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Insula's functional connectivity with ventromedial prefrontal cortex mediates the impact of trait alexithymia on state tobacco craving

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Abstract

Rationale—Alexithymia is a personality trait characterized by difficulty identifying and describing subjective emotional experiences. Decreased aptitude in the perception, evaluation, and communication of affectively laden mental states has been associated with reduced emotion regulation, more severe drug craving in addicts, and structural/functional alterations in insula and anterior cingulate cortex (ACC). The insula and ACC represent sites of convergence between the putative neural substrates of alexithymia and those perpetuating cigarette smoking.

Objectives—We examined the interrelations between alexithymia, tobacco craving, and insula/ACC neurocircuitry using resting-state functional connectivity (rsFC).

Methods—Overnight-deprived smokers ($n=24$) and non-smokers ($n=20$) completed six neuroimaging assessments on different days both in the absence of, and following, varenicline and/or nicotine administration. In this secondary analysis of data from a larger study, we assessed trait alexithymia and state tobacco craving using self-reports and examined the rsFC of bilateral insular subregions (anterior, middle, posterior) and dorsal ACC.

Results—Higher alexithymia in smokers predicted reduced rsFC strength between the right anterior insula (aI) and ventromedial prefrontal cortex (vmPFC). Higher alexithymia also

predicted more severe tobacco craving during nicotine withdrawal. Critically, the identified aI–vmPFC circuit fully mediated this alexithymia–craving relation. That is, elevated alexithymia predicted decreased aI–vmPFC rsFC and, in turn, decreased aI–vmPFC rsFC predicted increased craving during withdrawal. A moderated mediation analysis indicated that this aI–vmPFC mediational effect was not observed following drug administration.

Conclusions—These results suggest that a weakened right aI–vmPFC functional circuit confers increased liability for tobacco craving during smoking abstinence. Individual differences in alexithymia and/or aI–vmPFC functional coupling may be relevant factors for smoking cessation success.

Keywords

Alexithymia; Craving; Nicotine; Varenicline; Resting-state functional connectivity; Insula; Ventromedial prefrontal cortex; fMRI

Introduction

Individuals differ in their abilities to perceive, process, and regulate subjective emotional experiences. Emotional responses often precipitate regulatory mechanisms and the conscious awareness of such states may facilitate optimal regulation strategies (Ochsner and Gross 2005). Alexithymia is a personality trait characterized by a diminished capacity to identify and describe affective states as well as an externally oriented cognitive style (Parker et al. 2008; Taylor and Bagby 2004). The alexithymia construct is regarded as a stable personality trait in both healthy and drug addicted individuals (de Timary et al. 2008; Tolmunen et al. 2011) and has been linked with serotonergic and catecholaminergic genotypic variability (Kano et al. 2012; Swart et al. 2011).

Alexithymic characteristics are indicative of deficiencies in the subjective awareness, cognitive processing, and optimal regulation of emotions (Chen et al. 2011; Pollatos and Gramann 2012; Swart et al. 2009). As several neuropsychiatric conditions can be characterized by maladaptive affect regulation and given associations with autism (Silani et al. 2008), posttraumatic stress disorder (Frewen et al. 2008), eating disorders (Miyake et al. 2012), and drug addiction (Speranza et al. 2004), alexithymia may represent a vulnerability and/or negative prognostic factor for multiple conditions (Ogrodniczuk et al. 2011; Taylor 2000). With respect to drug addiction, deficits in the cognitive processing and regulation of emotions may contribute to the onset, exacerbation, and/or maintenance of drug use via negative reinforcement mechanisms (Baker et al. 2004; Cheetham et al. 2010; Kun and Demetrovics 2010).

Accumulating evidence from individuals addicted to various drugs implicates alexithymia as a negative outcome predictor. For example, higher levels of alexithymia are indicative of quicker time to relapse and reduced treatment engagement in alcohol, cocaine, and poly-drug abusers (Cleland et al. 2005; Keller et al. 1995; Loas et al. 1997b). Elevated alexithymia also predicts greater dependence, use severity, and compromised emotion regulation in alcoholics (Bruce et al. 2012; Stasiewicz et al. 2012; Thorberg et al. 2009). Craving, the strong subjective desire for a drug, is a particularly relevant clinical construct encompassing emotional and motivational phenomena that perpetuate drug use and precipitate relapse (Ferguson and Shiffman 2009). Emerging evidence connects increased alexithymia with more severe craving in alcoholics and methamphetamine addicts (Junghanns et al. 2005; Saladin et al. 2012; Thorberg et al. 2011), which may partly explain alexithymia's link with use severity and relapse propensity. Impaired awareness of emotional states and/or responsiveness to drug cues may contribute to reduced craving

mitigation abilities (Goldstein et al. 2009). As such, elucidating the relations between alexithymia in cigarette smokers, tobacco craving, and importantly, the underlying neurocircuitry involved may provide insight into individual differences that could serve to expedite implementation of tailored cessation interventions.

Neuroimaging data support the conceptualization of alexithymia as a neuropsychological construct. Higher degrees of alexithymia are associated with altered structure/function in canonical emotion-related brain regions including, the insula, anterior cingulate cortex (ACC), ventromedial prefrontal cortex (vmPFC), and amygdala (Wingbermhle et al. 2012). Structurally, alexithymia has been directly related to gray matter volume reductions in the insula, ACC, and vmPFC (Borci et al. 2009; Paradiso et al. 2008). Similarly, poorer emotional intelligence and interoceptive awareness, indirect features of alexithymia (Baughman et al. 2011; Herbert et al. 2011), have been linked with gray matter reductions in right anterior insula (aI), dorsal ACC, and vmPFC (Critchley et al. 2004; Takeuchi et al. 2011). These alexithymia-related structural aberrations are paralleled by functional alterations most consistently observed in the insula and ACC during affective processing tasks (e.g., Kano et al. 2007; Moriguchi et al. 2007; Pouga et al. 2010; Reker et al. 2010; Silani et al. 2008).

The insula, ACC, and vmPFC represent critical sites of convergence between the neural substrates of alexithymia and those perpetuating cigarette smoking. Specifically, increased activity in these regions has been consistently observed following drug-related cue presentation and often correlates with subjective tobacco craving (Chase et al. 2011; Engemann et al. 2012; Naqvi et al. 2007). Theoretical accounts suggest that interactions between the insula, ACC, and vmPFC underlie affective processes at multiple stages of the addiction cycle, particularly during drug withdrawal (Naqvi and Bechara 2010). Neuroimaging evidence indicates that the insula is involved in monitoring homeostatically relevant bodily sensations (Craig 2009; Critchley et al. 2004) and that the vmPFC is involved in the processing and regulation of emotion (Foland-Ross et al. 2010; Kim et al. 2011). While the insula, ACC, and vmPFC appear to constitute critical nodes in the neurocircuitry underlying alexithymia and drug addiction, little is known about the *circuit-level* interactions of these brain regions as a function of *trait* alexithymia or *state* tobacco craving.

Circuit-level interactions between brain regions can be investigated using resting-state functional connectivity (rsFC), the assessment of synchronized low-frequency fluctuations in the fMRI signal collected in the absence of explicit task demands. Such rsFC assessments have been increasingly employed (Fox and Raichle 2007) to interrogate functional circuits constrained to known neuroanatomical pathways (Greicius et al. 2009) including those associated with the insula and ACC (Cauda et al. 2011; Hong et al. 2009). With respect to the insula's functional organization, previous rsFC studies have identified three discernible subregions (anterior, middle, posterior) along a ventral-anterior to dorsal-posterior trajectory (Deen et al. 2011; Taylor et al. 2009). Parcellations of the insula using rsFC recapitulate those synthesized from anatomical and functional observations implicating the posterior insula (pI) in somatosensation and interoception, middle insula (mI) in cognitive and integration capacities, and aI in affective processing and subjective awareness (Craig 2009; Nieuwenhuys 2012). As such, we explored the influence of alexithymia on anterior, middle, and posterior insula's rsFC strength with other brain regions. Given the aI's critical role in the processing and awareness of affective states (Craig 2010; Kurth et al. 2010), we first examined this subregion. We also explored the dorsal ACC's rsFC using bilateral "seed" regions.

To probe the interrelations between alexithymia, craving, and rsFC, both abstinent smokers and nonsmokers completed six fMRI assessments. All participants were scanned under two general conditions: (1) in the absence of pharmacological manipulations (i.e., during nicotine withdrawal in smokers), and (2) after administration of varenicline and/or nicotine (four sessions), two modestly effective cessation aids that reduce withdrawal symptoms and tobacco craving in abstinent smokers. Assessment of smokers in both the absence and presence of these drug manipulations allowed us to determine if the relations between alexithymia, craving, and rsFC were specific to the withdrawn state. In this secondary analysis of data from a larger study (Sutherland et al. 2013b), we addressed three questions: (1) Does alexithymia predict individual differences in the functional coupling of the insula/ACC with other brain regions in smokers and/or nonsmokers, particularly the aI. (2) Does alexithymia predict tobacco craving severity in smokers, particularly during withdrawal. (3) Do specific brain circuits mediate such an alexithymia–craving relation?

Methods and materials

Participants

In total, 24 cigarette smokers (12 females) and 20 nonsmokers (10 females) completed the study. We recruited daily smokers who reported smoking 10 or more cigarettes per day for a minimum of 2 years and nonsmokers who reported no history of daily cigarette use and no smoking within the preceding 2 years. Smokers were 36 ± 10 years of age (mean $\pm$ SD), smoked 18 ± 8 cigarettes/day, reported daily cigarette use for 18 ± 11 years, and were moderately nicotine dependent (Fagerström scores: 5 ± 2 ; see Supplementary Information [SI] and Table S1 for participant details). As our nonsmokers were younger (30 ± 7 years; $p = 0.05$) than smokers, age was included as a covariate in group comparisons. Data from one male smoker and one male nonsmoker were excluded due to excessive head motion during MRI scanning. Before study onset, participants gave written informed consent in accordance with the National Institute on Drug Abuse Intramural Research Program Institutional Review Board.

Design and drugs

Both smokers and nonsmokers completed six fMRI assessments on different days in a two-drug, double-blind, placebo-controlled study. At three points during a varenicline administration regime (pre-pill, varenicline pill, placebo pill), participants were scanned twice, once each wearing a nicotine or placebo patch. After two initial pre-pill sessions, participants were administered varenicline (17.0 ± 4.2 days) and placebo pills (16.5 ± 3.4 days) and again completed nicotine and placebo patch scans towards the end of each pill interval (Fig. S1). In other words, participants were scanned twice without drugs (i.e., pre-pill/placebo-patch and placebo-pill/placebo-patch sessions) and four times after receiving pharmacological interventions (i.e., pre-pill/nicotine-patch, placebo-pill/nicotine-patch, varenicline-pill/nicotine-patch, and varenicline-pill/placebo-patch sessions). Examination of smokers in both the absence and presence of drugs allowed us to assess the *state/condition specificity* (e.g., only present during withdrawal) of any relations between alexithymia, craving, and rsFC. Varenicline (Chantix®, Pfizer) was administered according to standard guidelines and distributed in blister packs identical to sucrose placebo pills. Transdermal nicotine (NicoDerm CQ®, GSK) or placebo patches were applied to the back. We used a multiple dosing strategy to match daily nicotine intake, nonsmokers: 7 mg patches; smokers: 21, 28, 35, or 42 mg patches (for 10–15, 16–20, 21–25, and >25 cigarettes/day, respectively).

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We instructed smokers to have their last cigarette 12 h before their scheduled arrivals. Upon arrival, all participants were tested for recent drug and alcohol use and for expired carbon monoxide (CO) levels. Given that the half-life of CO during sleep can be up to 4–8 h (SRNT Subcommittee 2002), we used a guideline of less than or equal to 15 parts per million (ppm) to verify abstinence. Indicative of compliance, smokers' CO levels were lower on scan visits (6.9 ± 2.6 ppm) relative to visits not requiring abstinence (18.6 ± 8.9 ppm; $t_{22} = -7.8$, $p < 0.001$); nonsmokers' CO levels did not differ (1.9 ± 0.3 vs. 1.8 ± 0.4 ppm; $t_{18} = 1.1$, $p = 0.3$).

Self-reports

We assessed alexithymic traits and state variations in tobacco craving using previously validated and routinely employed self-reports. Participants completed the 20-item Toronto Alexithymia Scale (TAS-20; Bagby et al. 1994) once during the study and a total score was calculated. Higher scores indicate more alexithymic characteristics (range 20–100). Participants rated on a five point scale how much they agreed or disagreed with statements such as: “It is difficult for me to find the right words for my feelings,” “I prefer talking to people about their daily activities rather than their feelings,” and “I often don't know why I am angry.” As the TAS-20 total score is predictive of poorer drug abuse prognoses (Cleveland et al. 2005; Thorberg et al. 2011) and correlates with insula and ACC function (Meriau et al. 2006; Reker et al. 2010), we focused specifically on this *total score* in our analyses. Alexithymia is best characterized as a dimensional rather than a categorical construct (Chen et al. 2011; Mattila et al. 2010). While the TAS-20 score is a continuous variable, pre-defined cut-offs are used to identify “clinically” high (≥ 61) and low (< 51) alexithymic individuals (Taylor 2000). Our participants were not “clinically” alexithymic according to this criterion (range 22–55). We examined individual differences in alexithymic traits across participants free from psychiatric disorders (other than nicotine dependence).

Smokers' tobacco cravings were assessed after each scan sessions with the 12-item Tobacco Craving Questionnaire (TCQ; Heishman et al. 2008) which consists of four factors: emotionality, expectancy, compulsivity, and purposefulness. We examined the link between alexithymia and TCQ total and subscale scores with emphasis on the *emotionality factor*. The emotionality subscale (range 3–21: higher scores indicate more craving) contains three items: (1) “I would be less irritable now if I could smoke,” (2) “If I were smoking now, I could think more clearly,” and (3) “I could control things better now if I could smoke.” We also assessed mood states in both smokers and nonsmokers using the Positive and Negative Affect Schedule (PANAS; Watson et al. 1988). The TCQ and PANAS were completed ~ 5.5 h after patch application and ~ 2.5 h after MRI scanning.

rsFC data collection and processing

We acquired imaging data with a Siemens 3 T Magnetom Allegra scanner. During the 8-min resting scan, participants were instructed to simply relax with eyes closed and remain still. Resting data were collected ~ 2.5 –3 h after patch application (see SI for data collection parameters). We processed resting data as previously described (Sutherland et al. 2013a). Functional data were slice-time and motion corrected, aligned with anatomical images, and normalized into Talairach space (3 mm^3 voxels). Images were spatially blurred (6 mm kernel) and the time series underwent de-trending and band-pass filtering (0.01–0.1 Hz). Global fluctuations from non-neuronal physiological processes were reduced by regressing out nuisance signals: i.e., the first three principal components (PCs) derived from the time courses of white matter (WM) voxels and the first three PCs from cerebrospinal fluid (CSF) voxels (Behzadi et al. 2007). Motion-correction parameters also were used to remove signals related to head movement. Furthermore, we employed two additional strategies to reduce motion-related confounds (Sutherland et al. 2013a): (1) the censoring of volumes associated with large movements (Power et al. 2012), and (2) the use of a summary motion metric as a

confounding variable in group-level analyses (Satterthwaite et al. 2012). For each subject and session, we computed correlation coefficient (CC) images by correlating each voxel's time course with a reference time course from a predefined seed region. Resulting subject-level CC images were Fisher's Z-transformed (Z-images).

rsFC seeds—When considering insula's functional organization, previous studies have identified three discernible subregions along a ventral-anterior to dorsal-posterior trajectory with distinct rsFC topographies (Cauda et al. 2011; Deen et al. 2011; Taylor et al. 2009). To replicate and extend these findings, we examined the rsFC of right and left insular subregions using seeds (29 voxels; Fig. 1) centered on previously defined coordinates in the aI (aI: $x=\pm 34$; $y=14$; $z=-6$, Talairach [mm]), mI (mI: $x=\pm 36$; $y=4$; $z=2$), and pI ($x=\pm 38$; $y=-10$; $z=6$). We then identified and compared intrinsic connectivity networks (ICNs) associated with each insular subregion to confirm that these seeds extracted distinct topographies. Overall rsFC maps were created by averaging each participant's Z-images across all six scan sessions and submitting these session-averaged maps to group-level, one-sample *t*-tests. To determine if rsFC differed between aI, mI, and pI, we performed three paired-sample *t*-tests per hemisphere (aI vs. pI, aI vs. mI, mI vs. pI; $p_{\text{corrected}} < 0.001$; $p_{\text{voxel-wise}} < 10^{-6}$; cluster-extent: 10 voxels). We used this stringent threshold to control for α -inflation associated with multiple comparisons. As aberrant ACC function also has been linked with alexithymia, we examined the rsFC of the right and left dorsal ACC (dACC) using seeds centered on coordinates ($x=\pm 9$; $y=20$; $z=31$) previously linked with both alexithymia and cigarette cue reactivity/craving (Engelmann et al. 2012; Heinz et al. 2010).

rsFC analyses—To identify regions whose rsFC with a seed was influenced as a function of alexithymia and/or smoking status, we analyzed session-averaged Z-images in a whole-brain linear-mixed effects framework. We focused on session-averaged Z-images to relate trait alexithymia with stable “trait-like” rsFC independent of state variations. Subject-level Z-images from each seed were entered into separate models including factors for GROUP (smoker vs. nonsmoker), alexithymia (ALEX: TAS-20 score), and confounding variables of no interest (motion and age). In other words, we conducted whole-brain analyses of covariance (ANCOVAs) to identify brain areas whose rsFC with a seed region: (1) differed between smokers versus nonsmokers (GROUP main effect), (2) was predicted by alexithymia regardless of group (ALEX main effect), and/or (3) was differentially predicted by alexithymia in smokers versus nonsmokers (GROUP×ALEX interaction). We applied a threshold of $p_{\text{corrected}} < 0.006$ (Bonferroni: $\alpha=0.05/8$; $p_{\text{voxel-wise}} < 0.005$; cluster-extent: 64 voxels) to the statistical maps and extracted Z-values (i.e., rsFC strength) from identified clusters for further examination.

Mediation analyses—To examine a potential relation between alexithymia and craving, we initially performed correlation analyses between TAS-20 scores and TCQ ratings from smokers' first encounter (of two) with extended smoking deprivation in the absence of drug administration (i.e., session-specific values obtained under “full-withdrawal” during the pre-pill/placebo-patch session). We then conducted a mediation analysis testing whether the relation between alexithymia (*X*) and craving (*Y*) was explained by rsFC strength (*M*) in circuits identified in the group-level analyses above (model: alexithymia→rsFC→ craving). By convention, path “*c*” in this model refers to the total effect of alexithymia on craving, path “*a*” refers to the impact of alexithymia on rsFC, and path “*b*” refers to the effect of rsFC on craving (controlling for alexithymia). The mediation analysis decomposed the total effect of alexithymia on craving (path *c*) into *direct* (path *c'*) and indirect effects (path *ab*: i.e., $c=c'+ab$). rsFC is considered to completely mediate the relation between alexithymia and craving if the coefficients from paths *a*, *b*, and *ab* are significant and thus path *c'* differs from *c*. Age was included as a confounding variable and data are reported as unstandardized path

coefficients (β) and standard errors (SE). The ab indirect path is considered significant if the asymmetric, bias-corrected 95 % confidence interval (95 % CI), computed via a bootstrapping approach (Preacher and Hayes 2008), does not encompass zero.

To replicate results from smoker's first full-withdrawal session, we conducted another mediation analysis using data from smokers' second "full-withdrawal" session (i.e., placebo-pill/placebo-patch). Subsequently, additional mediation analyses were performed using data from the remaining four sessions when smokers received varenicline and/or nicotine to evaluate the *state/condition specificity* of the mediation effect during withdrawal. In statistical terms, such state specificity is indicated by a *moderated mediation effect*. A moderated mediation occurs when the effect of the independent variable (X : alexithymia) on the dependent variable (Y : craving) through a mediator variable (M : rsFC) differs depending on the level of a moderator variable (W : full-withdrawal vs. drug administration). A significant $M \times W$ interaction indicates that the indirect effect of X on Y through M varies across levels of W (Fig. S4). We determined the significance of the conditional indirect effect ($M \times W$ interaction) using the framework of Preacher and colleagues (2007). In sum, we examined whether the alexithymia $\rightarrow$ rsFC $\rightarrow$ craving relation differed between the first full-withdrawal session versus the session when varenicline and nicotine were co-administered.

Results

Insular subregions showed distinct rsFC topographies

Using the six seeds (right/left aI, mI, and pI), we identified overlapping yet distinct ICNs associated with insular sub-regions (Fig. S2). Specifically, when considering all participants and sessions: (1) the aI demonstrated greater rsFC strength with pregenual/rostral ACC relative to either the mI or pI, (2) the mI was more strongly interconnected with dorsal ACC and adjacent pre-supplemental motor area in comparison to the other two insular seeds, and (3) the pI showed greatest rsFC with mid-cingulate, supplemental motor area, and sensorimotor regions (Fig. 2). These results confirm that our preselected seeds extracted distinct topographies. Additionally, bilateral dACC seeds identified expected ICNs anchored by bilateral insula and posterior medial prefrontal regions (Fig. S3).

Alexithymia differentially predicted rsFC in smokers versus nonsmokers

We next performed separate whole-brain ANCOVAs to identify brain regions whose rsFC with these eight seeds was influenced as a function of smoking status (GROUP) and/or alexithymia (ALEX). TAS-20 scores differentially predicted session-averaged rsFC strength between right aI and vmPFC in smokers versus nonsmokers as indicated by a whole-brain GROUP $\times$ ALEX interaction (Fig. 3a). Specifically, higher TAS-20 scores predicted decreased rsFC in this right aI–vmPFC circuit in smokers but not in nonsmokers. No significant clusters were detected when considering either the whole-brain GROUP or ALEX main effects. Suggesting the *regional specificity* of alexithymia's impact on this aI–vmPFC circuit, no effects were detected when considering the homologous left aI seed, nor the left mI, left pI, or right pI seeds. Alexithymia differentially predicted rsFC strength between right mI and superior temporal gyrus (STG) in smokers versus nonsmokers in a fashion similar to that described above for the aI–vmPFC circuit (Table S2).

We also investigated the relation between TAS-20 scores and left/right dACC rsFC. Focusing on the left seed, alexithymia differentially predicted rsFC strength in a dACC–insula circuit in smokers versus nonsmokers (Fig. 3b). Similar GROUP $\times$ ALEX interactions were also detected when considering the right dACC's rsFC with bilateral STG, bilateral

inferior parietal lobule, left middle frontal gyrus, and right middle occipital gyrus (Table S2).

Alexithymia predicted craving during withdrawal

We performed correlation analyses on TAS-20 and TCQ scores from smokers' *first* full-withdrawal session. Focusing on the TCQ emotionality scale, higher TAS-20 scores predicted elevated craving during withdrawal ($r=0.45$, $p=0.03$; Fig. 4a). No relations were detected between TAS-20 and TCQ total or other subscale scores ($p>0.2$).

aI-vmPFC circuitry mediated alexithymia's influence on craving

As alexithymia correlated with both aI-vmPFC rsFC and TCQ emotionality ratings, we subsequently conducted a mediation analysis testing the hypothesis that the effect of trait alexithymia (X) on state craving (Y) was mediated by session-specific rsFC strength in the right aI-vmPFC circuit (M). As shown in Fig. 4b, the aI-vmPFC circuit fully mediated the alexithymia-craving relation during smoker's first full-withdrawal session. Specifically, when including the aI-vmPFC mediator in the model, alexithymia's direct effect on craving failed to reach significance (c' path: $\beta=0.2$, $SE=0.2$, $p=0.3$), whereas the indirect effect was significant (ab path: 95 % CI=0.02–0.46). These outcomes indicate that higher TAS-20 scores predicted reduced aI-vmPFC circuit strength and, in turn, reduced aI-vmPFC circuit strength predicted increased craving during withdrawal.

This mediation effect was internally replicated when considering smokers' second full-withdrawal sessions (95 % CI=0.1–0.9) but critically, not any of the other four sessions following varenicline and/or nicotine administration (Table S3). To statistically support the notion that the aI-vmPFC circuit mediated alexithymia's impact on craving only during withdrawal, we conducted a *moderated mediation analysis* comparing the alexithymia→aI-vmPFC→craving relation from the first full-withdrawal session versus the session when varenicline and nicotine were co-administered. We detected a significant moderate mediation effect indicating that the relation between alexithymia and craving was mediated by aI-vmPFC rsFC during withdrawal but not following drug administration ($M \times W$ interaction: $\beta=21.1$, $SE=9.9$, $p=0.04$; Fig. S4). This outcome provides evidence for the *state/condition specificity* of the aI-vmPFC mediational effect.

No relations between craving and rsFC in the right mI-STG (Table S2) or dACC-insula circuits (Fig. 3b) were detected ($p>0.2$). Because such a relation is a prerequisite for a mediation, these outcomes provide evidence for the *circuit specificity* of the aI-vmPFC mediation effect. Given that these circuits appeared unrelated to craving, they are not discussed further.

aI-vmPFC circuitry *did not* mediate alexithymia's influence on mood

To relate trait alexithymia with state self-reports from non-smokers, we performed correlation analyses between TAS-20 scores and PANAS ratings from the pre-pill/placebo-patch session. In nonsmokers, higher TAS-20 scores predicted lower PANAS positive ($r=-0.62$, $p=0.005$), but not negative affect ($r=0.15$, $p=0.5$; AFFECT×ALEX interaction: $F_{1,17}=10.3$, $p=0.005$). However, this alexithymia-mood relation was not mediated by the aI-vmPFC circuit described above (Fig. S5). These outcomes provide evidence for the *domain/construct specificity* of the aI-vmPFC mediational effect. In smokers, no relation between TAS-20 and positive or negative affect were detected ($p's>0.2$).

Discussion

Alexithymia is a stable personality trait associated with reduced emotional insight and structural/functional alterations in the insula and ACC (Swart et al. 2009; Wingbermuhle et al. 2012). Despite accumulating evidence indicative of a link between alexithymia and drug use (Bruce et al. 2012; Kun and Demetrovics 2010; Saladin et al. 2012), little research has investigated the neurobiological mechanisms contributing to this relation. In this secondary analysis of data from a larger study, we used rsFC to investigate the interrelations between alexithymia, tobacco craving, and the insula's circuit-level interactions with other brain regions. We identified a ventral-anterior to dorsal-posterior trajectory in the insula's functional organization and more importantly, observed that higher alexithymia in smokers predicted weaker rsFC between the right aI and vmPFC. Confirming the clinical relevance of this personality trait, we also observed that higher alexithymia predicted more severe tobacco craving during withdrawal. Critically, the aI–vmPFC circuit fully mediated this alexithymia–craving relation as higher TAS-20 scores forecasted a weaker circuit, and in turn, a weaker circuit conferred increased liability for craving. These results suggest that individual differences in alexithymic characteristics and/or aI–vmPFC rsFC may be relevant factors for smoking cessation success.

Our results support the tri-parcellation of insular organization along a ventral-anterior to dorsal-posterior gradient using rsFC (Cauda et al. 2011; Deen et al. 2011; Taylor et al. 2009). Such a parcellation is consistent with previous fractionations of the insula synthesized from functional, anatomical, physiological, and clinical data (Craig 2010; Kurth et al. 2010; Nieuwenhuys 2012). We observed that the pI was strongly interconnected with constituents of a commonly observed intrinsic sensorimotor network (Biswal et al. 1995) consistent with the pI's role in somatosensation and primary interoception (Craig 2002). The mI showed greatest coupling with the dorsal “cognitive division” of ACC (Bush et al. 2000) consistent with the mI's role in the initiation, maintenance, and adjustment of attentional resources (Dosenbach et al. 2006). Finally, the aI was strongly interconnected with the pregenual/rostral “emotional division” of ACC (Bush et al. 2000) consistent with the aI's role in the processing, generation, and awareness of affective states (Craig 2010; Kurth et al. 2010). A posterior-to-anterior integration of interoceptive information with cognitive and affective processing streams culminating in the aI has been conceptualized as the neurobiological instantiation of subjective emotional experience and awareness (Craig 2009, 2010) with an emphasis on the *right* aI regarding arousing or aversive states (Craig 2005; Critchley et al. 2004).

In light of the right aI's involvement with the processing of aversive emotional states, it is particularly notable that alexithymia differentially predicted rsFC between smokers versus nonsmokers in a specific right (but not left) insula circuit. Our observation that alexithymia predicted decreased aI–vmPFC circuit strength in smokers but not nonsmokers may be related to structural alterations in these regions associated with an extended smoking history. For example, increased gray matter density in the aI (Zhang et al. 2011) and decreased cortical thickness in the vmPFC (Kuhn et al. 2010) has been detected in smokers relative to nonsmokers. Such structural alterations corroborate functional/clinical observations implicating these same regions in the perpetuation of smoking behaviors (Franklin et al. 2011; Kober et al. 2010; Naqvi et al. 2007).

Specifically, theoretical accounts suggest that circuit-level interactions between the insula and vmPFC are associated with cognitive and affective processes at multiple stages of the addiction cycle (Naqvi and Bechara 2010). Altered insular function may underlie impaired insight, compromised self-awareness, and/or altered interoceptive abilities which have been conceptualized as critical factors underlying drug addiction (Goldstein et al. 2009; Kun and

Demetrovics 2010; Verdejo-Garcia et al. 2012). Furthermore, the vmPFC has been regarded as a critical hub in the neurocircuitry of affect regulation (cf., Kim et al. 2011; Myers-Schulz and Koenigs 2012). Neuroimaging evidence indicates that labeling negative emotional stimuli (“putting feelings into words”) results in increased activation of the vmPFC and, in turn, this increased vmPFC activity is thought to alleviate aversive emotional states via suppression of amygdala functioning (Foland-Ross et al. 2010; Lieberman et al. 2007). In chronic smokers deprived of nicotine, elevated amygdala activity covaries with increased smoking urges (Wang et al. 2007) and cigarette smoking dampens amygdala hyperactivity (Zubieta et al. 2005). Elevated insula, vmPFC, and amygdala responses to smoking-related cues have been associated with increased craving (Chase et al. 2011; Engelmann et al. 2012) and greater relapse susceptibility (Janes et al. 2010). A weakened right aI–vmPFC circuit may contribute to emotion dysregulation and drug craving particularly emergent during withdrawal.

Indeed, linking this weakened circuit with a clinically relevant outcome, we observed that right aI–vmPFC connectivity strength completely mediated the relation between alexithymia and craving during withdrawal. Converging evidence from multiple drugs of abuse connects elevated alexithymia with poorer prognoses (Speranza et al. 2004) including: reduced emotion regulation and treatment engagement in substance abusers (Cleland et al. 2005; Stasiewicz et al. 2012), greater dependence, use severity, and craving in alcoholics (Thorberg et al. 2009, 2011), and elevated aggression and craving in methamphetamine addicts (Payer et al. 2012; Saladin et al. 2012). Additionally, alexithymia has been reported to correlate with subcortical, temporal, and frontal brain activations during stress-guided imagery in cocaine addicts (Li and Sinha 2006) and increased aI gray matter density in smokers (Zhang et al. 2011). Our results confirm and extend these previous findings by relating higher alexithymia not only with more severe tobacco craving but also with reduced functional connectivity in a precise brain circuit. Specifically, if a smoker had a “weaker” circuit, that smoker was more likely to experience higher degrees of craving during withdrawal. Conversely, if a smoker had a “stronger” aI–vmPFC circuit, that smoker was less likely to experience higher degrees of craving during withdrawal. One possible interpretation is that a stronger aI–vmPFC circuit is “protective” against craving during smoking abstinence.

The TAS-20 describes a person’s level of difficulty identifying and describing emotions as well as their propensity to understand themselves as responding to outside influences rather than having an internal locus of control. Decreased abilities to perceive, evaluate, and communicate emotions may result in poorer emotion regulation and the persistence of aversive emotional states (Chen et al. 2011; Pollatos and Gramann 2012; Swart et al. 2009). Such deficits in the cognitive processing and regulation of emotions may contribute to the onset, exacerbation, and/or maintenance of drug use via negative reinforcement mechanisms (Baker et al. 2004; Cheetham et al. 2010; Kun and Demetrovics 2010). We speculate that someone who has difficulty processing affective information beyond recognizing an aversive feeling and who experiences relief via a cigarette may be drawn to smoking. Furthermore, the onset of a negative emotion (e.g., angry, sad, anxious) in an established smoker with higher degrees of alexithymia may be evaluated simply as “I need a cigarette.” In turn, relief may be obtained by smoking.

We conducted multiple supplemental analyses to more fully characterize the aI–vmPFC circuit and its associated behavioral consequences. First, we internally replicated the mediating role of the aI–vmPFC circuit in an alexithymia–craving relation during withdrawal by assessing smokers during two separate “full-withdrawal” sessions. Second, we provided evidence for the *state/conditional specificity* of the aI–vmPFC mediational effect by examining smokers following pharmacological interventions. A moderated

mediation analysis indicated that the aI–vmPFC circuit mediated the alexithymia–craving relationship during withdrawal but not following drug administration. This outcome indicates that the behavioral consequences of a weakened aI–vmPFC circuit only manifested during the withdrawn state. Finally, we provided evidence for the *domain/construct specificity* of the aI–vmPFC circuit by demonstrating that the circuit was unrelated to an alexithymia–mood relation observed in nonsmokers. The nonsmoker–mood results can also be viewed as a “negative control.” In other words, a significant correlation between alexithymia and a self-report measure was not sufficient to yield the aI–vmPFC mediational effect.

Our results regarding aI–vmPFC circuit–level interactions may also be considered in light of studies assessing the subjective value of rewards and decision making processes. Neuroimaging investigations have provided evidence that the vmPFC encodes the subjective value of rewards and actions (Hare et al. 2009; Kable and Glimcher 2009). In addition to alterations in insula and vmPFC functioning (Wingbermhle et al. 2012), alexithymia has also been associated with reduced hedonic capacity (cf., Loas et al. 1997a; Prince and Berenbaum 1993), reduced sensitivity to negative outcomes (Bibby and Ferguson 2011), and compromised performance in the Iowa Gambling Task (Ferguson et al. 2009; Kano et al. 2011). As the integration of interoceptive information (insula) with subjective value information (vmPFC) is critical for optimal decision making (Bechara and Damasio 2005), we speculate that reduced aI–vmPFC functional coupling may contribute to alterations in reward/punishment processing associated with alexithymia and/or nicotine addiction.

A weakened aI–vmPFC circuit appears to render smokers with high alexithymic tendencies particularly vulnerable to tobacco craving. As tobacco craving perpetuates smoking and precipitates relapse (Baker et al. 2012; Shiffman et al. 1997), our results suggest that individual differences in alexithymia may be a relevant factor for cessation success. We suggest that smokers higher in alexithymia may benefit from the acquisition of skills associated with the perception, processing, and regulation of emotions in the service of craving mitigation. Also, pharmacological agents such as venlafaxine, a serotonin and norepinephrine reuptake inhibitor, appear to augment emotional awareness (Cravello et al. 2009) and have been proposed as adjunct interventions for alcoholics with higher alexithymia (Thorberg et al. 2011). As venlafaxine improves cessation rates in some subgroups of smokers (Cinciripini et al. 2005), we speculate that smokers higher in alexithymia may be those most likely to benefit from such a pharmacological intervention. Strengthening the functional interaction between the right aI and vmPFC via behavioral therapies, pharmacological agents, or transcranial magnetic stimulation to the insula may promote smoking abstinence.

Our findings should be considered in light of remaining issues. First, while the TAS-20 has been psychometrically validated and is commonly used to explore relations between alexithymia, brain function, and drug abuse (Cleland et al. 2005; Thorberg et al. 2009; Wingbermhle et al. 2012), it is a self-report instrument designed to probe impaired introspective abilities. Thus, an impaired ability to introspect may lead to inaccuracies in participant evaluations. Second, the range of TAS-20 scores from our participants (i.e., 22–55) was rather limited relative to the full dynamic range of the instrument (i.e., 20–100) as well as that seen in other neuroimaging studies employing extreme-group analytical strategies (e.g., Kano et al. 2003). Third, further research is necessary to clarify the potential laterality of insular function with respect to nicotine addiction. Previously, we observed that elevated left insula–vmPFC rsFC was associated with increased withdrawal severity and was reduced by varenicline and nicotine administration (Sutherland et al. 2013a), suggesting a “susceptibility circuit” contributing to the perpetuation of smoking. Here, elevated right insula–vmPFC rsFC was associated with reduced tobacco craving suggesting a “protective

circuit” that may contribute to cessation success. The literature on insular laterality in nicotine addiction remains disparate. For example, although smoking disruption was noted following strokes affecting either the right or left insula, the effect appeared more robust for right-lateralized lesions (Naqvi et al. 2007). On the other hand, greater left insula gray matter density has been reported in smokers versus nonsmokers (Zhang et al. 2011). Finally, while preliminary evidence suggests higher alexithymia is related to quicker relapse (Loas et al. 1997b; Ziolkowski et al. 1995), the ability of alexithymia or aI-vmPFC circuit strength to predict cessation outcomes remains indeterminate.

Our results underscore the utility of examining functional connectivity to gain deeper insight into the altered neurocircuitry of addiction (Sutherland et al. 2013c). We triangulated the relationship between a stable personality trait previously associated with poorer drug abuse prognoses, state variability in a clinically relevant craving measure, and the functional connectivity strength of a precise brain circuit. Specifically, using a hypothesized insula seed and a whole-brain search strategy, we uncovered a right aI-vmPFC circuit associated with alexithymia whose weakened functional connectivity was found to confer increased liability for tobacco craving during smoking abstinence. Individual differences in alexithymia and/or aI-vmPFC functional connectivity strength may be relevant factors for smoking cessation success.

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Fig. 1.

Preselected functional connectivity seeds. We used three seeds positioned along a ventral-anterior to dorsal-posterior gradient in each hemisphere to interrogate the functional connectivity of insular sub-regions: right/left anterior insula (*al*), middle insula (*ml*), and posterior insula (*pl*). We also used right/left dorsal ACC (*dACC*) seeds to investigate the relation between alexithymia, tobacco craving, and functional connectivity

Fig. 2.

Statistical difference maps comparing the functional connectivity of insular subregions. (Left) aI versus pI: aI was more strongly interconnected with pregenual/rostral ACC (blue: aI > pI), whereas pI showed greater connectivity with mid-cingulate and sensorimotor regions (green: aI < pI). (Middle) aI versus mI: aI again showed greater connectivity with pregenual/rostral ACC (blue: aI > mI), whereas mI was more strongly connected with dACC/pre-supplemental motor area (red: aI < mI). (Right) mI versus pI: mI again showed greater connectivity with dACC (red: mI > pI), whereas pI showed greater connectivity with mid-cingulate and sensorimotor regions (green: mI < pI). Separate overall rsFC maps from each seed region are shown in Fig. S2

Fig. 3.

Alexithymia differentially predicted *session-averaged* functional connectivity strength in right insula circuitry when considering smokers versus nonsmokers. **(a)** A whole-brain GROUP×ALEX interaction indicated that rsFC between a right ventral-anterior insula seed (aI: blue) and vmPFC was differentially associated with TAS-20 scores in smokers versus nonsmokers. Higher TAS-20 scores indicated decreased connectivity strength in the aI–vmPFC circuit of smokers but not in nonsmokers. **(b)** Similarly, a GROUP×ALEX interaction indicated that rsFC between a left dorsal ACC seed (purple) and right dorsal-anterior insula was differentially associated with TAS-20 scores in smokers versus nonsmokers. See Table S2 for coordinates

Fig. 4.

Mediation model of the relation between trait alexithymia, state tobacco craving, and session-specific aI-vmPFC functional connectivity during nicotine withdrawal. **(a)** TAS-20 scores were positively correlated with TCQ-emotionality ratings, i.e., the *total effect* of alexithymia (X) on craving (Y) was significant (c path). **(b)** Connectivity strength in the aI-vmPFC circuit (M) fully mediated the effect of alexithymia (X) on craving (Y) as: (1) TAS-20 scores accounted for significant variance in aI-vmPFC rsFC (a path); (2) aI-vmPFC rsFC accounted for unique variance in TCQ ratings when controlling for TAS-20 (b path); (3) the *indirect* mediation effect was significant (ab path); and (4) alexithymia's *direct*

effect on craving was no longer significant when the aI–vmPFC mediator was included in the model (c' path). See Table S3 for path coefficient values. * $p < 0.05$