal cortex (Baxter, 1991; Drevets & Raichle, 1995; Martinot, Hardy, Feline, et al., 1990), electroencephalography (EEG) has evidenced asymmetry in frontal alpha (which is inversely associated with cortical activation), with increases in left (LH)-to-right (RH) hemispheric EEG alpha (reduced left frontal activation) in acute and remitted MDD (Davidson, Chapman, & Chapman, 1987; Gotlib, 1998; Henriques & Davidson, 1991; Stewart, Bismark, & Towers, 2010; Thibideau, Jorgensen, & Kim, 2006) as well in abstinent smokers with high trait depression (Gilbert, McClernon, Rabinovich, et al., 1999). Such findings can be contextualized within the arousal-valence model of affect which theorizes that affective status is mediated by the conjoint activation of a positive emotion/behavioral approach system in the left frontal cortex and a negative emotion/behavioral avoidance system in the right frontal cortex (Davidson, 2004). As such, relative left frontal alpha increases in individuals with a depression history and in persons at-risk for depression, may tap a "diathesis" that, when combined with biological stressors, triggers emotion-related psychopathology manifested as depression or anxiety (Davidson, 1992; Davidson, Ekman, Saron, et al., 1990; Davidson & Irwin, 1999; Heller, 1993).

As our recent study in healthy volunteers with a family history of depression showed that acute nicotine blocked both right frontal alpha increases and mood lowering induced by ATD (Knott, Thompson, Shah, et al., 2012), one objective of the present study is to extend these investigations by examining the moderating influence of acute nicotine administration on mood and frontal alpha effects of ATD in remitted MDD patients. As additional study objectives, nicotine–serotonergic interactions were evaluated with respect to both: (a) regional differences in alpha, as increased posterior alpha shown in MDD patients (vs. controls) has been found to be predictive of SSRI treatment response (Tanke, Kayser, Manna, et al., 2011), and (b) hemispheric differences in posterior alpha, as an opposite alpha asymmetry at posterior (vs. frontal) regions (i.e. RH less than LH activity) (Bruder, Sedoruk, Stewart, et al., 2008; Pollock & Schneider, 1989, 1990) has characterized depression in some (Bruder, Fong, Tenke, et al., 1997; Bruder, Tenke, Warner, et al., 2005; Kentgen, Tenke, Pine, et al., 2000; Reid, Dube, & Allen, 1998; Stewart, Towers, Coan, et al., 2011) but not all studies (Coutin-Churchman & Moreno, 2008; Knott, Mahoney, Kennedy, et al., 2000; Kwon, Youn, & Jung, 1996; Ricardo-Garcell, Gonzalez-Olivera, Miranda, et al., 2009; Saletu, Anderer, & Saletu-Zyhlarz, 2010; Weinbruch, Moratti, Elbert, et al., 2003). This finding has been interpreted within the arousal-valence models as neural evidence of reduced arousal and/or impaired processing of emotional stimuli (i.e. right posterior hypoactivity).

Furthermore, as previous studies have shown smoking status to moderate response both to ATD (Spring et al., 2007) and nicotine administration (Yamumoto, Rohan, Goletiani, et al., 2012), an exploratory study objective was to compare smokers and nonsmokers and the moderating effects of nicotine in these groups with respect to ATD-induced mood and alpha changes. In addition to alpha, the study also examined theta power (~4–7 Hz), which has been found to be sensitive to the acute effects of nicotine and nicotine abstinence in smokers (Gilbert et al., 1999; Knott, 2001). Frontal theta has also been found to be increased in MDD (Saletu et al., 2010), to be sensitive to the acute actions of SSRI antidepressants (Saletu, Grunberger, Anderer, et al., 1996), and in some studies is predictive of MDD patient response to antidepressant treatment (Alhaj, Wisniewski, Hamish, et al., 2011; Iosefescu, 2011).

It was expected that ATD would lower mood and induce depression-like EEG changes, including increases in both frontal (LH > RH) and posterior (RH > LH) alpha asymmetry, as well as in overall posterior alpha and frontal theta. These behavioral and neural effects with ATD were predicted to be more evident in nonsmokers and to be attenuated by acute nicotine, especially in smokers.

2. Methods

2.1. Participant selection

Potential volunteers (recruited via local newspaper and internet advertisements) were processed through two screening phases. The first consisted of a telephone interview assessing personal and family psychiatric history, health status and substance use. Potential participants subsequently underwent a direct interview in which trained study investigators (JB, AT, DS), in consultation with the study psychiatrist (JB), evaluated psychopathology via the Structured Clinical Interview (SCID) that gives current and lifetime psychiatric diagnoses according to the DSM-IV (First, Gibbon, Spitzer, et al., 1996). All participants had to be between 18 and 60 years of age and meet DSM-IV criteria for depression in remission for at least the past 3 months, and exhibit a score <8 on the 21-item Hamilton Rating Scale for Depression (HRDS) (Hamilton, 1967).

Volunteers also underwent a physical exam, which included a medical history, an electrocardiogram and routine laboratory tests (complete blood count, routine blood chemistry, urine analysis and toxicological screen for illicit drugs). In addition to reported medical problems identified in the initial telephone interview, exclusion criteria also included reported substance/alcohol abuse and dependence (not including nicotine), history of neurological problems (e.g. seizures and head trauma), use of medications (not including antidepressants), pregnancy or lactation, history of severe food allergies and a body mass index >35 kg/m^2. Of the 30 (22 female) volunteers included in the study (mean age = 31.5 years; SD ± 14.8), all of whom reported at least one major depressive episode, 19 were off antidepressant

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