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Joshua M. Carlson
joshcarl@nmu.edu

David Gilbert

Hege Riise

Brett Froeliger

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Serotonin Transporter Genotype and Depressive Symptoms Moderate Effects of Nicotine on Spatial Working Memory

Joshua M. Carlson
Southern Illinois University–Carbondale and
State University of New York at Stony Brook

David G. Gilbert, Hege Riise,
and Norka E. Rabinovich
Southern Illinois University–Carbondale

Chihiro Sugai
Southern Illinois University–Carbondale

Brett Froeliger
Southern Illinois University–Carbondale and
Duke University

Smokers may use nicotine to self-medicate for situation-specific or person-specific cognitive or affective deficits. Although evidence suggests that nicotine replacement therapy (NRT), relative to placebo, enhances spatial working memory (SWM) in smoking-abstinent smokers with schizophrenia, the extent to which NRT may be helpful in attenuating abstinence-related SWM in other groups with deficits in SWM is unknown. Depressive symptoms are associated with both tobacco smoking and deficits in SWM. Previous studies have found that smoking abstinence increases depressive affect and depression-related hemispheric asymmetries in brain activation. Although the serotonin neurotransmitter system is closely associated with depression and the effects of nicotine, the authors are not aware of any studies that have evaluated the possible role of individual differences in serotonin transporter (5-HTT) genotype and depressive symptoms as moderators of the effects of NRT on SWM. Thus, the current study assessed the effects of NRT (nicotine patch) on SWM in relation to: (1) depressive traits and (2) 5-HTT genotype. Smoking-deprived habitual smokers ($N = 64$) completed the dot recall test of SWM during counterbalanced and double-blind nicotine and placebo testing sessions. There was a marginal overall effect of NRT on SWM. More importantly, NRT enhanced SWM in 5-HTT short allele carriers, relative to those with two long alleles, and this enhancement in short-allele carriers was greater for individuals with higher levels of depressive symptoms.

Keywords: nicotine, depression, serotonin, genetics, spatial processing

There is a high prevalence of smoking in individuals with a mental health history; particularly schizophrenia and depression (Kirch, 2000). Smokers with more depressive episodes tend to have greater nicotine dependence (Breslau, Kilbey, & Andreski, 1991), greater tendency to relapse when trying to quit smoking (Glassman et al., 1988), and more depressive episodes when trying to quit smoking (Covey, Glassman, & Stetner, 1997). Additionally, it appears that in neurodegenerative disorders such as Parkinson's and Alzheimer's diseases there is a neuroprotective effect of nicotine where individuals who smoke are less likely to exhibit the symptoms of these diseases (Newhouse & Whitehouse, 2000). Although the causal nature of the relationship between nicotine usage and mental health is unclear, it has been hypothesized that individuals use nicotine to self-medicate for various mental deficits (Carmody, 1989; Hughes, Hatsukami, Mitchell, & Dahlgren, 1986; Newhouse, Potter, & Singh, 2004; Newhouse, Singh, & Potter, 2004). At a nonclinical level, individuals with high levels of neurotic, depressive, and anxious personality traits may use nicotine to alleviate negative mood symptoms associated with these negative affect related traits (Eysenck, 1980; Gilbert, Sharpe, Ramanaiah, Detwiler, & Anderson, 2000).

Consistent with the self-medication model, research has demonstrated that smokers with schizophrenia, relative to matched control smokers, show impairments in spatial working memory (SWM) during nicotine abstinence (George et al., 2002) and this impairment is alleviated upon resumption of nicotine usage (Sacco et al., 2005). Although NRT appears to reduce abstinence-related impairments of spatial processing in schizophrenia (George et al., 2002; Sacco et al., 2005), it is unclear as to what extent nicotine enhances (or nicotine deprivation in habitual smokers impairs) spatial processing in other individuals or populations

Joshua M. Carlson, Department of Psychology, Southern Illinois University–Carbondale, and Department of Biomedical Engineering, State University of New York at Stony Brook; David G. Gilbert, Hege Riise, Norka E. Rabinovich, and Chihiro Sugai, Department of Psychology, Southern Illinois University–Carbondale; Brett Froeliger, Department of Psychology, Southern Illinois University–Carbondale, and Duke University Medical Center, Durham.

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Correspondence concerning this article should be addressed to Joshua M. Carlson, Department of Biomedical Engineering Health Sciences Center, 18-030 State Univeristy of New York at Stony Brook, Stony Brook, NY 11794-8181. E-mail: carlsonjm79@gmail.com

with spatial processing deficits. Individuals with depressive traits, including those with major depressive disorder, have been found to exhibit SWM deficits (Henriques & Davidson, 1997; Miller, Fujioka, Chapman, & Chapman, 1995). Depression has been hypothesized to be associated with a general perceptual deficit in posterior right hemisphere (RH) processing (Heller, Etienne, & Miller, 1995). The spatial processing deficits of those high in depressive traits have been shown to be associated with decreased posterior RH activity (Henriques & Davidson, 1997; Miller et al., 1995; Rabe, Debener, Brocke, & Beauducel, 2005). In addition to these posterior brain asymmetries, depression is associated with frontal brain asymmetries (decreased LH relative to RH frontal cortical processing; Davidson, 1992; Davidson, Pizzagalli, Nitschke, & Putnam, 2002). Research indicates that negative affect-related frontal asymmetries are modulated by nicotine (Gilbert, Robinson, Chamberlin, & Spielberger, 1989) and that NRT decreases negative affect in smoking abstinent smokers (Gilbert, Rabinovich et al., 2008). The extent to which nicotine may improve depression related spatial processing is unknown, though a recent study (Gilbert, Carlson, Riise, Rabinovich, Sugai, & Froeliger, 2008) found that, in abstinent smokers, NRT enhanced LH processing and decreased RH processing of affective word stimuli and that NRTs effects on RH affective word processing were moderated by depressive traits. Nonetheless, while nicotine modulates affect-related information processing asymmetries (Gilbert et al., 1989), its influence on SWM is untested.

The serotonin transporter (5-HTT)-linked polymorphic region (5-HTTLPR) is a functional polymorphism in the promoter for the serotonin transporter gene that encodes a short (S) and a long (L) allele type. The homozygous L genotype (compared to S allele carriers) is associated with greater 5-HT reuptake and presumably lower levels of synaptic 5-HT (Hariri et al., 2002; Heinz et al., 2000; Lesch et al., 1996; Little et al., 1998). The S allele appears to be associated with increased emotional reactivity to life stressors (Hariri & Holmes, 2006; Joober, Sengupta, & Schmitz, 2007) and to interact with stressful life events in predicting depressive symptoms, clinical depression, and number of suicide attempts (Caspi et al., 2003). Nicotine enhances the release of serotonin, which may play a role in nicotine dependence (Ribeiro, Bettiker, Bogdanov, & Wurtman, 1993). Smoking-related behavior, including smoking to reduce negative mood, appears to be associated with interactions of 5-HTTLPR genotype and neuroticism (Hu et al., 2000; Lerman et al., 2000; but see Munafò, Roberts, Johnstone, Walton, & Yudkin, 2005 for alternative results). Additionally, individuals with the S allele of the 5-HTT gene have been shown to experience greater negative affect related tobacco abstinence symptoms (Gilbert, Zuo, et al., in press), which is consistent with previous associations of serotonergic hypofunctioning with nicotine abstinence in animal models (Harrison, Liem, & Markou, 2001) and with negative affect in human samples (Lesch & Merschdorf, 2000).

In summary, nicotine, 5-HTT genotype, and depression are associated with each other and S allele carriers have been found to experience greater severity of smoking abstinence symptoms (Gilbert et al., in press). Hariri and Holmes (2006) concluded that the S allele increases emotional reactivity to stressors. Given that most smokers experience smoking abstinence as a stressor, one might expect the S allele to be associated with heightened reactivity to nicotine abstinence. However, we are not aware of any study that has assessed whether nicotine replacement therapy (NRT) is effective in enhancing SWM in nicotine-deprived S allele carrying habitual smokers.

Therefore, the aim of the current study was to assess the roles of depressive symptoms and 5-HTT genotype on the putative benefits of NRT on SWM in overnight-deprived nicotine-dependent smokers. It was hypothesized that NRT in general would enhance SWM, that theses effects would be stronger in individuals with higher levels of depressive symptoms or in 5-HTT short allele carriers, and strongest in individuals who are both 5-HTT short allele carriers and have high levels of depressive symptoms.

Method

Participants

Thirty-one female and 33 male smokers ($N = 64$) between the ages of 18 to 50 ($M = 26$, $SD = 8.80$) who smoked an average of ≥10 ($M = 17$, $SD = 5.74$) cigarettes per day for the past year, and had a mean Fagerström Test of Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991) score of 4.00 ($SD = 1.91$) participated in the study. There were 5 African American, 3 multiracial, and 56 White participants in the sample.

Participants were recruited by newspaper ads and postings throughout a Midwestern university campus and surrounding community. Exclusion criteria included smoking fewer than 10 cigarettes per day for the past year, smoking cigarettes with Federal Trade Commission (FTC) nicotine deliveries of less than 0.6 mg/cigarette, reported use of psychoactive drugs or medications other than caffeine, marijuana, and alcohol, excessive alcohol use (30+ drinks/week), ages less than 18 or more than 50, non-English speaking, atypical sleep cycles, and serious medical, hearing, and visual problems. Participants were instructed not to smoke tobacco or drink alcohol for the 12 hours preceding each of the experimental sessions and not to smoke marijuana for at least 72 hours before the sessions. Only those who reported adhering to these requirements and who had breath CO concentrations of less than 10 ppm were included in data analyses.

Orientation Sessions

During an orientation session participants provided breath CO samples to verify habitual smoking ($M = 21.03$, $SD = 9.00$) and completed the Minnesota Multiple Personality Inventory-2 (Hathaway & McKinley, 1983) depression scale and the Fagerström Test of Nicotine Dependence (Heatherton et al., 1991).

Questionnaires

FTND. The FTND (Heatherton et al., 1991) is designed to assess nicotine dependence and is moderately predictive of severity of withdrawal distress and relapse to smoking (Piasecki et al., 2000).

Minnesota Multiple Personality Inventory-2. The Minnesota Multiple Personality Inventory-2 (MMPI-2) consists of empirically derived questionnaires designed to delineate clinical from nonclinical disorders. Here we used the MMPI depression scale as a measure of depressive affect and symptoms frequently associated with depression (Bence, Sabourin, Luty, & Thackrey, 2006; Wetzler; Kahn, Strauman, & Dubro, 1989). Within healthy populations the MMPI depression scale has been found to predict depressive symptoms (Gilbert et al., 2002) and asymmetrical neural responses (Gilbert et al., 2004) to smoking abstinence. The mean MMPI depression scale score for men (M = *18*.15, SD = 4.35) and women (M = 21.84, SD = 5.65) corresponded to T scores of 49.63 and 53.42, respectively, which did not significantly differ from each other, $p > .10$. T scores ranged from 29.60 to 68.84.

5-HT Transporter Genotyping

DNA was isolated from blood samples according to standard techniques. The 5-HTTLPR polymorphism of the 5-HTT was assessed by polymerase chain reaction (PCR) based on the conditions described by Yonan, Palmer, and Gilliam (2006). Specific primers and reaction conditions are available upon request. In our sample, there were 21 LL, 29 SL, and 14 SS individuals. These proportions corresponded to the Hardy-Weinberg distribution, $\chi^2(64) = 0.44$, $p = .51$. For statistical purposes, 5HTT gene is categorized as either S allele carriers (N = 43; one or two short [S] variants with 14 copies of a 20 to 23 base pair [bp] repeat unit, 430 bp) or homozygous LL (N = 21; two long variants consisting of 16 copies, 474 bp). As presented in Table 1, there were no significant difference between S allele carriers and LL individuals on a number of participant characteristics.

Experimental Procedures

Participants completed two counterbalanced experimental sessions: one with nicotine patch and the other with placebo patch. Before each experimental day, participants were instructed to abstain from smoking for 12 hours preceding the experimental session.

Assessment of smoking abstinence. Compliance with instructions for overnight smoking abstinence and smoking status were monitored using self-report and expired breath CO concentrations assessed with a MiniCO7 m (Catalyst Research Corporation, Owings Mills, MD). CO concentration had to be less than 10 ppm at the time of patch placement and to be less than or equal to that when returning to the lab 4 hours later to begin the experimental session. Mean CO values of 5.23 (SD = 3.04) and 5.20 (SD = 3.01) at the beginning of experimental sessions one and two, respectively, indicate participant compliance of smoking abstinence.

Patch administration. Patch administration was double-blind and counterbalanced for order. A researcher not involved in data collection or otherwise interacting with participants provided the appropriate nicotine or placebo patch and kept a record of which patch was given. The nicotine patch was a 14 mg Nicoderm transdermal patch; the placebo patch was an identical appearing patch provided by GlaxoSmithKline. To minimize the ability of participants to differentiate active and placebo patches by skin sensations (itching or irritation) we used a cover bandage with capsaicin cream. Both the active and placebo patches were placed in the center of a 6.5 cm × 7.0 cm cover bandage. Then a small amount (.05 ml) of capsaicin .075% cream (Capzasin-HP7, Chattem, Inc.) was applied to the Teflon-coated surface of the cover bandage, covering an area 5 mm wide immediately next to each of the edges of the bandage. Pilot testing demonstrated that this procedure reduced the ability of participants to detect differences between the active and placebo patch when applied. The patches were placed on the upper arm of smokers approximately 4 hours before the beginning of the experimental sessions.

SWM task. The dot recall SWM task implemented in the present experiment was modeled after the procedures used by George et al. (2002). This measure has been found to have adequate test–retest reliability and to be valid measure of SWM (Bollini, Arnold, & Keefe, 2000). Participants performed this task during both the nicotine and placebo patch experimental sessions. The task was displayed by a PC on an 18-inch LCD monitor using SuperLab 2.0 soft-

Table 1
Participant Characteristics for Each 5-HTT Genotype

5-HTT genotype	Frequencies			Means and *SDs*			
	N	Gender	Ethnicity	Number of cigarettes a day	Nicotine dependence (FTND)	Age	Depression (MMPID *T* Score)
S Carrier	43	21 Male 22 Female	39 White 2 African American 2 Multiracial	16.88 (6.10)	3.93 (1.78)	24.86 (7.79)	50.74 (10.02)
LL	21	12 Male 9 Female	17 White 3 African American 1 Multiracial	17.43 (5.06)	4.14 (2.20)	28.57 (10.33)	52.95 (11.58)

Note. Differences between means are not significant, all $ps > .10$.

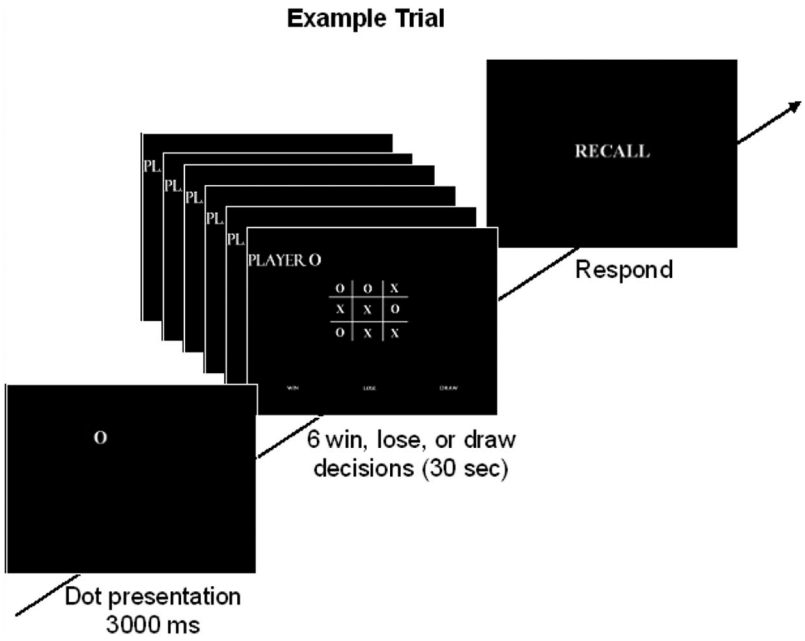

Figure 1. The Dot Recall task of spatial working memory (George et al., 2002) begins with a target dot presented at one of 16 predetermined locations. Participants then perform six tic-tack-toe distracter tasks. After this period of distraction, participants are required to recall the exact spatial location of the target dot with a computer mouse.

ware (Cedrus, Phoenix, AZ). The SWM task consisted of 13 trials, each with three sections. As depicted in Figure 1, the initial section consisted of a dot presented on the computer screen at one of 16 different predetermined locations for 3,000 ms. The second section consisted of six different distracter tic-tack-toe tasks, which cumulatively lasted for 30 seconds. Participants were required to indicate whether the tick-tack-toe game was an "X win, O win, or a draw." The final section required participants to indicate the location of the initial dot by moving and clicking the computer mouse over the initial dot location.

Statistical Analyses

The primary dependent measure of interest was the *Difference in Nicotine Replacement Therapy* (*NRT*) on participants' average distance from the target dot. This measure was used to assist in interpreting associations between differences in nicotine and placebo sessions and MMPI-2 Depression. The Difference in NRT was defined as the difference between a participant's performance with placebo patch and performance with nicotine patch (placebo distance from target in cm—nicotine distance from target in cm). Positive values indicated greater performance during nicotine relative to placebo sessions, while negative values indicated better performance during placebo relative to nicotine sessions. An analysis of covariance (ANCOVA) with between-subjects variables 5-HTT Genotype (short allele carriers vs. long-long type) and Gender (male vs. female) was run, with Depressive Symptoms (as measured with the MMPI Depression scale *T* scores) included as a continuous covariate.[1] Given that Depressive Symptoms was a variable of theoretical interest, the modal tested for all main and interaction effects including this continuous variable. Where appropriate, follow-up Pearson correlations were used to better understand interactions with Depressive Symptoms. For demonstration purposes, participants were dichotomized into having "high" or "low" levels of depression; overall performance for each level of Depression, 5-HTT Genotype and Nicotine are presented in Table 2.

Results

A one-sample *t* test was run on the Difference in NRT to assess whether there was an overall effect of NRT, relative to placebo patch, on SWM. The results suggest that, in general, nicotine marginally enhanced performance on SWM, $M = .14$, $SE = .08$, $t(63) = 1.80$, $p = .08$.

The results of the 5-HTT Genotype, Gender, and Depressive Symptoms ANCOVA revealed two important effects of 5-HTT Genotype on the Difference in NRT. First, there was a significant effect of 5-HTT Genotype, $F(1, 56) = 5.51$,

[1] Although our primary focus for this article was on the 5-HTT genotype and depressive symptoms, we did collect data for the DRD2 genotype and ran an additional analysis with DRD2. No significant associations were found with DRD2 on the dot recall task. This DRD2 analysis can be obtained from the corresponding author upon request.

Table 2
Mean Distance (cm) From the Target Dot by Condition

	High depression		Low depression	
	LL	S Carrier	LL	S Carrier
Nicotine	1.64	1.00	0.85	0.94
Placebo	1.47	1.41	0.92	1.00

$p < .05$, $\eta_p^2 = .09$ (Figure 2a), where short allele carriers ($M = .38$ cm, $SE = .10$) performed better with NRT on the dot recall task of SWM, whereas long-long (LL) individuals did not ($M = -.04$ cm, $SE = .13$). Second, there was a significant interaction of 5-HTT Genotype with Depressive Symptoms on the Difference in NRT on SWM, $F(1, 56) = 8.22$, $p < .01$, $\eta_p^2 = .13$. As graphically depicted in Figure 2, follow-up Pearson correlations revealed that for LL individuals there was a nonsignificant negative correlation between Depressive Symptoms and the Difference in NRT on SWM, $r = -.20$, $p > .05$ (Figure 2b), whereas for short allele carriers there was a positive correlation between Depressive Symptoms and the Difference in NRT on SWM, $r = .38$, $p < .05$ (Figure 2c). As presented in Table 2, participants with high levels of depression generally performed poorly during the placebo session, but S carriers appeared to benefit from NRT, whereas LL individuals did not. There were no effects of gender, $F(1, 56) = 1.11$, $p = .27$, $\eta_p^2 = .02$, or Depressive Symptoms, $F(1, 56) = 1.70$, $p = .20$, $\eta_p^2 = .03$, nor were there any additional interaction effects (all ps $> .10$). The 5-HTT Genotype, $F(1, 48) = 4.57$, $p = .05$, $\eta_p^2 = .09$, and the 5-HTT by Depressive Symptoms, $F(1, 48) = 6.93$, $p = .01$, $\eta_p^2 = .13$, effects both remained significant in a separate analysis of only White participants indicating that these effects were not mediated by ethnicity differences between the short allele carrier and LL groups.

Discussion

The finding that smoking-deprived 5-HTT S carriers, especially those high in depressive symptoms, performed better on a SWM task with NRT, whereas homozygous L individuals did not, is potentially quite important. These findings extend previous associations between 5-HTT genotype, depressive symptoms (Caspi et al., 2003; Joober et al., 2007), affect-related brain activity (Furmark et al., 2004; Hariri & Holmes, 2006; Hariri et al., 2002), and smoking behavior (Hu et al., 2000; Lerman et al., 2000). The present results suggest that 5-HTT genotype plays an important role in moderating the cognitive benefits of NRT after a period of nicotine deprivation; or alternatively, who experiences the most significant SWM deterioration during nicotine abstinence.

Although NRT on average marginally improved SWM, closer examination revealed that S allele carriers benefited from NRT and LL individuals did not. This suggests that the effects of NRT on SWM are individual specific and not universal. This notion is further supported by the positive correlation between depressive symptoms and the difference in NRT in 5-HTT short carriers (Figure 2c). Therefore, the results add support to trait based models of nicotine usage and suggest that multiple genetically and environmentally influenced traits moderate an individual's specific response to nicotine (Eysenck, 1980; Gilbert, 1995; Lerman et al., 2000). These results add to a growing body of literature suggesting the 5-HTT is intimately associated with depressive and negative affect-related symptoms

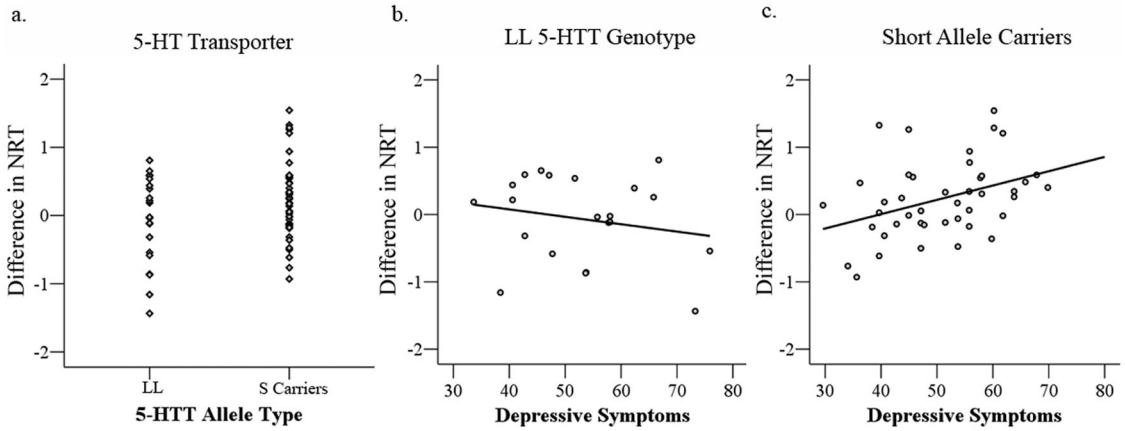

Figure 2. The 5-HTT genotype resulted in several effects of the Difference in NRT (calculated as the placebo distance from target in cm—nicotine distance from target in centimeters) on the SWM task. (a) Short allele carriers benefited more from NRT on SWM than homozygous LL. (b) For LL individuals there was a nonsignificant negative correlation between Depressive Symptoms (MMPI depression *T* scores) and the Difference in NRT ($r = -.20$, $p > .05$). (c) On the other hand, for short allele carriers there was a positive correlation between Depressive symptoms and the Difference in NRT ($r = .38$, $p < .05$).

(Caspi et al., 2003; Hariri & Holmes, 2006; Joober et al., 2007), in addition to smoking behaviors in smokers with high levels of neuroticism (Hu et al., 2000; Lerman et al., 2000). Although most smokers experience smoking abstinence as a stressor, 5-HTT S carriers in particular experience greater negative affect-related symptoms during nicotine abstinence (Gilbert, Zuo, et al., in press). Thus, our finding that 5-HTT S carriers, especially those high in depressive symptoms, benefit from NRT (after nicotine abstinence) on SWM is consistent with the hypothesis that S allele carriers are generally more responsive to stressors (Hariri & Holmes, 2006). It is not clear whether these effects of NRT simply reflect greater abstinence-related decrements in SWM in these populations or may reflect, at least in part, genuine benefits that are independent of nicotine withdrawal results from smoking abstinence.

Neuroimaging studies indicate that the amygdala is more sensitive to emotionally charged stimuli in S allele carriers, compared to LL individuals (Furmark et al., 2004; Hariri & Holmes, 2006; Hariri et al., 2002). The amygdala and hippocampus are involved in regulating the hypothalamic-pituitary-adrenal (HPA) axis response to stress (Campbell & Macqueen, 2004). Depression may be associated with a dysregulated HPA response, which could contribute to depressive symptoms and hippocampal volume loss (Sheline, Mittler, & Mintun, 2002). Hippocampal volumes are smaller in untreated depressed individuals (Hickie et al., 2005; MacMaster & Kusumakar, 2004; Sheline, Gado, & Kraemer, 2003) and are correlated with deficits in visual memory (Hickie et al., 2005). In a virtual reality task of spatial memory, sensitive to hippocampal damage, clinically depressed individuals displayed impaired performances relative to controls (Gould et al., 2007). Animal models implicate the hippocampus as an important mechanism in spatial memory and site of nicotine action on the 5-HT system (Kenny, File, & Rattray, 2001), which may underlie nicotine's antidepressant effects (Balfour & Ridley, 2000). Interestingly, other psychiatric populations associated with nicotine usage, such as those with Alzheimer's and schizophrenia, are also associated with reduced hippocampal volumes. Thus, this hippocampal system appears to be a likely substrate in which nicotine influences SWM in depressed individuals with dysfunctional 5-HT systems.

Our findings are consistent with the self-medication model of nicotine addiction (Carmody, 1989; Eysenck, 1980; Gilbert et al., 2000; Hughes et al., 1986; Newhouse, Potter, & Singh, 2004; Newhouse, Singh, & Potter, 2004), which posits that smokers use nicotine to compensate for situation- or person-specific deficits. Specifically, the results suggest that 5-HTT S allele carriers, especially those with high levels of depressive symptoms, may self medicate to reduce impairments in SWM. Similar SWM impairments have been observed in smokers with schizophrenia (George et al., 2002) and smoking alleviates this deficit (Sacco et al., 2005). Nicotine abstinence-related deficits in SWM and other cognitive abilities may lead individuals to perform uncharacteristically below their usual (self-expected) level of performance and therefore may result in enhanced negative affect (Gilbert, 1995). Therefore, depression-prone 5-HTT S allele carriers who in general do not respond well to stressful situations (Caspi et al., 2003) and experience greater negative affect during nicotine abstinence (Gilbert et al., in press) may be especially susceptible to self-medicate with nicotine to alleviate both cognitive/SWM deficits, but also the associated stress and frustration. Given that, 5-HTT S carriers high in neuroticism are typically unsuccessful in attempts to quit smoking (Hu et al., 2000), these individuals may benefit more from NRT or additional individualized interventions which attempt to compensate for these deficits. In particular, 5-HTT S carriers with high levels of depression, anxiety, or neuroticism may be responsive to antidepressant pharmacological treatments, which are effective in treating negative affect-related mood disorders (Tamminga et al., 2002) and nicotine addiction (Cinciripini et al., 1995). However, further research is needed to assess the validity of these clinical hypotheses.

Given that this is the first study to assess the combined effects of NRT, depression, and 5-HTT genotype on SWM the clinical implications of the results should be interpreted with caution. It remains unclear if the beneficial effects of NRT generalize to 5-HTT S carriers with clinical levels of depression and if highly depressed S carriers maintain nicotine usage as a form of self-medication. In addition, as noted above, it is not clear whether the exaggerated SWM deficits observed in the placebo, relative to the nicotine patch condition, simply reflect more severe withdrawal symptoms in those with low cognitive reserves. Future research should be directed at addressing these issues. Given that nicotine has been shown to enhance attention (Gilbert et al., 2004), the enhancement of SWM during NRT in 5-HTT S carriers may be a byproduct of NRT-related enhancements in attention or general cognitive processing. Additionally, it could be argued that individuals with high depressive symptoms are less engaged in the task and that NRT simply enhances motivation in these individuals. Although this explanation may be merited, it appears this could only be the case in 5HTT S carriers as there was no main effect of depressive symptoms. Future research using multiple (distinct) cognitive measures should be aimed at addressing the specifity of this NRT-related cognitive enhancement in 5-HTT S carriers (especially those high in depressive symptoms). Finally, while gender did not moderate the effects of NRT on SWM, menstrual cycle phase and oral contraceptive use were not assessed and could influence the effects. A recent meta-analysis of the effects of gender on response to NRT-related smoking cessation (Perkins & Scott, 2008) suggests that large sample sizes are needed to reliably demonstrate gender effects on NRT. Therefore, studies with larger samples are needed to determine the potential role of gender on the effects of NRT on SWM.

References

Balfour, D. J., & Ridley, D. L. (2000). The effects of nicotine on neural pathways implicated in depression: A factor in nicotine addiction? *Pharmacology Biochememistry and Behavior, 66,* 79–85.

Bence, V. M., Sabourin, C., Luty, D. T., & Thackrey, M. (2006). Differential sensitivity of the MMPI-2 depression scales and subscales. *Journal of Clinical Psychology, 51,* 375–377.

Bollini, A. M., Arnold, M. C., & Keefe, R. S. E. (2000). Test–retest reliability of the dot test of visuospatial working memory in patients with schizophrenia and controls. *Schizophrenia Research, 45,* 169–173.

Breslau, N., Kilbey, M., & Andreski, P. (1991). Nicotine dependence, major depression, and anxiety in young adults. *Archives in General Psychiatry, 48,* 1069–1074.

Campbell, S., & Macqueen, G. (2004). The role of the hippocampus in the pathophysiology of major depression. *Journal of Psychiatry Neuroscience, 29,* 417–426.

Carmody, T. P. (1989). Affect regulation, nicotine addiction, and smoking cessation. *Journal of Psychoactive Drugs, 21,* 331–342.

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., et al. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science, 301,* 386–389.

Cinciripini, P. M., Lapitsky, L., Seay, S., Wallfisch, A., Meyer, W. J. III, & van Vunakis, H. (1995). A placebo-controlled evaluation of the effects of buspironi on smoking cessation: Differences between high- and low-anxiety smoking cessation. *Journal of Clinical Psychopharmacology, 15,* 182–191.

Covey, L. S., Glassman, A. H., & Stetner, F. (1997). Major depression following smoking cessation. *American Journal of Psychiatry, 154,* 263–265.

Davidson, R. J. (1992). Anterior cerebral asymmetry and the nature of emotion. *Brain and Cognition, 20,* 125–151.

Davidson, R. J., Pizzagalli, D., Nitschke, J. B., & Putnam, K. (2002). Depression: Perspectives from affective neuroscience. *Annual Reviews in Psychology, 53,* 545–574.

Eysenck, H. J. (1980). *The causes and effects of smoking.* Beverly Hills, CA: Sage.

Furmark, T., Tillfors, M., Garpenstrand, H., Marteinsdottir, I., Langstrom, B., Oreland, L., et al. (2004). Serotonin transporter polymorphism related to amygdala excitability and symptom severity in patients with social phobia. *Neuroscience Letters, 362,* 189–192.

George, T. P., Vessicchio, J. C., Termine, A., Sahady, D. M., Head, C. A., Pepper, W. T., et al. (2002). Effects of smoking abstinence on visuospatial working memory function in schizophrenia. *Neuropsychopharmacology, 26,* 75–85.

Gilbert, D. G. (1995). *Smoking: Individual differences, psychopathology, and emotion.* Washington, DC: Taylor & Francis.

Gilbert, D. G., Carlson, J. M., Riise, H., Rabinovich, N. E., Sugai, C., & Froeliger, B. (2008). Effects of nicotine and depressive traits on affective priming of lateralized emotional word identification. *Experimental and Clinical Psychopharmacology, 16,* 293–300.

Gilbert, D. G., McClernon, F. J., Rabinovich, N. E., Plath, L., Masson, C. L., Anderson, A. E., et al. (2002). Mood disturbance fails to resolve across 31 days of cigarette abstinence in women. *Journal of Consulting and Clinical Psychology, 70,* 142–152.

Gilbert, D. G., McClernon, F. J., Rabinovich, N. E., Sugai, C., Plath, L. C., Asgaard, G., et al. (2004). Effects of quitting smoking on EEG activation and attention last for more than 31 days and are more severe with stress, dependence, DRD2 A1 allele, and depressive traits. *Nicotine and Tobacco Research, 6,* 249–267.

Gilbert, D. G., Rabinovich, N. E., Malpass, D., Mrnak, J., Riise, H., Adams, L., et al. (2008). Effects of nicotine on affect are moderated by stressor proximity and frequency, positive alternatives, and smoker status. *Nicotine & Tobacco Research, 10,* 1171–1183.

Gilbert, D. G., Robinson, J. H., Chamberlin, C. L., & Spielberger, C. D. (1989). Effects of smoking/nicotine on anxiety, heart rate, and lateralization of EEG during a stressful movie. *Psychophysiology, 26,* 311–320.

Gilbert, D. G., Sharpe, J. P., Ramanaiah, N. V., Detwiler, F. R. J., & Anderson, A. E. (2000). Development of a Situation x Trait Adaptive Response (STAR) model-based smoking motivation questionnaire. *Personality and Individual Differences, 29,* 65–84.

Gilbert, D. G., Zuo, Y., Rabinovich, N. E., Riise, H., Needham, R., & Huggenvik, J. I. (2009). Neurotransmission-related genetic polymorphisms, negative affectivity traits, and gender predict tobacco abstinence symptoms across 44 days with and without nicotine patch. *Journal of Abnormal Psychology, 118,* 322–334.

Glassman, A. H., Stetner, F., Walsh, B. T., Raizman, P. S., Fleiss, J. L., Cooper, T. B., et al. (1988). Heavy smokers, smoking cessation, and clonidine. Results of a double-blind, randomized trial. *Journal of the American Medical Association, 259,* 2863–2866.

Gould, N. F., Holmes, M. K., Fantie, B. D., Luckenbaugh, D. A., Pine, D. S., Gould, T. D., et al. (2007). Performance on a virtual reality spatial memory navigation task in depressed patients. *American Journal of Psychiatry, 164,* 516–519.

Hariri, A. R., & Holmes, A. (2006). Genetics of emotional regulation: The role of the serotonin transporter in neural function. *Trends in Cognitive Science, 10,* 182–191.

Hariri, A. R., Mattay, V. S., Tessitore, A., Kolachana, B., Fera, F., Goldman, D., et al. (2002). Serotonin transporter genetic variation and the response of the human amygdala. *Science, 297,* 400–403.

Harrison, A. A., Liem, Y. T., & Markou, A. (2001). Fluoxetine combined with a serotonin-1A receptor antagonist reversed reward deficits observed during nicotine and amphetamine withdrawal in rats. *Neuropsychopharmacology, 25,* 55–71.

Hathaway, S. R., & McKinley, J. C. (1983). *Minnesota Multiphasic Personality Inventory: Manual for administration and scoring.* Minneapolis: University of Minnesota Press.

Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., & Fagerström, K. O. (1991). The Fagerstrom Test for Nicotine Dependence: A revision of the Fagerström Tolerance Questionnaire. *British Journal of Addiction, 86,* 1119–1127.

Heinz, A., Jones, D. W., Mazzanti, C., Goldman, D., Ragan, P., Hommer, D., et al. (2000). A relationship between serotonin transporter genotype and in vivo protein expression and alcohol neurotoxicity. *Biological Psychiatry, 47,* 643–649.

Heller, W., Etienne, M. A., & Miller, G. A. (1995). Patterns of perceptual asymmetry in depression and anxiety: Implications for neuropsychological models of emotion and psychopathology. *Journal of Abnormal Psychology, 104,* 327–333.

Henriques, J. B., & Davidson, R. J. (1997). Brain electrical asymmetries during cognitive task performance in depressed and nondepressed subjects. *Biological Psychiatry, 42,* 1039–1050.

Hickie, I., Naismith, S., Ward, P. B., Turner, K., Scott, E., Mitchell, P., et al. (2005). Reduced hippocampal volumes and memory loss in patients with early- and late-onset depression. *British Journal of Psychiatry, 186,* 197–202.

Hu, S., Brody, C. L., Fisher, C., Gunzerath, L., Nelson, M. L., Sabol, S. Z., et al. (2000). Interaction between the serotonin transporter gene and neuroticism in cigarette smoking behavior. *Molecular Psychiatry, 5,* 181–188.

Hughes, J. R., Hatsukami, D. K., Mitchell, J. E., & Dahlgren, L. A. (1986). Prevalence of smoking among psychiatric outpatients. *American Journal of Psychiatry, 143,* 993–997.

Joober, R., Sengupta, S., & Schmitz, N. (2007). Serotonin transporter, stressful life events, and depression severity. *American Journal of Psychiatry, 164,* 829–830.

Kenny, P. J., File, S. E., & Rattray, M. (2001). Nicotine regulates 5-HT(1A) receptor gene expression in the cerebral cortex and dorsal hippocampus. *European Journal of Neuroscience, 13,* 1267–1271.

Kirch, D. G. (2000). Nicotine and major mental disorders. In M. Piasecki & P. Newhouse (Eds.), *Nicotine in psychiatry: Psychopathology and emerging therapeutics.* Washington, DC: American Psychiatric Press.

Lerman, C., Caporaso, N. E., Audrain, J., Main, D., Boyd, N. R., & Shields, P. G. (2000). Interacting effects of the serotonin transporter gene and neuroticism in smoking practices and nicotine dependence. *Molecular Psychiatry, 5,* 189–192.

Lesch, K. P., Bengel, D., Heils, A., Sabol, S. Z., Greenberg, B. D., Petri, S., et al. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science, 274,* 1527–1531.

Lesch, K. P., & Merschdorf, U. (2000). Impulsivity, aggression, and serotonin: A molecular psychobiological perspective. *Behavioral Sciences and the Law, 18,* 581–604.

Little, K. Y., McLaughlin, D. P., Zhang, L., Livermore, C. S., Dalack, G. W., McFinton, P. R., et al. (1998). Cocaine, ethanol, and genotype effects on human midbrain serotonin transporter binding sites and mRNA levels. *American Journal of Psychiatry, 155,* 207–213.

MacMaster, F. P., & Kusumakar, V. (2004). Hippocampal volume in early onset depression. *Biomedical Central Medicine, 2,* 2.

Miller, E. N., Fujioka, T. A., Chapman, L. J., & Chapman, J. P. (1995). Hemispheric asymmetries of function in patients with major affective disorders. *Journal of Psychiatric Research, 29,* 173–183.

Munafò, M. R., Roberts, K., Johnstone, E. C., Walton, R. T., & Yudkin, P. L. (2005). Association of serotonin transporter gene polymorphism with nicotine dependence: No evidence for an interaction with trait neuroticism. *Personality and Individual Differences, 38,* 843–850.

Newhouse, P., Potter, A., & Singh, A. (2004). Effects of nicotinic stimulation on cognitive performance. *Current Opinion in Pharmacology, 4,* 36–46.

Newhouse, P., Singh, A., & Potter, A. (2004). Nicotine and nicotinic receptor involvement in neuropsychoatric disorders. *Current Topics in Medical Chemistry, 4,* 267–282.

Newhouse, P., & Whitehouse, P. (2000). Nicotine cholinergic systems in Alzheimer's and Parkinson's Diseases. In M. Piasecki & P. Newhouse (Eds.), *Nicotine in psychiatry: Psychopathology and emerging therapeutics.* Washington, DC: American Psychiatric Press.

Perkins, K. A., & Scott, J. (2008). Sex differences in long-term smoking cessation rates due to nicotine patch. *Nicotine and Tobacco Research, 10,* 1245–1250.

Piasecki, T. M., Niaura, R., Shadel, W. G., Abrams, D., Goldstein, M., Fiore, M. C., et al. (2000). Smoking withdrawal dynamics in unaided quitters. *Journal of Abnormal Psychology, 109,* 74–86.

Rabe, S., Debener, S., Brocke, B., & Beauducel, A. (2005). Depression and its relation to posterior cortical activity during performance of neuropsychological verbal and spatial tasks. *Personality and Individual Differences, 39,* 601–611.

Ribeiro, E. B., Bettiker, R. L., Bogdanov, M., & Wurtman, R. J. (1993). Effects of systemic nicotine on serotonin release in rat brain. *Brain Research, 621,* 311–318.

Sacco, K. A., Termine, A., Seyal, A., Dudas, M. M., Vessicchio, J. C., Krishnan-Sarin, S., et al. (2005). Effects of cigarette smoking on spatial working memory and attentional deficits in schizophrenia: Involvement of nicotinic receptor mechanisms. *Archives of General Psychiatry, 62,* 649–659.

Sheline, Y. I., Gado, M. H., & Kraemer, H. C. (2003). Untreated depression and hippocampal volume loss. *American Journal of Psychiatry, 160,* 1516–1518.

Sheline, Y. I., Mittler, B. L., & Mintun, M. A. (2002). The hippocampus and depression. *European Psychiatry, 17*(Suppl. 3), 300–305.

Tamminga, C. A., Nemeroff, C. B., Blakely, R. D., Brady, L., Carter, C. S., Davis, K. L., et al. (2002). Developing novel treatments for mood disorders: Accelerating discovery. *Biological Psychiatry, 52,* 589–609.

Wetzler, S., Kahn, R., Strauman, T. J., & Dubro, A. (1989). Diagnosis of major depression by self-report. *Journal of Personality Assessment, 53,* 22–30.

Yonan, A. L., Palmer, A. A., & Gilliam, T. C. (2006). Hardy-Weinberg disequilibrium identified genotyping error of the serotonin transporter (SLC6A4) promoter polymorphism. *Psychiatric Genetics, 16,* 31–34.

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