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Functional network connectivity predicts treatment outcome during treatment of nicotine use disorder

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ABSTRACT

Altered resting state functional connectivity (rsFC) and functional network connectivity (FNC), which is a measure of coherence between brain networks, may be associated with nicotine use disorder (NUD). We hypothesized that higher connectivity between insula and 1) dorsal anterior cingulate cortex (dACC) and 2) dorsolateral prefrontal cortex (dlPFC) would predict better treatment outcomes. We also performed an exploratory analysis of the associations between FNC values between additional key frontal and striatal regions and treatment outcomes. One hundred and forty four individuals with NUD underwent a resting state session during functional MRI prior to randomization to treatment with varenicline (n = 82) or placebo. Group independent component analysis (ICA) was utilized to extract individual subject components and time series from intrinsic connectivity networks in aforementioned regions, and FNC between all possible pairs were calculated. Higher FNC between insula and dACC (rho = 0.21) was significantly correlated with lower levels of baseline smoking quantity but did not predict treatment outcome upon controlling for baseline smoking. Higher FNC between putamen and dACC, caudate and dACC, and caudate and dlPFC significantly predicted worse treatment outcome in participants reporting high subjective withdrawal before the scan. FNC between key regions hold promise as biomarkers to predict outcome in NUD.

1. Introduction

Nicotine use disorder (NUD) is a major public health problem, and relapse rates remain high for individuals undergoing treatment; the vast majority relapse by 6 months (Richmond and Kehoe, 2007). Finding reliable markers of relapse vulnerability has the potential to improve treatment outcomes; it could both identify individuals who require higher treatment intensity (Leventhal et al., 2012) and improve treatment-matching efforts (Mann et al., 2014).

Functional neuroimaging can be used to measure the coherence in blood oxygen dependent (BOLD) signal during resting state between brain regions (resting state connectivity; rsFC) or networks (functional network connectivity; FNC). These measures have potential to be useful biomarkers of NUD severity and relapse risk (Fedota and Stein, 2015; Sutherland et al., 2012). In particular, networks such as the default mode network (DMN), executive control network (ECN), and salience network (SN) (Fedota and Stein, 2015), and regions within these networks including the rostral anterior cingulate cortex (rACC), ventromedial prefrontal cortex (vmPFC), precuneus and posterior cingulate cortex (PCC) (DMN), dorsolateral prefrontal cortex (dlPFC) and lateral parietal cortex (ECN), insula and dorsal anterior cingulate cortex (dACC)/dorsomedial prefrontal cortex (dmPFC) (SN), and caudate and putamen (striatum) are likely related to NUD severity and outcome during treatment (Fedota and Stein, 2015). RsFC and FNC would be feasible to obtain in clinical settings compared to other functional neuroimaging measures (i.e., task-based measures), given the ease of acquisition for resting state data, and thus lower cost (Fedota and Stein, 2015). More robust outcome predictors are needed as, so far, few self-report measures have proven to be reliable. For example, even self-reported nicotine dependence severity shows inconsistent predictive value (Berlin et al., 2016; McPherson et al., 2014), and recent work in the same subject sample examined in the present manuscript found that a variety of predictors previously identified (mood, impulsiveness, age) were not predictive of treatment outcome (Wilcox et al., 2017).

RsFC is altered in individuals with NUD. Although one study showed greater rsFC between fronto-parietal cortex and medial

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(mPFC) in smokers compared to controls (Janes et al., 2012), most studies demonstrate reduced rsFC (Bi et al., 2016; Fedota et al., 2016, 2015; Fedota and Stein, 2015; Zanchi et al., 2015) or more negative rsFC (anti-correlation, negative coupling) between prefrontal cortical, cingulate, insular, and striatal regions in smokers relative to controls or in individuals with more severe dependence compared to those with less severe dependence (Stoeckel et al., 2016; Yuan et al., 2016). In line with the growing evidence that low rsFC between many of these key regions is a marker of the presence of NUD and/or the degree of dependence severity, high rsFC, especially between insula and dmPFC (Addicott et al., 2015; Janes et al., 2010) or dACC (Janes et al., 2010), and between insula and dlPFC (Janes et al., 2010) predicts better outcomes during treatment. Additionally, increases in connectivity between ventral striatum and PFC/ACC (Sweitzer et al., 2016) over 24 h of abstinence also predicts better later outcomes during treatment, whereas decreases with abstinence predicts worse outcomes.

Varenicline is an established treatment for NUD (Hartmann-Boyce et al., 2014), and its efficacy is likely mediated, in part, by reductions in craving (Ashare et al., 2012; Hajek et al., 2011; Hitsman et al., 2013), although this has not been observed in all studies of varenicline (Jhanjee et al., 2015). Investigations into the effects of varenicline on withdrawal have been even more mixed with some showing improvements in withdrawal (Hitsman et al., 2013) and others not (Brandon et al., 2011; Jhanjee et al., 2015). Finally, there is some evidence to suggest that varenicline may be acting via improvements in inhibitory control and attention (and thus impulsiveness) as well (Austin et al., 2014; Rhodes et al., 2012). Varenicline has been observed to decrease connectivity between insula and rACC, parahippocampus, dACC, PCC (Sutherland et al., 2013a) but to what degree these changes in rsFC are related to improving craving, withdrawal or treatment outcomes is not known.

In this study, we chose to do an exploratory analysis in a dataset of 144 individuals who were randomized to varenicline or placebo, and who also underwent a baseline resting state scan. Six small-sized *a priori* networks (the word “networks” will hereafter be used interchangeably with “regions”) which fell primarily on 6 key brain regions [caudate and putamen (striatum), dlPFC (ECN), rACC (DMN), dACC and insula (SN)] were selected for this study based on the preceding literature review establishing the likely importance of rsFC between striatum ECN, DMN, and SN (Fedota and Stein, 2015; Lerman et al., 2014; Sutherland et al., 2012) in NUD severity. We chose an approach which could be replicated using pre-existing templates that are downloadable (Allen et al., 2014) (http://mialab.mrn.org/data/index.html) and measured FNC between all possible pairs of these 6 apriori regions (15 pairs). Our overall goal was to investigate the degree to which FNC values could serve as clinically-relevant biomarkers of disorder severity. We had 2 primary aims: 1) To investigate whether higher FNC between insula-dACC and insula-dlPFC was associated with better treatment outcomes, in support of previous literature (Addicott et al., 2015; Janes et al., 2010) 2) To explore whether FNC between 6 a priori regions could predict treatment outcomes in general, or differentially on varenicline versus placebo. We hoped these findings would further clarify the mixed results in the literature and lead us to identify clinically relevant markers of nicotine dependence severity.

2. Methods

2.1. Subjects

Subjects were treatment-seeking cigarette smokers between the ages of 18 and 55 recruited through newspapers and flyers and enrolled in a randomized, double-blind, placebo-controlled trial of varenicline. Inclusion criteria were that individuals smoke at least 10 cigarettes per day and that they had not previously taken varenicline. Participants were excluded if they were currently pregnant/nursing, used illicit drugs (excluding marijuana) in the past 60 days (confirmed by urine toxicology screen), had serious health concerns (cardiovascular disease, uncontrolled hypertension, had hepatic or renal disease, diabetes), or if they met DSM-IV criteria for psychotic, bipolar, or major depressive disorder in the past year. 205 individuals were treated for 12 weeks and, of these, 144 underwent a 6-min resting state scan prior to initiation of medications (male $n=91$; varenicline $n=82$), and their data were used for the analyses that follow.

2.2. Clinical trial design

Consistent with previous trials (Gonzales et al., 2006) patients were titrated on varenicline to 1 mg twice daily by day 7. All participants received a 30 min baseline motivational enhancement session and brief (10 min) counseling visits with their assigned therapist at each assessment (2, 6, 12 weeks) (Littlewood et al., submitted for publication). A target quit date was set for day 8. The manuscript summarizing clinical results is currently under review (Littlewood et al.), and results show that varenicline-treated participants were three times more likely to achieve prolonged abstinence compared to placebo.

Although abstinence is commonly used as a measure of success in smoking cessation trials, rates of complete abstinence were low in the placebo group ($n=3$ at 12 weeks for 30 day point prevalence), rendering logistic regression problematic as a method of analysis for measuring the interaction term (FNC*TrGrp), given small sample bias (King and Zeng, 2001). We therefore chose a continuous variable for our primary outcome measure which was a value for the total number of cigarettes smoked (NumCig) in the previous 28 days at the 6 week visit, and in the previous 30 days at the 12 week visit. NumCig at the screen visit for the previous 60 days (NumCig at Screen) was also calculated and used as the baseline smoking variable. Including NumCig at Screen as a predictor is analogous to (and the method often preferred over) predicting a change score (Vickers and Altman, 2001).

For the primary analyses (NumCig), missing data for outcomes (dropouts) were imputed to an adjusted screen visit value [e.g. (NumCig at screen visit)*28/60 = NumCig at 6 weeks; dropout numbers: $n=29$ (15 varenicline)/144 by week 6 and 45 (24 varenicline)/144 by week 12] (Table 4). Imputing to baseline is a common approach for smoking cessation clinical trials (Ebbert et al., 2015; Higgins et al., 2008) even when rates of dropout approach ours. We also ran all analyses in the subgroup of subjects with complete data ($n=99$) who followed up at week 12, not using imputed outcomes (Table 5).

2.3. Measures

Withdrawal was measured with the Wisconsin Smoking Withdrawal Scale (WSWS) (Welsch et al., 1999) and craving with the Questionnaire of Smoking Urges (QSU) (Cox et al., 2001) 15–30 min prior to the scan. Participants were asked to be abstinent for 2 h prior to the scan visit (there were only 8 participants who did not report being abstinent 2 h prior to the scan). All participants were asked how many hours it had been since they last smoked at the time of the scan. Nicotine dependence severity was measured with the Fagerstrom Test for Nicotine Dependence (FTND) (Heatherton et al., 1991) at the screen visit. The time-line follow-back procedure (TLFB) (Sobell and Sobell, 1996) was used to record tobacco product, alcohol, and marijuana use in the 60 days prior to the screen and during the interim period between each follow-up assessment.

2.4. MRI acquisition and preprocessing

All fMRI scans were acquired on a Siemens 3 T Trio scanner located at the Mind Research Network in Albuquerque NM. The resting state sessions were 6 min in length, during which participants were asked to stare at the cross on the screen, stay awake and alert, but to clear their mind and not think about anything in particular as if their brain was at rest. Further details on acquisition and preprocessing methods are