The relationship between reward-based learning and nicotine dependence in smokers with schizophrenia

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1. Introduction

Estimates indicate that 70–85% of individuals with schizophrenia are cigarette smokers (Lasser et al., 2000; de Leon and Diaz, 2005; Workgroup on Substance Use Disorders, 2006). These psychiatric smokers remain difficult to treat (McChargue et al., 2002; Williams and Ziedonis, 2004), with quit rates consistently lower in smokers with schizophrenia than in non-psychiatric control smokers (George et al., 2008; Fagerström and Aubin, 2009). However, it is unclear what etiological mechanisms may underlie the common co-occurrence of nicotine dependence and schizophrenia. Anhedonia, defined as decreased reactivity to pleasurable stimuli or diminished pleasure in daily activities, has been linked to cigarette smoking. Increased levels of anhedonia are reported among cigarette smokers and are considered to be a risk factor for smoking relapse among psychiatric patients (Leventhal et al., 2008, 2009; Cook et al., 2010). In fact, smokers with increased rates of anhedonia and low positive affect report increased craving to smoke and are a high priority group for smoking cessation interventions (Ameringer and Leventhal, 2010).

In schizophrenia, anhedonia is a well-established clinical phenomenon that has been described throughout historical conceptualizations of the illness (Chapman et al., 1976; Wolf, 2006). Over the last twenty years, research has advanced our understanding of the nature of anhedonia and blunted positive emotional reactivity among individuals with schizophrenia (Kring, 1999; Kring and Caponigro, 2011). Findings in this area suggest that individuals with schizophrenia are impaired in their expression of positive emotion, but report normative subjective experience of emotion in response to pleasurable stimuli (e.g., Kring, 1999).

More recent research has highlighted differences between expected versus experienced pleasure in our understanding of anhedonia in schizophrenia. Cumulatively, findings support decreased anticipation of pleasure (i.e., anticipatory pleasure) and normative experience of positive emotion during exposure to pleasurable stimuli (i.e., consummatory pleasure; Gard et al., 2007; Cohen and...
Minor, 2010). However, one recent study suggested that consummatory pleasure may also be compromised in this population (Strauss et al., 2011). Unique neurobiological processes are thought to underlie anticipatory and consummatory pleasure, with nucleus accumbens activation linked to anticipatory, but not consummatory, processes in nonpsychiatric groups (Knutson et al., 2001; Berridge and Robinson, 2003). Impairments in anticipatory pleasure have been specifically associated with anhedonia and functional impairment in schizophrenia (Gard et al., 2007). Related research also has highlighted an inability to maintain positive emotion and failure to translate this emotion into adaptive behavior as key features of anhedonia in this disorder (e.g., Kring and Werner, 2004; Heerey et al., 2008).

Building on findings characterizing the nature of anhedonia in schizophrenia, recent research suggests that reward system dysfunction contributes to reduced hedonic capacity in this population (e.g., Pizzagalli et al., 2005; Dillon et al., 2008; Gold et al., 2008). Behavioral and biological indices of reward system dysfunction have been associated with anhedonic symptoms in schizophrenia and related disorders (Simon et al., 2010). A critical component of reward system functioning is the ability to engage in reward-based learning (e.g., the ability to learn associations between neutral and unconditioned rewarding stimuli and to produce behavioral change via positive reinforcement). Recent research examining the acquisition of reward-based learning in schizophrenia has generated debate about the presence and nature of acquisition deficits (e.g., Waltz et al., 2007; Heerey et al., 2008). Within this limited literature, several studies show impairments in acquisition of reinforcement learning in this group (Waltz et al., 2007; Gold et al., 2008; Murray et al., 2008; Weiler et al., 2009). However, two recent investigations have found no differences in the acquisition of reward-based learning in schizophrenia as compared to non-psychiatric controls (Heerey et al., 2008; Herbener, 2009). Preliminary research examining reward learning in schizophrenia has also shown deficits in reversal learning (Murray et al., 2008; Weiler et al., 2009) and more rapid decay of reward-based memory (Herbener, 2009). Impairments in reward-based learning may be an important etiological mechanism contributing to the experience of anhedonia in schizophrenia. However, the form and function of these deficits in schizophrenia remain unclear, and little is known about the relationship between reward-based learning and nicotine use in this population.

Preclinical and clinical research have established nicotine as a pharmacological agent that directly affects reward-based learning (Kenny and Markou, 2006; Barr et al., 2008). Acute administration of nicotine has been associated with increased responsiveness to non-drug reward, whereas withdrawal has been associated with insensitivity to reward (Epping-Jordan et al., 1998; Kenny and Markou, 2006). For example, among healthy nonsmokers, a single dose of nicotine was found to enhance the acquisition of reward-based learning (Barr et al., 2008). This study used a computerized signal-detection task assessing change in behavior in response to differential monetary rewards. The study included participants who were smokers with schizophrenia (SWS), nonsmokers with schizophrenia (NCL), and healthy nonsmokers (NCL). Nicotine withdrawal was assessed using the Minnesota Nicotine Withdrawal Scale (MNWS) (Hughes and Hatsukami, 1986). The following baseline biological assessments were performed: a breath test for recent alcohol use (AlcoMate Prestige Al6000) and for expired breath carbon monoxide (CO) level (Micro 4 Smokerlyzer). On the second day, participants completed a 30-minute computerized signal detection task on a Dell Optiplex 760 computer using E-Prime software (version 2.0; see Pizzagalli et al., 2005 for a full description of the task). This signal detection task provides an objective characterization of reward responsiveness and is designed to measure shift in responding toward a differentially more frequently rewarded stimulus. Participants are instructed to win as much money as possible by identifying, in each trial, which of two stimuli (short or long mouth) is presented on a cartoon face. To allow for the emergence of a response bias, the short (11.5 mm) and long (13 mm) mouth were perceptually similar and presented very briefly (100 ms); more critically, correct identification of one stimulus was rewarded three times more frequently (n = 30/block) than correct identification of the other stimulus (n = 10/block). The stimulus reinforced more frequently was defined as the “rich” stimulus, whereas the less reinforced stimulus was referred to as the “lean” stimulus. The

### Table 1

Demographic, smoking and clinical variables of smokers with schizophrenia (SWS) and control smokers (NCL).  

<table>
<thead>
<tr>
<th></th>
<th>SWS (n = 15)</th>
<th>NCL (n = 16)</th>
<th>SWS vs. NCL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>S.D.</td>
<td>M</td>
</tr>
<tr>
<td>Age</td>
<td>54.87</td>
<td>6.51</td>
<td>50.38</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>100%</td>
<td>NA</td>
<td>93.8%</td>
</tr>
<tr>
<td>Education</td>
<td>53.3%</td>
<td>NA</td>
<td>31.3%</td>
</tr>
<tr>
<td>Race (% partial college)</td>
<td>80.0%</td>
<td>NA</td>
<td>50.0%</td>
</tr>
<tr>
<td>Marital status</td>
<td>60.0%</td>
<td>NA</td>
<td>37.5%</td>
</tr>
<tr>
<td>Employment (% unemployed)</td>
<td>80.0%</td>
<td>NA</td>
<td>37.5%</td>
</tr>
<tr>
<td>FTND</td>
<td>4.67</td>
<td>2.06</td>
<td>4.38</td>
</tr>
<tr>
<td>Number of cigarettes/day</td>
<td>28.67</td>
<td>16.98</td>
<td>15.81</td>
</tr>
<tr>
<td>QSU-Brief Total (baseline)</td>
<td>3.25</td>
<td>1.56</td>
<td>2.03</td>
</tr>
<tr>
<td>MNWS Total (baseline)</td>
<td>10.08</td>
<td>7.11</td>
<td>4.59</td>
</tr>
<tr>
<td>CO level (baseline)</td>
<td>18.63</td>
<td>7.57</td>
<td>12.59</td>
</tr>
<tr>
<td>BDI-II Total</td>
<td>10.93</td>
<td>8.52</td>
<td>3.93</td>
</tr>
<tr>
<td>PANSS positive symptoms</td>
<td>17.67</td>
<td>6.33</td>
<td>N/A</td>
</tr>
<tr>
<td>PANSS negative symptoms</td>
<td>11.80</td>
<td>4.93</td>
<td>N/A</td>
</tr>
<tr>
<td>PANSS general symptoms</td>
<td>28.47</td>
<td>7.15</td>
<td>N/A</td>
</tr>
<tr>
<td>BPRS Total</td>
<td>35.07</td>
<td>8.96</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Note: SWS = smokers with schizophrenia; NCL = non-psychiatric controls; FTND = Fagerström Test for Nicotine Dependence (Heatherton et al., 1991); QSU = Questionnaire on Smoking Urges — Brief Form (Cox et al., 2001); MNWS = Minnesota Nicotine Withdrawal Scale (Hughes and Hatsukami, 1986); CO = carbon monoxide; BDI-II = Beck Depression Inventory-II (Beck et al., 1996); PANSS = Positive and Negative Syndrome Scale (Kay et al., 1986); BPRS = Brief Psychiatric Rating Scale (Overall and Gorham, 1962).
stimulus (short or long mouth) selected for the “rich” stimulus was counterbalanced within participant groups. After two practice trials designed to ensure task comprehension, a total of 200 trials across two 100-trial blocks (Block 1, Block 2) were completed. All participants were told they could earn up to $6 for completion of this task, depending on performance. Participants were permitted to smoke ad lib during circumscribed time periods throughout the two study visits. Breath tests for recent alcohol use and for expired breath carbon monoxide (CO) level were performed prior to the task. breathed breath was used to examine between group differences in smoking variables in the SWS group. A Mann–Whitney U test was performed to examine between group differences in cigarettes per day. Mixed-model repeated measures ANOVAs with two within-subject factors of Stimulus (rich, lean) and Block (Block 1, Block 2) and one between-subject factor of Group (SWS, NCL) were performed on measures of accuracy and reaction time. For response bias and discriminability, mixed-model repeated measures ANOVAs with Block and Group as factors were performed. ANOVA was utilized to examine group differences in response bias across blocks as this statistical test is considered to be robust to violations of normality. A one-way ANOVA test was performed to examine group differences on reward learning.

3. Results

3.1. Demographic and smoking variables

In the final sample (N=31), SWS (n=15) and NCL (n=16) groups were matched with respect to demographics, with the exception of employment (SWS were more likely to be unemployed; see Table 1). Consistent with the literature (e.g., Williams et al., 2007), SWS exhibited differences in smoking variables. Although the SWS group did not differ from the NCL group on a standard measure of nicotine dependence (FTND), SWS demonstrated higher baseline CO and reported smoking greater numbers of cigarettes per day compared with NCLs. In addition, SWS exhibited greater nonstatin urge to smoke (QUIS-brief) and withdrawal symptoms (MNWS) compared with NCL participants (p’s<0.05).

3.2. Signal detection task manipulation

3.2.1. Response bias

There were no significant main effects of Block or Group on response bias (F’s<1.4, p’s>0.25); similarly, the interaction was not significant (F(1, 29) = 0.001, p>0.07). Mean response bias (averaged across blocks) did not differ between SWS (M=0.16, S.D.=0.19) and NCL (M=0.08, S.D.=0.20) groups (all p>0.10).

3.2.2. Discriminability

There were no significant main effects of Block or Group or the interaction between variables on discriminability, indicating no difference in the ability of the SWS (M=0.50, S.D.=0.29) and NCL (M=0.57, S.D.=0.29) groups to differentiate between the rich and lean stimuli (all p>0.10).

3.2.3. Reaction time

Across SWS and NCL groups, a trend main effect of Block indicated faster RT on trials in Block 2 (M=607.76 ms, S.D.=162.91) compared with Block 1 (M=640.91 ms, S.D.=182.52), F(1, 29) = 4.01, p = 0.06. A main effect of Stimulus indicated that RT was significantly faster to rich (M=606.83 ms, S.D.=165.38), versus lean, stimuli (M=641.85 ms, S.D.=173.30), F(1, 29) = 10.71, p = 0.003. No differences were found between groups or for interactions among variables. Differences in RT during the task in the SWS (M=676.13 ms, S.D.=239.59) and NCL (M=572.55 ms, S.D.=231.98) groups were also not statistically significant (p = 0.09).

3.2.4. Hit rate

The main effect of Stimulus was significant, F(1, 29) = 18.85, p<0.001, due to the fact that, as expected, rich stimuli were more correctly identified (79.9%) compared with lean stimuli (69.4%). A trend interaction of Group × Block emerged (F(1, 29) = 2.91, p = 0.10), due to a decline in hit rate between Block 1 and 2 within the SWS group (75.3% vs. 72.0%), but an increase in hit rates in the NCL group (74.6% vs. 76.6%). There were no significant main effects of Block, Group or other interactions. SWS (73.6%) and NCL (75.6%) groups were similar in their mean accuracy rates averaged across the two blocks (p = 0.62).

3.2.5. Reward learning

SWS (M = 0.03, S.D. = 0.10) and NCL (M = 0.02, S.D. = 0.21) groups demonstrated similar patterns of change in response bias between Block 1 and Block 2 (p = 0.42).

3.3. Reward-based learning and cigarette smoking

As mentioned above, initial data screening showed that response bias (Block 1, Block 2 and total) was significantly positively skewed and leptokurtic within the SWS group. As a result, nonparametric statistics (Spearman rank-order correlations) were calculated for all relationships between response bias (Block 1, Block 2, and total) and variables of interest within this sample. In the SWS group, increased nicotine dependence (FTND score) was correlated with decreased response bias toward the reinforced stimulus (rich stimulus) during Block 1, r(12) = −0.66, p = 0.02, and for total response bias across the task (Block 1 + 2; see Fig. 1A), r(12) = −0.59, p = 0.05, with a trend noted for the relationship between nicotine dependence and response bias during Block 2, r(12) = −0.50, p = 0.10. This relationship was not evident in the NCL sample (all p values >0.54). Average
number of cigarettes smoked per day was not significantly correlated with response bias indices in either the SWS or NCL groups. In addition, reward learning was negatively associated with CO level in SWS (see Fig. 1B), \( r(15) = -0.54, p = 0.04 \), but not NCL (\( p = 0.47 \)).

3.4. Anhedonia and cigarette smoking

Clinician-administered and self-report measures of anhedonia/affective blunting were related to increased smoking behavior among SWS, but not control, subjects. Specifically, in SWS, baseline nicotine withdrawal (as assessed by the MNWS) was positively correlated with blunted affect as measured by the PANSS, \( r(13) = 0.60, p = 0.03 \). Similarly, SWS urge to smoke was positively associated with loss of pleasure/anhedonia on the BDI-II, \( r(15) = 0.60, p = 0.02 \). These relationships were not demonstrated in the NCL group.

4. Discussion

Results from this study identified a pattern of reward-based learning that was directly linked to biochemical and behavioral measures of cigarette smoking among SWS. Using a laboratory-based probabilistic reward task, we found that reduced acquisition of reward-based learning in SWS was related to increased levels of nicotine dependence, as assessed by the FTND. The relationship between nicotine dependence and reward-based learning was evident within Block 1 and across the total task, with a trend suggesting a similar relationship in Block 2. In addition, SWS smokers’ impaired learning (i.e., poorer reward learning throughout the course of the task) was related to increased levels of expired CO. Finally, self-report and clinician-rated measures of anhedonia (e.g., BDI-II loss of pleasure, PANSS blunted affect) were significantly associated with proxy measures of increased nicotine dependence (e.g., QSU-brief, MNWS) in SWS. These results emerge from multimodal assessments of anhedonia/reward-based learning and smoking behavior. Findings support the presence of a relationship between anhedonia/reward-based learning impairments and nicotine use in schizophrenia. Importantly, these relationships among smoking variables, performance on the signal detection task, and anhedonia were absent in NCL smokers. Such findings indicate that impairments in reward learning may nor be similarly related to cigarette smoking in smokers within the general population.

The current findings suggest that anhedonia and deficits in the acquisition of reward-based learning may contribute to the severity of nicotine dependence in SWS. Of note, these results were found using a well-validated measure of nicotine dependence, the FTND (Heatherton et al., 1991). However, data did not demonstrate similar relationships between self-report of average number of cigarettes smoked per day and reward-based learning in SWS. Importantly, our significant findings were based on the FTND which is a stronger assessment tool with established psychometric validity and broader-based measurement of nicotine dependence.

Significant associations between related measures of nicotine dependence and anhedonic symptoms support the presence of a relationship between reward system impairment and nicotine use in schizophrenia. Specifically, greater reported withdrawal symptoms and urge to smoke were related to increased severity of clinician-assessed blunted affect and self-reported anhedonia in SWS. Our findings are consistent with literature indicating that cigarette smoking and relapse to smoking may be more directly associated with blunted hedonic responses and reward system dysfunction in psychiatric smokers (Leventhal et al., 2008, 2009; Cook et al., 2010). This study extends these findings to individuals with schizophrenia.

The empirical evidence emerging from this study supports the conceptualization that SWS who are heavier smokers may utilize nicotine within cigarettes to ameliorate existing deficits in reward-based learning and responsivity. The degree of heavy smoking in schizophrenia patients may represent a marker of illness severity, particularly in terms of reward processing and negative symptoms (i.e., blunted affect as measured by the PANSS and loss of pleasure/anhedonia as measured on the BDI-II). Given the demonstrated pharmacological properties of nicotine among animal and nonpsychiatric human subjects (i.e., nicotine functions to increase the reinforcing properties of environmental stimuli; Kenny and Markou, 2006; Barr et al., 2008), SWS may engage in this drug-use behavior as a means of improving reward-based learning. Consistent with this idea, SWS who are less dependent on nicotine demonstrate increased hedonic capacity (based on multimodal assessments of anhedonia and nicotine dependence) and thus may be less reliant on nicotine for enhancement of reward system functioning. However, future studies are needed to replicate findings from the existing study and further evaluate this interpretation, including examination of how nicotine withdrawal may affect reward-based learning in SWS.

Contrary to our initial hypothesis, no significant differences emerged between groups on measures of acquisition of reward-based learning (i.e., response bias). The absence of significant group differences could be the result of the small sample size and restricted power in this pilot study. Alternatively, the use of two smoking groups and the potentially powerful effects of nicotine use on reward-based learning may mask the presence of any reward-based learning deficits intrinsic to the disorder of schizophrenia (e.g., Barr et al., 2008). Lastly, individuals with schizophrenia, irrespective of their nicotine use, may not have deficits in the acquisition of reward-based learning (e.g., Heer ey et al., 2008). Findings from the current study are consistent with two other studies that found no differences in the acquisition of reward-based learning between individuals with schizophrenia and non-psychiatric control participants (Heer ey et al., 2008; Herbener, 2009). However, other studies support the presence of acquisition deficits in schizophrenia (Waltz et al., 2007; Gold et al., 2008; Murray et al., 2008; Weiler et al., 2009). Importantly, few of these studies have assessed and controlled for co-occurring nicotine dependence in their examination of reward-based learning in schizophrenia (e.g., Heer ey et al., 2008; Weiler et
al., 2009). Rates of smoking are extremely high among individuals with schizophrenia (e.g., 70–85%; de Leon and Diaz, 2005; Workgroup on Substance Use Disorders, 2006), and failure to evaluate the role of co-occurring nicotine use in research examining reward-based learning in schizophrenia may be central to the conflicting debate about these deficits. Thus, the current investigation is among the first to attempt to elucidate the relationship between reward learning and co-occurring nicotine dependence in this group. A number of methodological limitations of this study should be noted. First, the sample size is limited, and replication of these results is needed with larger samples. In addition, although consistent with smoking rates in this population, SWS smokers exhibited differences when compared to NCL smokers in various smoking and clinical characteristics (e.g., cigarettes/day, baseline CO level, withdrawal and depressed mood). Due to sample size restrictions, we were unable to control for depression in analyses examining relationships between reward learning and nicotine dependence. Thus, co-occurring depression cannot be eliminated as a potential third variable that could account for observed relationships between reward learning and smoking behavior in SWS. Despite these limitations, this study is among the first to investigate the relationships among reward system functioning, anhedonia, and smoking in individuals with schizophrenia. Findings indicate unique associations between nicotine dependence and reward-based learning deficits in SWS smokers that were not evident in NCL smokers. Future studies are needed to replicate and extend these findings in SWS and to continue to determine the mechanisms that might explain high rates of smoking among these psychiatrically ill individuals. Future development of a conceptual model to more clearly delineate causal relations among reward-based learning, anhedonia, and nicotine dependence in smokers with schizophrenia will improve current and future smoking cessation treatments in this population.

Acknowledgment

This study was supported by a VA Center Grant (Co-PIs: Kaplan, Gulliver). During this project, Dr. Pizzagalli was partially supported by NIMH grants (R01 MH68376, R21 MH78979), Dr. Levitt was partially supported by a VA Merit Award, and Dr. Liverant was partially supported by a VA Career Development Award. The authors wish to acknowledge Casey Pabian and Virginia Davis CNS for their assistance in recruiting participants for this study. The authors also acknowledge the administrative support of Marie Fairbanks. All participants who volunteered for this research study are thanked for their important contributions to the study.

Dr. Pizzagalli is the inventor of the software program used in this study. In the past three years, Dr. Pizzagalli received research support and consulting fees from Advanced Neuro Technology (ANT) and honoraria and consulting fees from AstraZeneca for studies unrelated to the current project. All other authors declare no conflicts of interest.

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