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Effects of Nicotine and Depressive Traits on Affective Priming of Lateralized Emotional Word Identification

David G. Gilbert, Joshua M. Carlson, Hege Riise, Norka E. Rabinovich, Chihiro Sugai,
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Based on evidence suggesting that depressive traits, emotional information processing, and the effects of nicotine may be mediated by lateralized brain mechanisms, analyses assessed the influence of depressive traits and nicotine patch on emotional priming of lateralized emotional word identification in 61 habitual smokers. Consistent with hypotheses, nicotine as compared to placebo patch enhanced right visual field (RVF) emotional word identification while decreasing performance of emotional word identification in the left visual field (LVF). Nicotine also enhanced positive affect and decreased negative affect. Consistent with the Heller model of depression, scoring high in depressive traits was associated with a general decrease in LVF emotional word identification. Additionally, this general LVF deficit was especially pronounced for positive word identification in individuals scoring high in trait depression. Positive primes facilitated positive target identification in the RVF and negative primes facilitated negative target identification in the LVF. Thus, nicotine promoted a LVF word-identification deficit similar to that observed in those with depressive traits. However, nicotine also enhanced RVF processing and reduced negative affect, whereas it enhanced positive affect.

Keywords: depression, nicotine, emotion, cerebral asymmetry, affect, priming

Although a large empirical literature indicates that emotional information is differentially processed in the right relative to the left cerebral hemisphere (LH), the exact nature of this processing is still debated, and little is known about the effects of drugs and individual differences in such processing. The two primary models of asymmetrical affect-related processing are the right hemisphere (RH) model and the valence model. The RH model claims that the RH is specialized for the processing of emotional expression, perception, and experience independent of emotional valence (positive vs. negative character). Support for the RH model comes from human lesion (Adolphs, Damasio, Tranel, & Damasio, 1996), split-brain (Benowitz et al., 1983), divided visual field (Atchley, Ilardi, & Enloe, 2003; Atchley, Stringer, Mathias, Ilardi, & Minatrea, 2007), and electrocortical (Kestenbaum & Nelson, 1992) studies. In contrast, the valence model contends that the left dorsolateral prefrontal cortex (DLPFC) is involved to a greater extent in the processing of positively valenced emotions and approach-

related behaviors whereas the right DLPFC is more associated with negatively valenced emotions and withdrawal-related behaviors. Support for the valence model is provided by frontal lesioned patients (Gainotti, 1972), electroencephalography (EEG) (Davidson, 1992; Schaffer, Davidson, & Saron, 1983), functional neuroimaging (Dolcos, LaBar, & Cabeza, 2004; Pizzagalli, Shackman, & Davidson, 2003), and behavioral studies (Natale, Gur, & Gur, 1983; Smith & Bulman-Fleming, 2005). As reviewed below, hemispheric asymmetries have also been observed in depression-prone individuals and after administration of nicotine and other psychoactive drugs.

Substantial evidence suggests that depressive and anxious traits are correlated with reduced left (LH < RH) frontal EEG activation (Coan & Allen, 2004; Thibodeau, Jorgensen, & Kim, 2006) and reduced right (LH > RH) posterior parietal activation (Heller & Nitschke, 1997) that are associated with impairments in LVF perceptual processing (Heller, Etienne, & Miller, 1995). These similarities in individuals with depressive traits with those with anxious traits might be expected given the high comorbidity of anxiety and depression and the psychometric association of anxious and depressive traits under the general higher-order factor of neuroticism or negative affectivity (Costa & McCrae, 1992; Eysenck, 1980). Reductions in left frontal activity have been observed in both subclinically and clinically depressed, relative to nondepressed, individuals (Schaffer et al., 1983). Right parietotemporal deficits in depression have been reported in behavioral (Heller et al., 1995; Jaeger, Borod, & Peselow, 1987) and neurophysiological (Davidson, Chapman, Chapman, & Henriques, 1990; Kayser,

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Bruder, Tenke, Stewart, & Quitkin, 2000; Rabe, Debener, Brocke, & Beauducel, 2005) studies of perception. Therefore, depression is associated with both frontal affect-related and posterior perception-related asymmetries. Findings of brain asymmetries associated with state and trait anger are associated with greater left than right frontal activation (Harmon-Jones & Sigelman, 2001).

In divided visual field studies (Atchley et al., 2003, 2007), relative to nondepressed individuals, current and previously depressed individuals have increased accuracy for RH negative (compared to positive) words and nondepressed individuals have increased accuracy for RH positive words (compared to negative words). However, it is unclear whether the effects of depressive traits on hemispherically biased emotional information are moderated by nicotine, a drug with putative antidepressant and negative affect-reducing effects (Kalman, Morrisette, & George, 2005; Lerman et al., 1998; McClernon, Hiott, Westman, Rose, & Levin, 2006; Salin-Pascual, Rosas, Jimenez-Genchi, Rivera-Meza, & Delgado-Parra, 1996). As noted below, limited evidence and theory suggest that nicotine may alter asymmetries in emotional information processing.

The lateralized neural network (LNN) hypothesis of the Situation \times Trait Adaptive Response (STAR) model of nicotine's effects on emotional information processing (Gilbert & Welser, 1989) is based on many of the conceptualizations, findings, and proposals indicated by Tucker and Williamson (1984). The LNN model proposes that nicotine enhances left frontal-dominant positive affect-related and verbal information processing and reduces right frontal-dominant negative affect-related information processing, especially in individuals prone to negative affect (Gilbert, 1995). Although there are only a few explicit tests of the LNN, convergent support for this hypothesis comes from several sources (reviewed by Gilbert et al., 2005) including: (a) affect-related EEG asymmetries (reviewed above); (b) greater LH densities of cholinergic and dopaminergic receptors, that are directly modulated by nicotine (Glick, Ross, & Hough, 1982; Tucker & Williamson, 1984); (c) lateralized nicotinic and dopaminergic drug effects on response time and accuracy to stimuli presented to the LVF versus RVF (Gilbert et al., 2005; Hartley, Ireland, Arnold, & Spencer, 1991; McClernon, Gilbert, & Radtke, 2003); and (d) asymmetric emotion-related nicotinic neuromodulation (Gilbert, Robinson, Chamberlin, & Spielberger, 1989; Gilbert, McClernon et al., 2004; 2007; Rose et al., 2003). Given that smokers nearly universally report that one of their primary motivations for tobacco smoking is to reduce negative affect (Gilbert, Sharpe, Ramanaiah, Detwiler, & Anderson, 2000; Spielberger, 1986) and the lack of understanding when and how nicotine modulates affect (Kalman, 2002), it is important to gain further understanding of the basic mechanisms by which nicotine and nicotine withdrawal modulate affective information processing.

The most general assumption of the present study was that prime and target valences differentially influence emotional word identification in the LVF and RVF. Based on the above-reviewed evidence, it was assumed that emotionally positive words would be better recognized in the RVF and

emotionally negative words would be better recognized in the LVF, especially when primed with emotionally positive and negative words, respectively. Our primary hypotheses were that depressive traits and nicotine would moderate hemispheric asymmetries in the processing of emotional words. Based on the LNN model, it was hypothesized that nicotine would enhance LH-dominant positive affect-related information processing and thereby reciprocally inhibit RH-dominant negative affect-related information processing. Specifically, nicotine was expected to enhance the identification of words presented in the RVF, decrease the identification of words presented to the LVF, increase positive affect, and decrease negative affect. Additionally, depressive trait scores were expected to predict in a linear manner the effects of nicotine on LH enhancement of positive words and RH attenuation of negative words. More specifically, it was predicted that level of trait depression should be negatively correlated with LVF accuracy and positively correlated with RVF accuracy while on nicotine, but not placebo. Finally, nicotine was expected to enhance the effects of positive word primes and to decrease the effects of emotionally negative word primes. Gender was also included in analyses because some studies have found gender differences in response to nicotine (reviewed by Perkins, Donny, & Caggiula, 1999).

Method

Participants

Participants included in this report were 28 female (13 on oral contraceptives) and 33 male smokers with a mean age of 25.8 years (8.6 *SD*) who smoked an average of 17.1 (5.9 *SD*) cigarettes per day. Five were African American, three multiracial, and the remaining were White. Education level was as follows: (a) two some high school, (b) 13 high school, (c) 33 some college, eight 2-year college degree, one 4-year college degree, and four graduate degree completed. Slightly over half (33) were full-time students, three were part-time students, and 22 were not students. The average participants had a moderate score ($M = 4.05$, 2.0 *SD*) on the Fagerström Test of Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerström, 1991). Mean MMPI depression scale score was 18.76 ($SD = 4.22$) for men and 21.32 ($SD = 6.10$) for women, that correspond to *T* scores of 51 and 54, respectively using gender-based norms (Hathaway & McKinley, 1983). Participants earned monetary compensation for completion of the study.

Participants were recruited by ads throughout a Midwestern university community by local newspaper and university newspaper ads and by university and community wide postings. Exclusion criteria included smoking fewer than 10 cigarettes/day for the past year, smoking cigarettes with nicotine deliveries <0.6 mg/cigarette, reported use of psychoactive drugs (illicit or legal) or medications other than caffeine, marijuana, and alcohol, excessive alcohol use (30+ drinks/day), marijuana use more often than twice per 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 had breath CO concentrations of less than 10 ppm were included in data analyses.

Equipment and Materials

The experiment programmed in SuperLab 2.0 software (Cedrus, San Pedro, CA) was presented via a Pentium III PC with an LCD monitor. A Cedrus RB-530 response pad was used to record subject responses.

Questionnaires

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

Minnesota multiple personality inventory-2. The MMPI-2 (Hathaway & McKinley, 1983) is an empirically derived set of questionnaires designed to differentiate clinical from nonclinical disorders. In the present case, the MMPI2 depression scale was used as a measure of trait disposition toward depression and depressive affect. The MMPI-2 depression scale has been found to differentiate individuals with major depressive disorder from controls with good sensitivity and specificity (Bence, Sabourin, Luty, & Thackrey, 2006; Wetzler, Kahn, Strauman, & Dubro, 1989) and to predict increases in depressive symptoms (Gilbert et al., 1998, 2002) and hemispheric EEG asymmetries in response to smoking abstinence (Gilbert et al., 2004).

Positive and negative affectivity schedule (PANAS). The PANAS (Watson, Clark, & Tellegen, 1988) is a well-validated and widely used measure that consists of two subscales of 10 items each, one measuring positive and the other negative affect.

Procedure

Divided visual field semantic priming (DVFSP) Task. The DVFSP task was similar to that used by Atchley, Ilardi, and Enloe (2003) to characterize hemispheric processing advantages for positively and negatively valent words across visual field in depression. Each participant attended two experimental sessions (one nicotine and placebo), each with two experimental blocks of 144 prime-target trials, displayed on a computer screen at a distance of 150 cm (maintained by chinrest). All prime and target words were person-descriptive adjectives of positive valence (e.g., SMART, HAPPY, BRAVE) or negative valence (e.g., DIRTY, CRUEL, LAZY), adjectives and nouns were selected from sources of compiled valence norms from both clinical and nonclinical populations (Gotlib, McLachlan, & Katz, 1988; Siegle, 1995), and balanced for word length and production frequency (Kucera & Francis, 1967), as well as arousal intensity. Lateralized target words were offset by

pseudowords in the opposite visual field, which consisted of the same number of letters as the target words, but were not meaningful English words. Each trial consisted of a fixation cross, presented for 500 ms, followed by the centrally presented prime word displayed for 300 ms (followed by a 20 ms mask). A left/right lateralized target word (with a corresponding foveal eccentricity of 2.5 degrees from fixation to the inside letter of the word) and emotionally neutral pseudoword (in the opposite visual field with the same degree of eccentricity) were presented for 185 milliseconds, then masked for 20 milliseconds. Participants were allotted a maximum of 2,000 milliseconds to indicate the target valence with a response pad (see Figure 1). At the end of each block, participants completed the PANAS.

The DVFSP task examines the effects of lateralized affective processing as well as the effects of centrally presented affective stimuli priming stimuli on lateralized affective processing. In contrast, dot probe tests (e.g., MacLeod & Mathews, 1988) do not always assess attentional bias as a function of visual field, though they could easily be used to assess the effects of nicotine and other drugs on attentional bias to one visual field (and presumably hemisphere) relative to the other. Dot probe tasks typically are used to assess the extent to which peripheral emotional stimuli automatically facilitate the processing of neutral targets at congruent relative to incongruent spatial locations.

Orientation and experimental sessions. During an orientation session participants provided breath samples to verify habitual smoking (mean carbon monoxide concentration = 21.26, $SD = 8.52$) and completed a battery of questionnaires including the MMPI depression scale the FTND, measures of smoking history, life stress, and personality that are being used across a series of studies designed to assess relationships between these measures. Participants were verified for abstinence at the start of each session before receiving nicotine patch on one day and placebo patch on the other. The experimental sessions were separated by a minimum of 48 hours and a maximum (with a few exceptions) by 2 weeks. 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.

Patch administration. Patch administration was double-blind with placement on the upper arm of smokers about 4 hours before the beginning of the experimental sessions by an individual not involved in data collection. The nicotine patch was a 14 mg Nicoderm transdermal patch; the placebo patch was identical in appearance. Immediately before patch each application and again approximately 4 hours later, just before the onset of the experimental tasks, symptoms of illness or nicotine overdose were assessed with 11-point scales to assess "nausea," "sickness," and "dizziness." Six individuals were eliminated from study analysis because of nausea/illness scores in excess of "4."

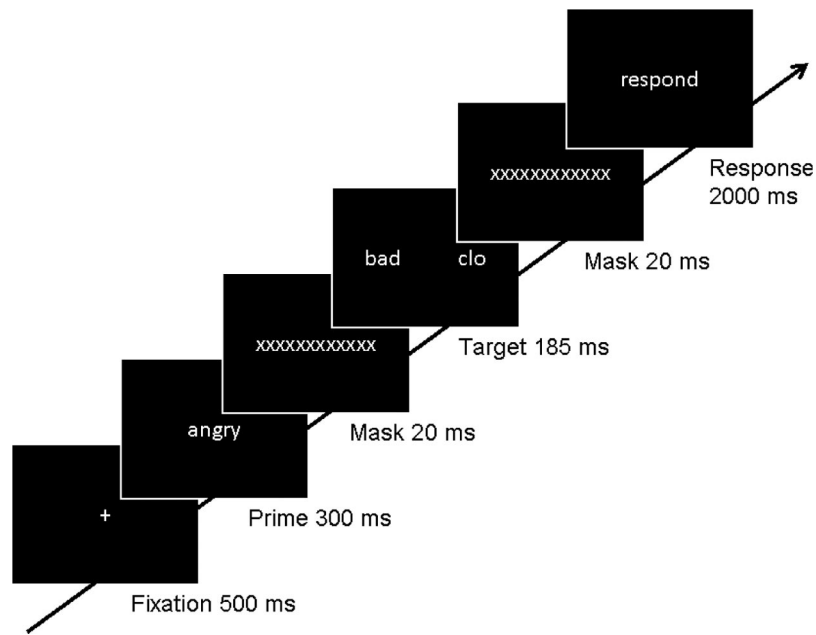


Figure 1. Each trial began with a central fixation cue followed by a positively or negatively valenced word prime (immediately masked). Positive and negative target words were presented to either the left or right side of the computer screen and paired with pseudowords on the opposite side of the display (immediately masked). Subjects responded to the valence of the target word.

Analytic Procedures

A mixed effects regression analysis including within subjects factors Patch Type (nicotine vs. placebo), Prime Valence (positive vs. negative), Target Valence (positive vs. negative), Visual Field (left vs. right), Block (first vs. second), and the between subjects factor Gender (male vs. female) was run on the dependent measure of accuracy. MMPI trait depression was used in a separate mixed effects analysis to test the hypothesis that depressive traits moderate the effects of nicotine on emotional priming and lateralized target detection. Where appropriate, Pearson correlational analyses are used to better characterize interactions with trait depression. History of clinical depressive disorder was not assessed and selection was not based on a criterion or cutoff score because the goal was to assess the potential moderating effects of the continuum of depressive disposition in the normal population using the full range of scores as a predictor. A mixed effects regression analysis was used instead of an analysis of variance design because regression analysis is a more powerful and appropriate analysis. Specifically, mixed regression analysis allows the use of the full range depression scores and thereby eliminated the loss of power associated that would have occurred had depression scores been dichotomized or trichotomized, as would have been required by an ANOVA.

Results

DVFSP Task Performance

There was a significant interaction between Patch Type and VF, $F(1, 1813) = 10.70, p = .001$. Follow-up post hoc

analyses indicated that, relative to placebo, nicotine enhanced target accuracy in the RVF (nicotine $M = 71.27$, placebo $M = 68.58, p < .05$) and decreased accuracy in the LVF (nicotine $M = 55.24$, placebo $M = 57.29, p < .05$, Figure 2). No other effects of Patch Type approached or reached significance. There were no significant interactions involving Gender with Patch Type.

There were several effects of VF and valence independent of Patch Type in the DVFSP. There was a main effect

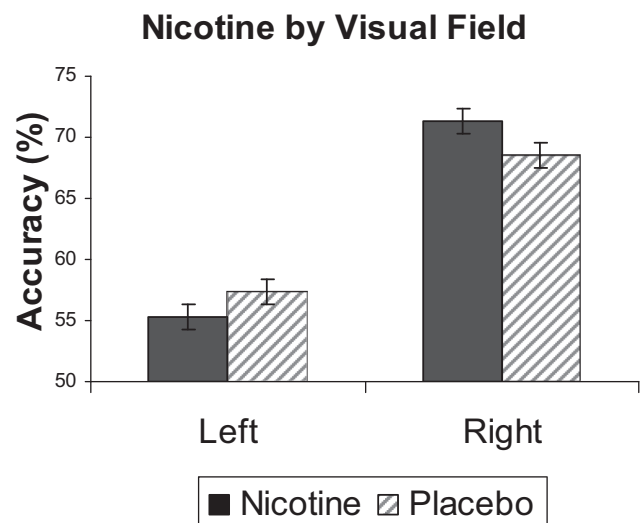


Figure 2. Nicotine, relative to placebo, decreased accuracy in the left visual field, but increased accuracy in the right visual field.

of VF, $F(1, 1813) = 356.07, p < .001$, where targets presented to the RVF ($M = 69.93\%$) had a higher percent correct than LVF targets ($M = 56.27\%$). There was an effect of Target Valence, $F(1, 1813) = 36.95, p < .001$, where positive targets ($M = 65.30\%$) were correctly identified more often than negative targets ($M = 60.89\%$). However, there was a Block by Target Valence interaction, $F(1, 1813) = 11.45, p < .001$, where positive targets (65.88%) were identified with greater accuracy than negative targets (59.03%) in Block 1, but accuracies for negative targets significantly improved from Block 1 to Block 2 (62.76%) and did not significantly differ from positive targets (64.71%) in Block 2. Prime Valence interacted with Target Valence, $F(1, 1813) = 29.37, p < .001$ and Target Valence interacted with VF, $F(1, 1813) = 120.61, p < .001$. Both of these interactions were subsumed and better explained by a three-way interaction including Prime Valence, Target Valence, and VF, $F(1, 57) = 6.44, p < .05$. The greatest accuracies were found for positive targets in the RVF preceded by positive primes ($M = 77.94\%$). On the other hand, in the LVF, negative primes followed by negative targets produced the highest percent correct ($M = 60.86\%$, see Figure 3).

Depressive traits moderated several effects. First, there was a Depression by VF interaction, $F(1, 1751) = 28.58, p < .001$, where accuracy for RVF targets was not influenced by Depression, but accuracy for LVF targets was negatively correlated with trait depression, $r = .28, p < .05$. Additionally, the predicted Patch Type by Depression by VF interaction approached significance, $F(1, 1751) = 3.40, p = .065$. Follow-up analyses of this interaction showed that nicotine, relative to placebo, decreased LVF accuracies progressively more as trait depression increased, $r = -.31, p < .05$. A Depression by Target Valence interaction approached significance, $F(1, 1751) = 3.31, p = .069$. Finally, a predicted Depression by Target Valence by VF interaction

approached significance, $F(1, 1751) = 3.69, p = .055$, where accuracies for LVF positive targets decreased as trait depression increased, $r = .30, p < .05$. Depression did not influence performance in any other conditions.

Effects of Nicotine on Positive and Negative Affect

A Patch Type by Block repeated measures ANOVA on positive affect revealed a main effect of patch type, $F(1, 60) = 9.22, p = .004$, where nicotine ($M = 34.92$) enhanced positive affect relative to placebo ($M = 30.51$). There were no other main or interaction effects. A Patch Type by Block repeated measures ANOVA on negative affect revealed a trend, $F(1, 60) = 3.58, p = .06$, for nicotine to decrease negative ($M = 7.59$) affect relative to placebo ($M = 8.88$). There were no significant interactions involving Gender with Patch Type.

Discussion

The present findings extend support for the lateralized processing of emotionally positive versus negative information and the moderation of these effects by depressive traits and nicotine. Consistent with the LNN model of nicotine's effects on emotional information processing (Gilbert & Welser, 1989), nicotine enhanced RVF and decreased LVF target accuracy, while increasing positive mood and decreasing negative mood. Thus, nicotine promoted a RH word-identification deficit similar to that observed in those with depressive traits. The discussion below first addresses the moderating effects of depressive traits, then the more general findings of lateralized target detection, and finally the effects of nicotine on lateralized target detection.

Effects of Depressive Traits

Consistent with a posterior RH deficit in depression (Heller & Nitschke, 1997) accuracy for LVF targets decreased as trait depression increased. Research suggests this posterior RH deficit in depression is associated with impairments in spatial processing (Rabe et al., 2005) mediated by posterior cortex. However, our results are consistent with other research suggesting a more general posterior deficit in those high in depression traits (Heller et al., 1995) that may co-occur with affect-related frontal asymmetries. That is, the general decrease in LVF performance in trait depression was coupled with a valence-specific deficit where individuals with high trait depression performed more poorly on positively valenced LVF stimuli than individuals low in trait depression. Therefore, instead of an increased sensitivity to negative stimuli there was a reduced sensitivity to positive stimuli in individuals with high levels of trait depression in the LVF/RH. Similarly, Atchley and colleagues (2007) found a LVF bias in never-depressed individuals for positive targets and a LVF bias in depressed individuals for negative targets. Thus, our finding replicates earlier findings (Atchley et al., 2003; Schaffer et al., 1983) that support the view that the RH is a substrate for depressive information processing and associated traits.

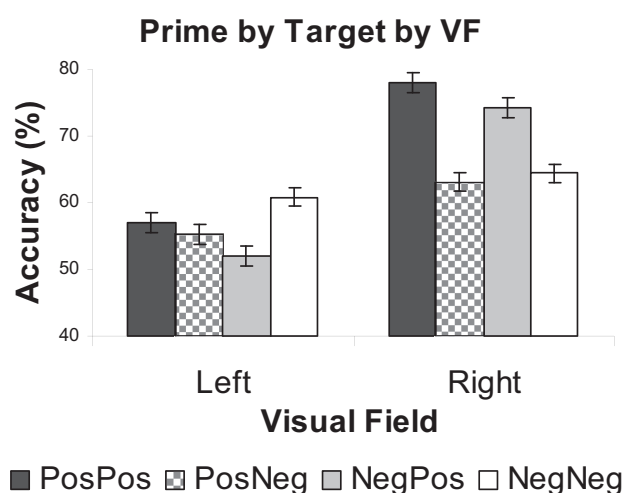


Figure 3. Positive primes followed by positive targets (PosPos) produced higher accuracies in the right visual field than all other prime and target combinations whereas negative primes followed by negative targets (NegNeg) produced higher accuracies in the left visual field than all other prime and target combinations.

Asymmetrical Emotional Word Processing

Positive word primes facilitated RVF positive word identification, whereas negative word primes facilitated LVF negative word identification independent of level of trait depressive traits. This prime valence by target valence by VF interaction is consistent with other research (e.g., Natale et al., 1983) suggesting that emotional valence is differentially processed in the two hemispheres. Given that the majority of research in support of the RH model has used pictorial emotional stimuli (Adolphs et al., 1996; Benowitz et al., 1983) it may be that the RH model is appropriate for certain types of visual stimuli. However, in the case of abstract emotional words, it appears that the valence model more appropriately explains this portion of our data.

Nicotine Effects

Overall, our results support the view that, in nicotine-deprived habitual smokers, nicotine enhances RVF/LH and decreases LVF/RH emotional information processing (word identification). These findings are consistent with the LNN model (Gilbert & Welsler, 1989) and the growing literature suggesting nicotine enhances RVF performance for abstract verbal and numeric visual stimuli (Gilbert et al., 2005; McClernon et al., 2003) in nicotine-deprived smokers. Nicotine also enhanced positive affect and tended to decrease negative affect.

Although it was expected that nicotine's lateralized effects would interact with prime and target valence, this was not found. The lack of valence effects could be because of the rapid display properties of the word stimuli. Previous research is consistent with the view that nicotine's effects on mood are most potent with temporally distal emotional events or stimuli (Gilbert et al., in press; and reviewed by Gilbert, 1995). Although rapid emotional word processing was not modulated by nicotine, posttask mood ratings were influenced by nicotine, which may represent a delayed affective response associated with nicotine asymmetries. These observed effects of nicotine on mood are consistent with nicotine's putative antidepressant effects (McClernon et al., 2006; Salin-Pascual et al., 1996).

The tendency of nicotine to produce a RH word-identification deficit similar to that observed in those with depressive traits is paradoxical because of nicotine's previously identified potential antidepressant effects and observed modulation of mood in the current study. However, given that (a) depression is associated with both a hyperactive right frontal and hypoactive right posterior cortex and that (b) nicotine appears to nonselectively decrease RH activity, a likely side effect of nicotine's potential antidepressant effects (which may be mediated by decreasing RH activity) would be additional decreased posterior RH processing and the associated perceptual deficits in highly depressed individuals. Indeed, there was a negative correlation between trait depression and LVF accuracy while participants were on nicotine, but not placebo patch. Thus, the potential antidepressant effects of nicotine associated with enhanced positive and decreased negative mood appear to be coupled

with a general RH perceptual deficit. In summary, the results provide further support for the notion that nicotine differentially affects hemispheric processing and associated behavior and affect. Specifically, nicotine appears to have an initial influence on perceptual encoding and a later influence on affective processing and mood (Gilbert, 1995).

Clinical and Theoretical Implications

There are a number of theoretical implications of the present findings that could eventually influence clinical interventions. First, the finding that nicotine enhanced processing of information presented to the LH while reducing that presented to the RH has implications for novel drug and behavioral treatments. Specifically, such treatments would be similar to nicotine replacement therapy (NRT) to the degree that they enhance LH information processing/activation and dampen relative RH information processing/activation. Evidence (reviewed by Gilbert, 1995; and by Gilbert et al., 2005) suggests that dopaminergic and cholinergic functioning may be relatively more left than right lateralized in the brain. Similarly, the tendency of nicotine in the present study to both increase LH function and to decrease RH functioning suggests that behavioral interventions should be targeted to both increase LH-dominant processing (approach behavior, positive affect, and long-term goal orientation) and to decrease RH-dominant functioning (avoidance behavior, negative affect, impulsivity, and discounting of long-term rewards).

Study Limitations and Future Directions

Limitations of the present investigation are important to consider. The sample size was relatively modest, was relatively young and was limited to tobacco smokers. It is not clear what the observed effects of NRT would be on younger smokers and in individuals who are not yet dependent. Similarly, it is not clear what the effects of NRT are in older smokers, who are an understudied population. Furthermore, although gender differences were not found for the effects of nicotine or other variables, our sample was of only modest size and was not adequate to characterize potential effects of menstrual cycle and oral contraceptive use. Additionally, although MMPI depression scores are elevated in those with major depressive disorder, formal psychiatric disorders were not assessed and, because of our limited sample size, the relationships of the dependent measures to anxiety or other forms of negative affect were not assessed. Although it is possible to argue that the effect sizes of nicotine on mood and LH versus RH word processing were only modest, these effects could have clinical importance, as suggested by the demonstrated efficacy of NRT in promoting smoking abstinence.

Importantly, it is not clear whether the effects of nicotine in the present study reflect absolute effects or only the alleviation of withdrawal effects in nicotine-deprived smokers. Future studies in this area would benefit from larger samples that would allow the assessment of modulatory effects of additional individual difference variables. Finally, nicotine administration

by patch has different pharmacokinetics than that of tobacco smoking. Thus, replications with acute smoking studies are needed.

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