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Greater externalizing personality traits predict less error-related insula and anterior cingulate cortex activity in acutely abstinent cigarette smokers

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ABSTRACT

Attenuated activity in performance-monitoring brain regions following erroneous actions may contribute to the repetition of maladaptive behaviors such as continued drug use. Externalizing is a broad personality construct characterized by deficient impulse control, vulnerability to addiction and reduced neurobiological indices of error processing. The insula and dorsal anterior cingulate cortex (dACC) are regions critically linked with error processing as well as the perpetuation of cigarette smoking. As such, we examined the interrelations between externalizing tendencies, erroneous task performance, and error-related insula and dACC activity in overnight-deprived smokers ($n = 24$) and non-smokers ($n = 20$). Participants completed a self-report measure assessing externalizing tendencies (Externalizing Spectrum Inventory) and a speeded Flanker task during functional magnetic resonance imaging scanning. We observed that higher externalizing tendencies correlated with the occurrence of more performance errors among smokers but not non-smokers. Suggesting a neurobiological contribution to such suboptimal performance among smokers, higher externalizing also predicted less recruitment of the right insula and dACC following error commission. Critically, this error-related activity fully mediated the relationship between externalizing traits and error rates. That is, higher externalizing scores predicted less error-related right insula and dACC activity and, in turn, less error-related activity predicted more errors. Relating such regional activity with a clinically relevant construct, less error-related right insula and dACC responses correlated with higher tobacco craving during abstinence. Given that inadequate error-related neuronal responses may contribute to continued drug use despite negative consequences, these results suggest that externalizing tendencies and/or compromised error processing among subsets of smokers may be relevant factors for smoking cessation success.

Keywords Anterior cingulate cortex, errors, functional magnetic resonance imaging (fMRI) impulsivity, insula, nicotine abstinence.

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INTRODUCTION

Online monitoring of actions and their outcomes is necessary for adapting to dynamic environments and optimizing goal-directed behavior. A diminished capacity for performance monitoring has been described in a number of neuropsychiatric conditions (Ullsperger 2006; Melcher, Falkai & Gruber 2008), including drug abuse (Garavan & Stout 2005). The bilateral insulae and dorsal anterior cingulate cortex (dACC) are critical nodes in the brain's performance-monitoring network showing increased activity in situations requiring behavioral adaptation, particularly following errors (Dosenbach *et al.* 2006; Seeley *et al.* 2007; Ullsperger *et al.* 2010). Whereas dACC activity is conceptualized as signaling the need for behavioral adjustments (Ridderinkhof *et al.* 2004), insula activity is associated with the subjective awareness, autonomic arousal and/or motivational significance

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accompanying erroneous actions (Hester *et al.* 2005; Klein, Ullsperger & Danielmeier 2013). Diminished error-related activity in these regions is a common characteristic of drug abuse having been observed when considering chronic cocaine (Kaufman *et al.* 2003), methamphetamine (London *et al.* 2005), opiate (Forman *et al.* 2004), cannabis (Hester, Nestor & Garavan 2009) and nicotine users (Luijten, van Meel & Franken 2011). Critically, compromised insula and/or dACC function may contribute to the persistence of suboptimal responses, maladaptive behaviors and/or impulsive actions despite the knowledge of negative consequences to self or others (Goldstein & Volkow 2002; Goldstein *et al.* 2009).

Diminished error-related brain activity is also linked with such personality characteristics as impulsivity (Luijten *et al.* 2011; Hoffmann, Wascher & Falkenstein 2012), risk-taking (Santesso & Segalowitz 2009) and antisocial tendencies (Chang, Davies & Gavin 2010). These personality dimensions have been conceptualized as facets of a broader construct labeled externalizing (Krueger *et al.* 2007; Patrick, Durbin & Moser 2012). The externalizing construct generally reflects an increased proneness to impulsive behavioral tendencies, has a strong genetic basis, lies on a continuum and is regarded as a dispositional factor for several neuropsychiatric conditions, including attention deficit hyperactivity disorder, antisocial personality disorder and addiction (Krueger *et al.* 2002). High-externalizing individuals show reduced amplitudes in the error-related negativity (ERN), an electrophysiological index of dACC-related error processing (Hall, Bernat & Patrick 2007; Olvet & Hajcak 2008; Nelson, Patrick & Bernat 2011). Thus, personality traits in general and externalizing tendencies in particular may account for individual variation in error processing and, in turn, behavioral performance. Elucidating such individual variation could aid in the fractionation of the smoker phenotype and contribute to the implementation of tailored strategies for smoking cessation.

Regarding smoking behaviors, greater externalizing tendencies are linked with an earlier age of smoking initiation, higher overall cigarette consumption and reduced cessation success in adolescents (Leff *et al.* 2003; Moolchan *et al.* 2007; Fischer *et al.* 2012). Similarly, higher trait impulsivity correlates with elevated cigarette cue-reactivity and tobacco craving (Doran, McChargue & Spring 2008; VanderVeen *et al.* 2008). The insula and ACC, in addition to other brain regions, show increased activity following drug-cue presentation, which often correlates with smokers' subjective tobacco cravings (Wang *et al.* 2007; Garavan 2010; Chase *et al.* 2011; Engelmann *et al.* 2012). Accordingly, several perspectives have emerged relating dysregulated insula and ACC function with subjective drug urges, impaired behavioral monitoring and maladaptive decision making (Paulus 2007; Goldstein *et al.* 2009; Naqvi & Bechara 2009; Garavan 2010). During early smoking abstinence, the insula, serving an interoceptive monitoring role (Craig 2009), is thought to track homeostatically relevant body sensations and modulate affective, motivational and attentional processes accordingly (Naqvi & Bechara 2010; Sutherland *et al.* 2013a). Increased insula and dACC activity subserving interoceptive- and/or craving-related processes may be accompanied by ruminative thoughts and/or planning for future drug use, which could then limit cognitive resources available for exogenous information processing and endogenous performance monitoring (Sutherland *et al.* 2012b). Given that most smoking cessation attempts fail within the first week (Hughes, Keely & Naud 2004), assessment of individual differences in insula and dACC functioning during acute abstinence may provide insight into the neurobiological mechanisms contributing to the persistence of cigarette smoking.

Toward this end, we investigated the interrelations between externalizing personality traits, behavioral task performance, and error-related insula and dACC activity in overnight-deprived smokers and non-smokers. Participants completed a self-report questionnaire assessing externalizing tendencies (Krueger *et al.* 2007; Venables & Patrick 2012) and a speeded Flanker task during functional magnetic resonance imaging (fMRI) scanning allowing for assessment of regional error-related activity. All participants were scanned under two general conditions: (1) in the absence of pharmacological manipulations (i.e. during nicotine withdrawal in smokers) and (2) following administration of varenicline and/or nicotine, two modestly efficacious smoking cessation aids. Assessment of smokers in both the absence and the presence of these pharmacological manipulations allowed us to determine if the relations between externalizing traits, task performance and error-related brain activity were specific to the acutely withdrawn state. We hypothesized that (1) abstinent smokers relative to non-smokers (between-group assessment) would show less error-related activity in the insula and dACC in line with the findings from other drugs of abuse; (2) higher externalizing tendencies in abstinent smokers and/or non-smokers (within-group assessment) would be predictive of suboptimal task performance (i.e. higher error rates) and less engagement of the insula and dACC following errors; and (3) less error-related insula and dACC activity would correlate with higher tobacco craving in smokers.

METHODS

Participants

A total of 24 cigarette smokers (12 females) and 20 non-smokers (10 females) completed the study. Two

participants, one male smoker and one male non-smoker, were excluded from analyses due to poor behavioral performance and excessive head motion during scanning, respectively. Participants were right-handed, 18–55 years of age, and reported no history of drug dependence (other than nicotine in smokers), neurologic or psychiatric disorders, or contraindications for MRI scanning. We recruited non-treatment-seeking smokers who reported smoking 10 or more cigarettes per day for a minimum of 2 years. Smokers were 35 ± 10 years of age (mean ± SD), smoked 18 ± 8 cigarettes/day, reported daily cigarette use for 18 ± 11 years, and were moderately nicotine dependent (Fagerström scores: 5 ± 2; see Supporting Information Table S1 for details). We recruited non-smokers who reported no history of daily nicotine use and no smoking within the preceding 2 years. Smokers and non-smokers were matched for sex, age and race/ethnicity. We obtained written informed consent in accordance with the NIDA-IRP Institutional Review Board.

Procedures

As part of a larger study, both smokers and non-smokers completed six fMRI sessions on different days in a two-drug, double-blind, placebo-controlled study (Sutherland *et al*. 2012a, 2013a,b). At three points during a varenicline administration regime (i.e. pre-pill, varenicline pill, placebo pill), participants were scanned twice, once each wearing either a nicotine or a placebo patch. After the two initial pre-pill sessions, participants were administered varenicline and placebo pills for ~2 weeks each (randomized order) and again completed nicotine and placebo patch scans toward the end of each pill interval (Supporting Information Fig. S1). In other words, participants were scanned both in the absence (pre-pill/placebo patch and placebo pill/placebo patch) and in the presence of pharmacological interventions (pre-pill/nicotine patch, placebo pill/nicotine patch, varenicline pill/nicotine patch and varenicline pill/placebo patch). Examination of smokers in these two general states allowed us to assess the *state/condition specificity* (e.g. only present during withdrawal) of any relations between externalizing, task performance and error-related brain activity. Below, we focus on the pre-pill/placebo patch session (i.e. smokers' first 'full-withdrawal session').

We instructed smokers to have their last cigarette 12 hours before their scheduled arrivals. Before data collection, participants were tested for recent drug and alcohol use and for expired carbon monoxide (CO) levels. As CO half-life during sleep can be up to 4–8 hours (SRNT-Subcommittee on Biochemical Verification 2002), we used a guideline of ≤15 parts per million (ppm) to verify overnight abstinence. Indicative of compliance, smokers' CO levels were lower on scan days (6.7 ± 3.2 ppm) relative to the initial orientation/consent visit, which did not require abstinence (18.1 ± 9.0 ppm), $t(22) = -7.2$, $P < 0.001$. MRI scanning occurred ~2 hours after CO measurements.

Self-report questionnaires

We measured trait-level externalizing tendencies and state-level tobacco craving using previously validated self-report instruments. We used the Externalizing Spectrum Inventory (ESI, 159-item version; Krueger *et al*. 2007; Venables & Patrick 2012), which queries participants regarding personality trait and past-behavioral indicators to quantify externalizing tendencies. The ESI assesses the higher order construct of externalizing across lower order facets, such as behavioral disinhibition, impulsivity, aggression, irresponsibility, boredom proneness and illicit drug use. Participants completed the ESI once during this study, generally at the third visit under their randomized drug condition for that day, since externalizing is a trait measure that would not be expected to vary by drug condition. Participants rated items (e.g. '*If I could control my impulses, my life would be much better*') on a 4-point scale as being false, mostly false, mostly true and true. A total ESI score was calculated and expressed as a proportion (range: 0.0–1.0) such that higher scores reflect greater externalizing tendencies. As ESI total scores index a general lack of inhibitory control (Patrick *et al*. 2012) and higher scores have been linked with reduced ERN amplitude (Hall *et al*. 2007; Nelson *et al*. 2011), we focused specifically on this *total score* in our analyses.

Smokers' tobacco cravings were assessed each session ~2.5 hours after the Flanker task with the 12-item, short form of the Tobacco Craving Questionnaire (TCQ; Heishman, Singleton & Pickworth 2008). The TCQ consists of four factors: emotionality, expectancy, compulsivity and purposefulness. We examined the putative links between error-related brain activity and TCQ total and subscale scores with emphasis on the *purposefulness factor*. The purposefulness subscale (range 3–21: higher scores reflect more craving) is thought to assess craving aspects related to intentions and *planning* to smoke (Heishman, Singleton & Moolchan 2003). This subscale contains three items: (1) '*If I had a lit cigarette in my hand, I probably would smoke it*'; (2) '*It would be hard to pass up the chance to smoke*'; and (3) '*I could not easily limit how much I smoked right now*'.

Flanker task

Participants performed a modified, speeded Flanker task known to reliably induce interference effects and error-related brain activity. On each trial, participants were shown a five-letter stimulus array consisting of four

flanker items for 150 milliseconds (HH_HH or SS_SS). The center target letter (H or S) was presented 100 milliseconds after the onset of the flanking stimuli and remained on the screen for 50 milliseconds. Thus, four types of stimulus arrays were presented with equal frequency across the entire task: two congruent ($n = 260$; HHHHH or SSSSS) and two incongruent arrays ($n = 260$; HHSHH or SSHSS). We instructed participants to identify the target letter with a button press using the left or right index finger (counterbalanced across participants) as quickly and accurately as possible. To adjust task difficulty and ensure an adequate number of errors, we generated an individualized response deadline from a practice run (130 trials) performed in a mock scanner. The mean reaction time (RT) plus one standard deviation from all correct-response trials during this practice run was used as the deadline during fMRI data collection. When a participant failed to meet this deadline, feedback appeared to indicate a missed response and encourage faster responding on subsequent trials (no feedback was presented following either correct or error trials). Between trials, participants viewed a central fixation cross with a variable intertrial interval (2–6 seconds). Task performance measures were RTs, error rates (errors of commission) and missed response rates (errors of omission). Participants completed the task in four, 9-minute runs with short rest periods between each.

MRI data collection and analysis

Whole-brain–blood oxygenation level-dependent (BOLD) echo-planar imaging data were acquired with a Siemens 3T Magnetom Allegra scanner (Erlangen, Germany). Thirty-three 5-mm-thick slices were acquired in the sagittal plane [272 volumes/run, repetition time (TR) = 2000 milliseconds, echo time (TE) = 27 milliseconds, flip angle (FA) = 80°, field of view = 220 mm in a 64×64 matrix]. Imaging data were collected with a delay (332 milliseconds) between volume collections to aid the processing of simultaneously recorded EEG data (not discussed further). Structural images were acquired using a magnetization prepared rapid gradient-echo sequence (TR = 2500 milliseconds; TE = 4.38 milliseconds; FA = 8°; voxel size = 1 mm^3).

We processed and analyzed imaging data with AFNI (Cox 1996). Functional images were slice-time and motion corrected and aligned to anatomical images. Functional time series were normalized to percent signal change and submitted to voxel-wise multiple regression. For each participant, we modeled six task-related regressors (error, correct and missed responses for congruent and incongruent trials) as impulse functions time-locked to stimulus-array onset and convolved with a model hemodynamic response (gamma) function and its temporal derivative. Six motion-correction parameters also were included to account for residual head motion. To assess error-related brain activity, we calculated subject-level contrast images comparing hemodynamic responses to error versus correct responses for incongruent trials. Incongruent trials were used to estimate error-related brain activity for two reasons: (1) to hold constant the influence of interference effects (i.e. incongruent versus congruent trials) and (2) the majority of errors occurred on incongruent trials, which therefore provided a greater number of occurrences for assessment. These contrast images were normalized into Talairach space with re-sampled 3-mm isotropic voxels and spatially blurred using a 3-mm Gaussian kernel.

To identify regions of interest (ROIs) showing increased error-related activity (errors > correct), we performed a whole-brain group-level, one-sample *t*-test. We applied a voxel-wise threshold of $P < 10^{-5}$ to the resulting statistical map with a minimum cluster size of 10 voxels ($P_{corrected} < 0.001$). To characterize the relationship between ESI scores and error-related brain activity, we extracted percent signal change values from group-level ROIs by averaging across all voxels within a ROI.

Statistical analyses

We examined the influence of self-reported externalizing tendencies on behavioral and brain measures by conducting analyses of covariance (ANCOVAs) to determine if *ESI* scores correlated with task performance and error-related ROI activity among smokers and/or non-smokers (*GROUP*). A significant *ESI* × *GROUP* interaction in these ANCOVAs indicated that the correlations between ESI scores and the dependent variable significantly differed between smokers and non-smokers. We used a Bonferroni adjustment to control for α-inflation when characterizing multiple correlations within the smoker group.

We subsequently conducted mediation analyses, testing whether the relationship between ESI scores (X) and performance measures (Y) was explained by regionally specific error-related brain activity (M), model: ESI scores → ROI activity → performance. By convention, 'path c' in these mediation models refers to the *total effect* of ESI scores on performance, 'path a' refers to the impact of ESI scores on ROI activity and 'path b' refers to the effect of ROI activity on performance (controlling for ESI). The mediation analyses decomposed the *total effect* of ESI on performance (path c) into *direct* (path c′) and *indirect effects* (path ab; i.e. $c = c' + ab$). Error-related ROI activity was considered to completely mediate the relationship between ESI and performance if the coefficients from paths a, b and ab were significant and thus path c′ differed from path c. Mediation results are reported as

Table 1 Flanker task performance measures among smokers, non-smokers and all participants.

GROUP	TRIAL	Error rate (%)	RT (milliseconds)		Missed (%)
			Correct trials	*Error trials*	
Smokers ($n = 23$)					
	Incongruent	22.1 (2.5)[a]	482 (11)[a]	388 (18)[a]	20.0 (2.5)[a,b]
	Congruent	5.9 (1.0)[a]	434 (8)[a]	429 (12)[a]	12.3 (2.0)[a,b]
	Overall	14.0 (1.6)	443 (10)		16.1 (2.0)[b]
Non-smokers ($n = 19$)					
	Incongruent	19.5 (2.5)[a]	485 (9)[a]	417 (10)[a]	11.5 (1.1)[a,b]
	Congruent	5.1 (0.8)[a]	442 (10)[a]	453 (11)[a]	7.2 (1.0)[a,b]
	Overall	12.3 (1.6)	456 (10)		9.4 (0.9)[b]
All ($n = 42$)					
	Incongruent	20.9 (1.8)[a]	483 (7)[a]	401 (11)[a]	16.2 (1.6)[a]
	Congruent	5.5 (0.6)[a]	438 (6)[a]	440 (8)[a]	10.0 (1.2)[a]
	Overall	13.2 (1.1)	449 (7)		13.1 (1.3)

Note: Data are expressed as mean (standard error of the mean). [a]Significant trial-type difference (i.e. incongruent versus congruent). [b]Significant group-wise difference (i.e. smoker versus non-smoker). See also Supporting Information Fig. S2. Post-error slowing data can be found in Supporting Information Table S2.

unstandardized path coefficients (β) and standard errors (SE). The ab indirect path was considered significant if the bootstrapped 95 percent confidence interval (95% CI) (Preacher & Hayes 2008) did not encompass zero. Lastly, we performed correlation analyses to explore the association between error-related ROI activity and tobacco craving and/or nicotine dependence.

RESULTS

Task performance

As expected, Flanker interference effects were observed on task performance measures (error rates, RT and miss rates) in smokers and non-smokers (Table 1). We assessed error rates in a TRIAL type (incongruent versus congruent) × GROUP (smoker versus non-smoker) mixed-effects analysis of variance (ANOVA). Both smokers and non-smokers showed higher error rates on incongruent versus congruent trials [$F(1,40) = 109.7$, $P < 0.001$] in the absence of a TRIAL × GROUP interaction ($P = 0.5$) or GROUP main effect ($P = 0.4$).

We then assessed RT in a RESPONSE outcome (correct versus error) × TRIAL type × GROUP mixed-effects ANOVA. RT was modulated by response outcome and trial type similarly in both smokers and non-smokers, as indicated by a non-significant RESPONSE × TRIAL × GROUP interaction [$F(1,40) = 0.1$, $P = 0.7$]. Specifically, we observed a RESPONSE × TRIAL interaction [$F(1,40) = 54.4$, $P < 0.001$; Supporting Information Fig. S2] such that incongruent (versus congruent) RT was *slower* on correct trials [$t(41) = -10.8$, $P_{corrected} < 0.001$; Bonferroni corrected for two comparisons ($\alpha = 0.05/2 = 0.025$)], but *faster* on incorrect trials [$t(41) = 3.5$, $P_{corrected} = 0.002$]. These error rate and RT outcomes indicated that more impulsive/disinhibited responding (i.e. faster RT), executed before the full processing of incongruent stimuli, was associated with increased error rates. Data regarding post-error slowing can be found in Supporting Information Table S2.

We also assessed miss rates in a TRIAL × GROUP mixed-effects ANOVA. Both smokers and non-smokers showed higher miss rates on incongruent versus congruent trials [$F(1,40) = 24.1$, $P < 0.001$], consistent with incongruent-stimulus processing necessitating additional cognitive resources. In addition, abstinent smokers showed higher miss rates than non-smokers [$F(1,40) = 8.4$, $P = 0.006$] in the absence of a significant TRIAL × GROUP interaction ($P = 0.2$). These outcomes indicated that acutely abstinent smokers experienced more lapses in attention during task performance relative to non-smokers.

Error-related brain activity

Among all participants, errors produced increased activation in a network of regions including the bilateral insulae extending into the inferior frontal gyri (IFG) and dACC extending into the pre-supplemental motor area (pre-SMA) (Fig. 1). In addition, errors produced increased activation in bilateral inferior parietal lobe, bilateral thalamus, left inferior frontal gyrus, cuneus and brainstem (Table 2). These regions are routinely observed during performance monitoring in general and error processing in particular (Klein *et al.* 2007; King *et al.* 2010; Ullsperger *et al.* 2010). No differences in activity were detected between smokers and non-smokers at the whole brain or ROI levels (P's > 0.2).

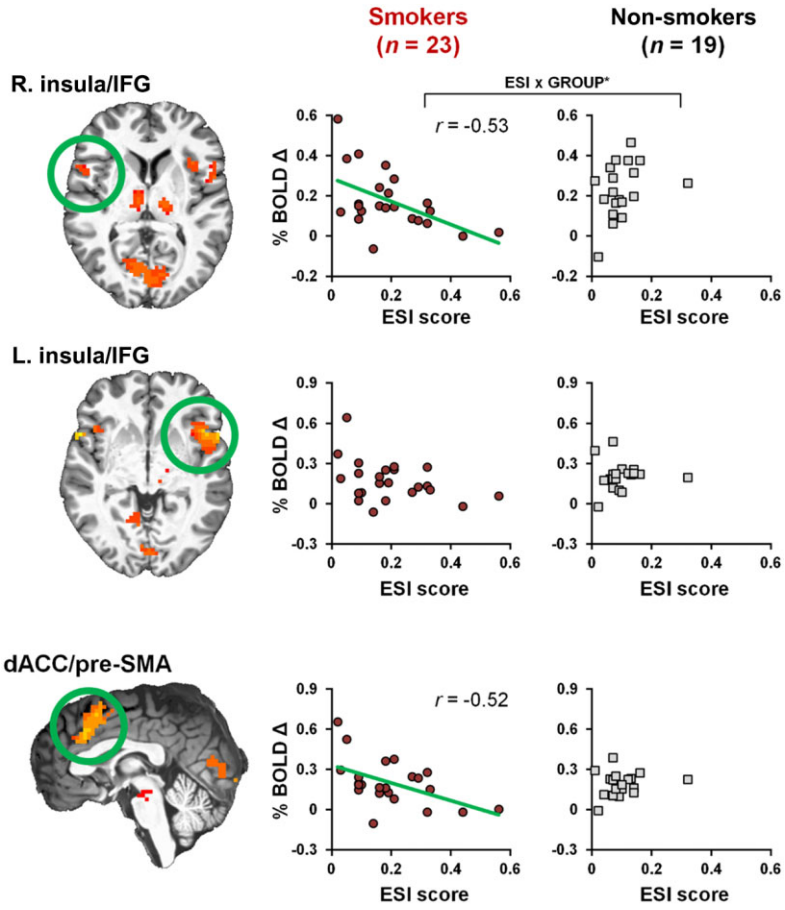

Figure 1 Greater externalizing tendencies predicted less error-related brain activity in acutely abstinent smokers. (Left) Error commission was associated with increased activation notably in the right and left insula and dorsal anterior cingulate cortex (dACC). (Middle and right) Correlations between self-reported externalizing tendencies [Externalizing Spectrum Inventory (ESI) score] and regional error-related activity (% BOLD Δ) among smokers (middle column) and non-smokers (right column). Higher ESI scores indicated less right insula recruitment following error commission among smokers, but not non-smokers as indicated by a significant ESI × GROUP interaction. A similar although non-significant outcome was observed when considering left insula activity. Higher ESI scores also indicated less dACC recruitment following errors among smokers. See Table 2 for region of interest coordinates. *$P < 0.05$

Table 2 Error-related brain activity.

	Center coordinates (Talairach)			
Region	*x*	*y*	*z*	*Cluster size (voxels)*
Insula/IFG (R)	55	15	3	64
Insula/IFG (L)	−46	14	1	174
dACC/pre-SMA (B)	1	18	42	344
Inferior parietal lobe (R)	59	−45	37	36
Inferior parietal lobe (L)	−42	−47	38	36
Thalamus (R)	9	−13	9	22
Thalamus (L)	−12	−19	6	45
Inferior frontal gyrus (L)	−52	6	27	10
Cueneus (B)	3	−74	6	156
Brainstem (B)	−1	−24	27	10

Note: Error-related activity was assessed at the whole-brain level (errors > correct; threshold *$P_{voxel\text{-}wise} < 10^{-5}$; cluster extent: 10 voxels). Voxel size: $3 \times 3 \times 3$ mm^3 (one voxel = 27 µl). Talairach coordinates X: left (−), right (+); Y: posterior (−), anterior (+); Z: inferior (−), superior (+). B: bilateral; L: left; R: right. Of particular interest, errors produced increased activation in clusters within the bilateral insulae that extended into the neighboring inferior frontal gyri (labeled as insula/IFG) and within the dorsal ACC extending into the pre-supplemental motor area (labeled as dACC/pre-SMA). dACC = dorsal anterior cingulate cortex; IFG = inferior frontal gyri; SMA = supplemental motor area.

Externalizing traits predicted task performance measures in smokers

When considering *between*-group differences, ESI scores were higher among smokers (0.20 ± 0.13) relative to non-smokers (0.10 ± 0.07); $t(40) = 2.9$, $P = 0.006$. We then assessed the influence of ESI scores on performance measures *within* groups by performing ANCOVAs (Supporting Information Table S3, Supporting Information Fig. S3). With respect to overall error rates, higher ESI scores were associated with the commission of more errors among smokers [$r(21) = 0.50$, $P_{corrected} = 0.045$], but not non-smokers [$r(17) = 0.07$, $P = 0.7$], ESI × GROUP: $F(2,39) = 3.6$, $P = 0.04$. Similarly, higher ESI scores were associated with faster overall RT among smokers [$r(21) = -0.64$, $P_{corrected} = 0.003$], but not non-smokers [$r(17) = -0.29$, $P = 0.2$], ESI × GROUP: $F(2,39) = 7.7$, $P = 0.002$. ESI scores also were positively correlated with miss rates among smokers, although this association failed to reach significance when corrected for multiple comparisons [$r(21) = 0.44$, $P_{corrected} = 0.09$]. As such, miss rates are not discussed further.

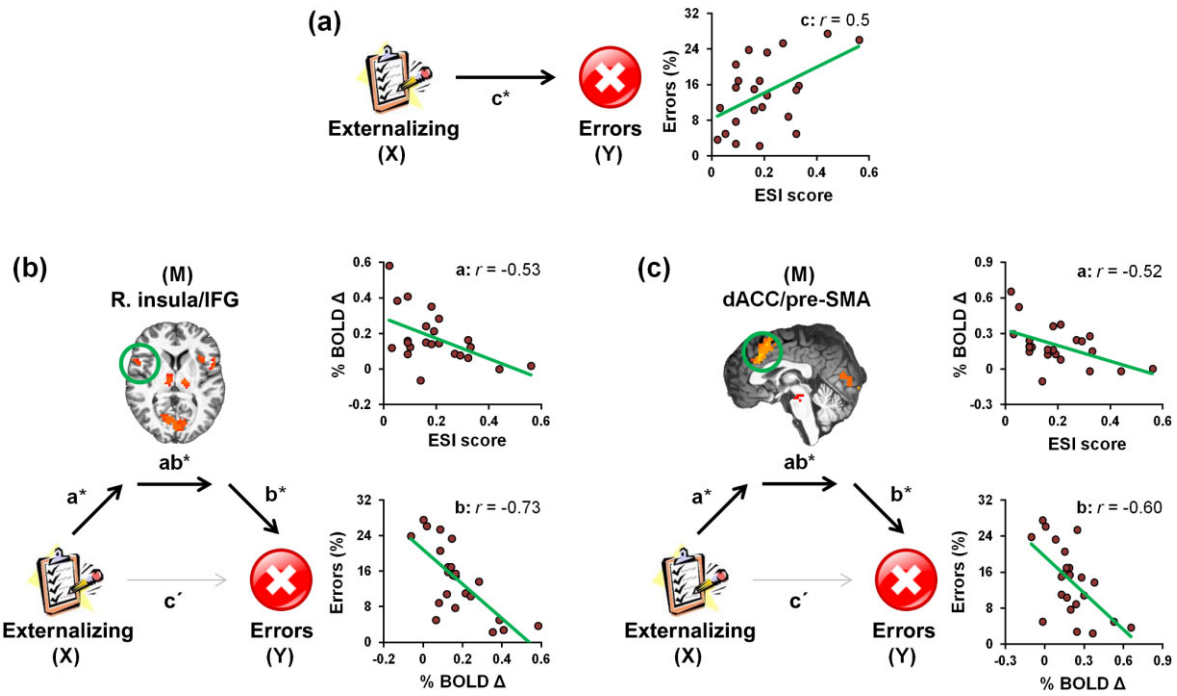

Figure 2 Mediation models of the association between externalizing tendencies, error rates and error-related brain activity among acutely abstinent smokers. (a) Externalizing Spectrum Inventory (ESI) scores were positively correlated with error rates (i.e. the total effect of X on Y was significant, c path). (b) Error-related right insula activity (M) fully mediated the effect of ESI scores (X) on error rates (Y) as: (1) ESI scores accounted for significant variance in insula activity (a path); (2) insula activity accounted for unique variance in error rates when controlling for ESI scores (b path); (3) the indirect mediation effect was significant (ab path); and (4) ESI's direct effect on errors was no longer significant when the insula mediator was included in the model (c′ path). (c) Similarly, error-related dorsal anterior cingulate cortex (dACC) activity (M) mediated the effect of ESI scores (X) on error rates (Y) when included as the sole mediator in a separate model. See Table 3 for path coefficients. *$P < 0.05$

Externalizing traits predicted less error-related brain activity in smokers

When considering error-related ROI activity, higher ESI scores were associated with less right insula/IFG activity among smokers [$r(21) = -0.53$, $P_{corrected} = 0.03$; Bonferroni corrected for three comparisons (left, right insula and dACC; $\alpha = 0.05/3$)], but not non-smokers [$r(17) = 0.33$, $P = 0.2$], ESI × GROUP: $F(2,39) = 4.1$, $P = 0.02$ (Fig. 1). We observed similar, albeit non-significant, outcomes when considering the relation between ESI scores and left insula/IFG activity [smokers: $r(21) = -0.4$, $P_{corrected} > 0.05$; non-smokers: $r(17) = 0.02$, $P = 0.9$; ESI × GROUP: $F(2,39) = 2.5$, $P = 0.09$]. Additionally, higher ESI scores were also associated with less error-related dACC/preSMA activity among smokers [$r(21) = -0.52$, $P_{corrected} = 0.04$], but not non-smokers [$r(17) = 0.18$, $P = 0.5$], although the ESI × GROUP interaction failed to reach significance, $F(2,39) = 2.5$, $P = 0.1$. Correlations between ESI scores and all ROIs showing error-related activity are presented in Supporting Information Table S4.

Error-related activity mediated externalizing's influence on smokers' performance

As externalizing traits correlated with both behavioral and brain measures during acute nicotine withdrawal, we subsequently conducted mediation analyses testing the hypothesis that the impact of ESI scores (X) on error rates (Y) was mediated by right insula and dACC activity (M) (Fig. 2; Table 3). Error-related right insula activity fully mediated the relation between ESI scores and error rates (Fig. 2b). Specifically, when including the insula mediator in the model, ESI's direct effect on error rates failed to reach significance (c′ path: $\beta = 9.6$, SE = 10.3, $P = 0.4$), whereas the indirect effect was significant (ab path: 95% CI: 7.0, 36.4). We observed a similar outcome when employing error-related dACC activity as the sole mediator in a separate model (c′ path: $\beta = 15.2$, SE = 11.7, $P = 0.2$; ab path: 95% CI: 2.7, 30.3; Fig. 2c). Indicative of *state/condition specificity*, these insula and dACC meditational relations appeared critically linked with acute nicotine withdrawal as such effects were not detected following nicotinic receptor stimulation by

Table 3 Path coefficients from separate mediation analyses characterizing the relations between externalizing tendencies (X), error rates (Y) and error-related brain activity (M) in acutely abstinent smokers.

	PATH				
Region	*a* *X-M*	*b* *M-Y*	*c* *X-Y (total)*	*c′* *Direct*	*ab* *Indirect*
Insula/IFG (R)[a]	−0.6 (0.2)**	−34.0 (9.4)**	29.2 (11.0)*	9.6 (10.3)	7.0, 36.4
dACC/pre-SMA (B)[a]	−0.7 (0.2)*	−21.1 (9.1)*	29.2 (11.0)*	15.2 (11.7)	2.7, 30.3
Inferior parietal lobe (R)	−0.6 (0.2)*	−17.5 (10.9)	29.2 (11.0)*	19.25 (12.2)	−2.0, 28.9

Note: For paths a, b, c and c′, values are reported as unstandardized path coefficients (standard error). For the ab path, values reported are the upper and lower bounds of the bootstrapped 95 percent confidence interval (95% CI). [a]See Fig. 2 for a schematic representation of these mediation analyses. *$P < 0.05$, **$P < 0.01$. dACC = dorsal anterior cingulate cortex; IFG = inferior frontal gyri; SMA = supplemental motor area.

varenicline and/or nicotine (Supporting Information Table S5, Supporting Information Fig. S4). These outcomes suggest that higher ESI scores predicted less error-related right insula and dACC activity and, in turn, less error-related activity predicted more performance errors *only* during nicotine withdrawal.

We subsequently conducted additional mediation analyses to provide support for the *regional* and *domain* specificity of the right insula and dACC mediational effects. Indicative of *regional specificity* and thus providing a negative control, error-related *right inferior parietal lobe* activity (activity that was negatively correlated with ESI scores in smokers, Supporting Information Table S4) did not mediate the relation between *ESI scores and error rates* (Supporting Information Table S6). Indicative of *domain specificity*, neither error-related right insula nor dACC activity mediated the relation between *ESI scores and RT* (Supporting Information Table S7).

Less error-related right insula and dACC activity indicated more tobacco craving

Finally, we conducted exploratory correlation analyses between TCQ ratings and error-related right insula and dACC activity (Fig. 3). Focusing on the TCQ-purposefulness subscale, higher levels of craving in acutely abstinent smokers were correlated with less error-related right insula [$r(21) = -0.49$, $P = 0.02$] and dACC activity [$r(21) = -0.45$, $P = 0.03$]. No significant correlations were detected between error-related activity and other TCQ-subscale scores (right insula: P's > 0.14; dACC: P's > 0.08), TCQ total scores [right insula: $r(21) = -0.37$, $P = 0.08$; dACC: $r(21) = -0.35$, $P = 0.1$], or Fagerström ratings (right insula: $P = 0.12$; dACC: $P = 0.2$).

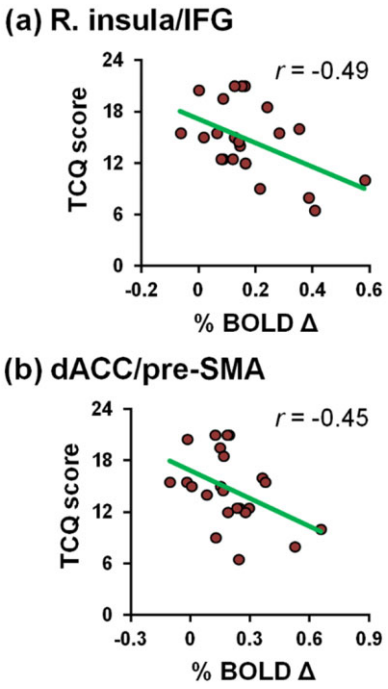

Figure 3 Error-related activity and tobacco craving among acutely abstinent smokers. Less error-related right insula (a) and dorsal anterior cingulate cortex (dACC) (b) activity correlated with higher scores on the TCQ-purposefulness subscale

DISCUSSION

Externalizing is a broad personality construct generally reflecting increased proneness to impulsive behaviors and is linked with reduced electrophysiological correlates of error processing (Hall *et al.* 2007; Nelson *et al.* 2011; Patrick *et al.* 2012). Given that reduced activity in canonical error-processing brain regions has been conceptualized as a contributing factor to continued drug use (Kaufman *et al.* 2003; Garavan & Stout 2005; Goldstein *et al.* 2009), we investigated the interrelations between externalizing tendencies, task performance and error-related brain activity in overnight-deprived cigarette smokers and non-smokers. We observed that higher externalizing tendencies among smokers were associated with a less optimal (increased error rates) and more impulsive task performance style (faster RTs). Indicative

of a neurobiological contribution to this suboptimal performance style, higher externalizing tendencies also were associated with less recruitment of the right insula and dACC following error commission. Critically, this error-related brain activity fully mediated the externalizing-performance relation as higher ESI scores indicated less right insula and dACC activity and, in turn, less error-related activity indicated the occurrence of more errors. As deficits in monitoring ongoing behaviors may contribute to the repetition of maladaptive responses and disadvantageous decisions, our results suggest that externalizing traits and/or error-related right insula/dACC activity may be relevant factors for smoking cessation success.

Behaviorally, smokers self-reporting higher degrees of externalizing committed more errors while also executing their responses more quickly. Such behavioral outcomes may have treatment implications as similar performance indices assessed during early abstinence have been used to predict smoking relapse (Patterson *et al.* 2010). Furthermore, Bold *et al.* (2013) noted that abstinent smokers who committed more errors in a sustained attention task showed greater difficulties inhibiting drug use impulses as indicated by quicker times to smoke when given the opportunity. Elevated externalizing tendencies themselves also predict subsequent tobacco use and have been associated with earlier age of smoking initiation as well as reduced cessation success in adolescents (Leff *et al.* 2003; Moolchan *et al.* 2007; Fischer *et al.* 2012). In parallel, trait impulsivity, a lower order facet of the broad externalizing construct, has been linked with elevated cigarette cue-reactivity (Doran *et al.* 2008) and increased abstinence-induced tobacco craving (VanderVeen *et al.* 2008). The affective and cognitive consequences of smoking abstinence appear to serve as more potent negative reinforcers in smokers with elevated impulsivity (Doran *et al.* 2006), which may account for greater difficulties in abstinence maintenance among such individuals (Doran *et al.* 2004). Despite accumulating evidence linking behavioral and personality indicators of externalizing tendencies with smoking behaviors, little research has examined the neurobiological mechanisms contributing to such a relation.

To this end, mechanistically, we observed that smokers higher in externalizing showed reduced recruitment of the right insula and dACC following error commission. Furthermore, we observed a pattern of correlations consistent with the hypothesis that the effect of externalizing on error rates was mediated by error-related activity in the right insula and dACC. Critically and indicative of state/conditional specificity, we observed these mediation effects only during nicotine withdrawal but not following drug administration (i.e. varenicline and nicotine). Whereas previous studies have noted *between*-group differences in error-related brain activity when comparing non-drug using controls with cocaine (Kaufman *et al.* 2003), methamphetamine (London *et al.* 2005), opiate (Forman *et al.* 2004), cannabis (Hester *et al.* 2009) and nicotine abusers (Luijten *et al.* 2011), our results suggest that *within*-group variations in externalizing traits account for additional variability in brain measures. Elucidating such individual variations may prove beneficial for facilitating the implementation of individualized treatment regimens.

The bilateral insulae and dACC are primary constituents of the so-called salience network and often co-activate in situations necessitating behavioral change (Dosenbach *et al.* 2006; Seeley *et al.* 2007; Ullsperger *et al.* 2010). The right insula appears to play a central role in the response of this network to errors, as input to other nodes has been suggested to propagate through this critical outflow hub (Ham *et al.* 2013). The bilateral insulae are further implicated in the conscious awareness of errors (Hester *et al.* 2005; Klein *et al.* 2013). With respect to drug abuse, right insula activity is lower in cannabis users performing an error awareness task and such activity is negatively correlated with amount of recent drug use (Hester *et al.* 2009). Furthermore, the dACC is thought to signal the need for behavioral adjustments following salient events via increased interactions with such regions as the lateral prefrontal cortex (Ridderinkhof *et al.* 2004; Ham *et al.* 2013). Using a modified Flanker task incorporating smoking cues to examine error processing in minimally deprived smokers, Luijten *et al.* (2011) detected reduced electrophysiological correlates of initial error processing (i.e. ERN amplitude) as well as reductions in a second event-related potential thought to index the motivational significance of an error (i.e. the error positivity, Pe). Our results demonstrating less error-related insula and dACC activity associated with higher externalizing are consistent with the findings of Luijten *et al.* (2011) who further observed smaller ERN amplitudes associated with greater trait impulsivity.

Taken together, one interpretation of our results is that insufficient recruitment of the right insula and dACC following error commission underlies decreased error awareness and/or a motivational insensitivity to errors in higher externalizing smokers during early smoking abstinence. This attenuated error response appears to be accompanied by the continued occurrence of suboptimal behaviors. These observations are consistent with the hypothesis that inadequate brain responses to errors contribute to continued drug use despite negative consequences (Goldstein & Volkow 2002; Goldstein *et al.* 2009) in some individuals.

Relating individual variation in brain activity with a clinically relevant construct, we further observed that

less error-related right insula and dACC activity conferred increased liability for tobacco craving during early smoking abstinence. Specifically, less error-related activity was associated with higher scores on the TCQ-purposefulness subscale. As craving is a multi-faceted psychological construct, the TCQ was developed as a multi-dimensional instrument (Heishman *et al.* 2003, 2008). The dimensions of craving assessed by the TCQ are as follows: emotionality (anticipation of withdrawal relief by smoking), expectancy (anticipation of positive outcomes by smoking), compulsivity (inability to control smoking) and purposefulness (intentions and planning to smoke). Our finding that error-related insula and dACC activity significantly correlated with only the TCQ-purposefulness subscale supports the notion that distinct neural circuits contribute to these various facets of tobacco craving. We have previously shown that insula and ventromedial prefrontal circuitry (regions implicated in emotional processing and regulation, e.g. Myers-Schulz & Koenigs 2012), selectively relate to the TCQ-emotionality subscale (Sutherland *et al.* 2013b). In light of the involvement of insula/dACC circuitry in goal-directed behaviors, it is not surprising that the error-related ROI activity described herein selectively correlated with the TCQ-purposefulness subscale.

Recent theorizing has related the insula's role in interoception with multiple stages of the addiction cycle (Paulus 2007; Craig 2009; Naqvi & Bechara 2010; Sutherland *et al.* 2013a). These views posit that insular reactivity and subsequent network dysregulation contribute to alterations in interoceptive functions and the phenomenological experience of drug craving that then limit cognitive resources available for behavioral monitoring and optimal decision making (Sutherland *et al.* 2012b). Systems-level perspectives highlight three large-scale brain networks and their roles in these psychological processes: the salience network (SN; Seeley *et al.* 2007), the default-mode network (DMN; Raichle *et al.* 2001) and the executive control network (ECN; Fox *et al.* 2005). The insulae and ACC are critical nodes of the SN, which plays a role in directing attention toward either internal or external stimuli by toggling dynamic activity between the typically anticorrelated DMN and ECN (Fox *et al.* 2005; Sridharan, Levitin & Menon 2008; Hamilton *et al.* 2011). As the DMN is generally associated with endogenous information processing and the ECN with exogenous information processing, intermittent failures to adequately suppress the DMN (Sonuga-Barke & Castellanos 2007) and/or maladaptive interactions between components of these two networks (Weissman *et al.* 2006; Kelly *et al.* 2008) represent systems-level mechanisms contributing to suboptimal goal-directed behavior in various neuropsychiatric conditions (Menon 2011) and during nicotine withdrawal (Sutherland *et al.* 2012b). In other words, the neurobiological mechanisms associated with the processing of endogenous, homeostatically relevant bodily states (i.e. abstinence-induced processes) may impede exogenous information processing and behavioral self-monitoring. This line of reasoning leads to the speculation that certain pharmacological agents such as methylphenidate, which augments error processing and associated brain activity in healthy volunteers (Hester *et al.* 2012), may restore optimal network dynamics and provide smoking cessation benefits as an adjunct intervention for high-externalizing smokers.

Our findings should be considered in light of several issues. First, we failed to detect group differences in error-related brain activity when comparing acutely abstinent smokers and non-smokers. However, this outcome is in line with the observations from electrophysiological studies that similarly did not detect smoker versus non-smoker differences in ERN amplitude when using a Flanker task comparable to that used in the current study (Franken, van Strien & Kuijpers 2010), but did detect such differences when incorporating cigarette cues into the task (Luijten *et al.* 2011). Such observations are consistent with the notion that presentation of cigarette cues and associated craving induction limits cognitive resources. Second, the range of ESI scores observed in our non-smokers was rather limited relative to that from the smoker cohort as well as the full dynamic range of the instrument. This limited range may account for an inability to detect significant associations between externalizing tendencies and error-related brain activity in the non-smoker group. Third, while the ESI assesses externalizing tendencies via personality trait and past-behavioral indicators, we cannot discount the possibility that state-like variations (e.g. smoking abstinence) influenced ESI scores. Fourth, regarding post-error slowing, we observed that RT among smokers was modestly, but significantly slower on trials following an error relative to trials following a correct response (Supporting Information Table S2). While the current task implementation was not designed or optimized to assess post-error slowing, we did not observe a post-error slowing effect among non-smokers. Fifth, given the correlational nature of the present study, an alternative explanation of the relationship between error-related right insula/dACC activity and error rates is that such ROI activity may 'habituate' as individuals commit more errors. Relatedly, while we used ESI scores as the predictor variable (X) and task performance or error-related brain activity as dependent variables (Y) in our analyses, the opposite approach is equally valid. Nonetheless, our results provide evidence for a relationship between the externalizing construct, error-related insula and dACC activity, and task performance indices. Finally, while reduced ERN amplitude has been

used to predict treatment outcomes in cocaine abusers (Marhe, van de Wetering & Franken 2013), the ability of error-related right insula or dACC activity to predict smoking cessation outcomes remains indeterminate.

In conclusion, our results highlight the utility of examining individual variation in personality traits, task performance and regional brain activity to elucidate neurobiological mechanisms potentially contributing to the persistence of drug use in general and cigarette smoking in particular. Specifically, we observed that higher externalizing tendencies in acutely abstinent smokers were associated with less recruitment of the right insula and dACC following error commission and that such diminished regional activity was associated with the occurrence of more errors during task performance. Additionally, diminished error-related right insula and dACC activity correlated with higher degrees of tobacco craving. Externalizing tendencies and/or compromised error processing in subsets of smokers during early abstinence may be relevant targets for smoking cessation treatments in the service of curtailing maladaptive behaviors and disadvantageous decisions precipitating relapse.

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Disclosure/Conflict of Interest

None reported.

Authors Contribution

MTS, BJS, TJR and EAS were responsible for the study concept and design. AJC, MTS, BJS and TJR contributed to data acquisition. MTS, AJC and TJR assisted with data analysis. MTS and AJC wrote the manuscript. BJS, TJR and EAS provided revision of the manuscript for intellectual content. All authors critically reviewed content and approved final version for publication.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1 Study design schematic

Figure S2 Reaction time (RT) among all participants was modulated by response outcome and trial type

Figure S3 Scatter plots depicting the relation between self-reported externalizing tendencies (ESI score) and task performance measures (error rates, RT and miss rates) within the smoker (left) and non-smoker groups (right)

Figure S4 Moderated mediation analysis examining the indirect effect of externalizing traits on error rates through error-related ROI activity as a function of drug session/condition in smokers

Table S1 Participant characteristics

Table S2 Post-error versus post-correct reaction time (RT) during acute nicotine withdrawal

Table S3 Correlations between self-reported externalizing tendencies and task performance measures in smokers and non-smokers during acute nicotine withdrawal

Table S4 Correlations between self-reported externalizing and error-related ROI activity among acutely abstinent smokers and non-smokers

Table S5 Path coefficients from the mediation analyses for all six scan sessions exploring the relations between externalizing tendencies (X), error rates (Y) and error-related brain activity (M)

Table S6 Path coefficients from the mediation analyses characterizing the relations between externalizing tendencies (X), error rates (Y) and error-related brain activity (M) during nicotine withdrawal

Table S7 Path coefficients from the mediation analyses characterizing the relations between externalizing tendencies (X), RT (Y) and error-related brain activity (M) during acute nicotine withdrawal