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Salience network coupling is linked to both tobacco smoking and symptoms of Attention Deficit Hyperactivity Disorder (ADHD)

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Abstract

Introduction—Attention deficit hyperactivity disorder (ADHD) symptoms, even those below diagnostic threshold, enhance the likelihood of nicotine dependence, suggesting a neurobiological link between disorders. Of particular interest is the salience network (SN), which mediates attention to salient internal/external stimuli to guide behavior and is anchored by the dorsal anterior cingulate cortex (dACC) and bilateral anterior insula (AI). Disrupted interactions between the SN and the default mode (DMN) and central executive networks (CEN) have been noted in both ADHD and nicotine dependence. Further, enhanced intra-SN coupling between the dACC-AI influences aspects of nicotine dependence such as reactivity to smoking cues.

Methods—To identify links between SN functional connectivity and ADHD symptoms in nicotine dependence, we compared 21 nicotine dependent individuals with 17 non-smokers on ADHD symptoms as measured by the ADHD self-report scale (ASRS) and resting state intra and inter-SN functional connectivity.

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Contributors

Conceived and designed the experiments: JMG, AEE, MF. Performed the experiments: MR JMG. Oversaw clinical aspects: GP, Analyzed the data: BBF, JMG, ACJ. Created in house software for imaging analysis BBF, Wrote the paper: ACJ. All authors have approved the final article.

Conflict of Interest

Eden Evins received research grant funding and/or study supplies to her institution from Forum Pharmaceuticals, GSK, and Pfizer, and has performed consulting work for Reckitt Benckiser and Pfizer. M. Fava was a consultant to Forum Pharmaceuticals and Envivo Pharmaceuticals. For a complete list of lifetime disclosures for M. Maurizio Fava, please see http://mghcme.org/faculty/faculty-detail/maurizio_fava. No conflict declared for A. Janes, J. Gilman, B. Frederick, M. Radoman, or G. Pachas.

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Results—Relative to healthy controls, nicotine dependent individuals had significantly higher ASRS scores and greater dACC-AI coupling. No group differences were noted on inter-SN network coupling. A significant association was found between ASRS and dACC-AI coupling both in the entire cohort and specifically when evaluating nicotine dependent individuals alone.

Conclusions—The greater ASRS scores in nicotine dependent individuals is in line with existent literature and the stronger dACC-AI coupling in smokers further supports the role of this network in nicotine dependence. The significant association between dACC-AI coupling and ASRS suggests that intra-SN coupling strength may impact neurocognitive functioning associated with both ADHD symptoms and nicotine dependence.

Keywords

Salience Network; Nicotine Dependence; Attention deficit hyperactivity disorder; insula; dorsal anterior cingulate cortex

1. Introduction

Smoking rates are significantly higher in those with psychiatric disorders, accounting for 40% of all cigarettes smoked (SAMHSA 2013). For example, the rates of smoking are almost two-fold greater in those with Attention Deficit Hyperactivity Disorder (ADHD) relative to psychiatrically healthy individuals (Pomerleau et al., 1995; Lambert et al., 1998). In fact, the risk for smoking and earlier initiation of nicotine use is associated with ADHD symptoms, even when these symptoms are below the threshold for clinical diagnosis (Kollins et al., 2005). Links between ADHD symptoms and nicotine dependence raise the possibility of shared neurobiological underpinnings between the disorders. One potential area of linkage may be disruptions of the salience network (SN), which is anchored by the dorsal anterior cingulate cortex (dACC) and bilateral anterior insula (AI). Generally, the SN is thought to integrate internal and extrapersonal information to guide behavior (Menon and Uddin, 2010), which is relevant in nicotine dependence, given the influence of salient internal (subjective feelings of craving, withdrawal) and external stimuli (smoking-related cues) on the motivation to smoke. The SN's role in focusing attention and guiding behavior also fits with the hallmark symptoms of ADHD including inattention, hyperactivity, and impulsivity (NIMH, 2017).

Salience network involvement in both disorders is supported by a wealth of information linking the primary nodes of this network with both ADHD and nicotine dependence. Specifically, the dACC strongly contributes to the pathophysiology of ADHD (for review see: Bush, 2011). Those with ADHD also have greater insula reactivity during affective processing (Wilbertz et al., 2017) and show insula and dACC hypo-activity during inhibitory tasks (Janssen et al., 2015). Insula function also plays a key role in nicotine use in human (Dias et al., 2006; Naqvi et al., 2007; Janes et al., 2010, 2015, 2017), and rodent models (Forget et al., 2010; Pushparaj et al., 2013), while dACC function and neurochemistry has been linked to difficulty ignoring smoking cues (Luijten et al., 2012; Janes et al., 2013). In terms of functional connectivity, ADHD and smoking withdrawal impacts the resource allocation index (RAI), which is a measure of SN-centered interactions with the executive control and default mode networks (ECN, DMN; Cai et al., 2015; Lerman et al., 2014).

Specifically, relative to healthy adolescents, those with ADHD show reduced RAI scores and decreased SN-ECN connectivity (Cai et al., 2015; von Rhein et al., 2017), suggesting that reduced communication between the SN and networks such as the ECN may contribute to ADHD. Evaluating SN relationships with both the ECN and DMN by evaluating RAI is critical given evidence that the SN facilitates switching between ECN and DMN dominated states allowing for effective cognition (Menon and Uddin, 2010). Connectivity within the SN, between the dACC and dorsal anterior insula, also plays a role in nicotine dependence, as connectivity strength between these regions is associated with reactivity to smoking cues (Janes et al., 2015) and severity of nicotine dependence (Moran et al., 2012; Wilcox et al., 2017). However, recent work showed that dACC-insula connectivity strength was not predictive of smoking relapse when controlling for baseline smoking (Wilcox et al., 2017) calling into question the specific role of dACC-AI coupling in nicotine dependence.

To address the SN's role in nicotine dependence, and links with ADHD, we compared nicotine dependent individuals and healthy controls on intra- and inter- SN connectivity using RAI scores and dACC-AI coupling respectively. For inter-SN connectivity we focused on the bilateral dorsal anterior insula given our prior work indicating this subregion's connectivity with the dACC was associated with smoking cue-reactivity (Janes et al., 2015). To evaluate ADHD symptoms, scores on the ADHD self-report scale (ASRS; Kessler et al., 2005) were compared between groups and the relationship between the ASRS and SN connectivity measures were assessed. The ASRS was chosen as this is a validated measure that has been successfully implemented in substance abusing populations (Daigre et al., 2009; Dakwar et al., 2012). While a score of 4 or higher on the ASRS is consistent with ADHD symptoms status, this metric allows for the assessment of ADHD symptoms ranging above and below threshold, which is critical given the link between ADHD symptoms and the development of nicotine dependence. Based on the existent literature discussed above we expect nicotine dependent individuals to show greater ADHD symptoms and enhanced intra-SN connectivity and reduced RAI scores.

2. Methods

Seventeen healthy controls (8 women, 9 men) and 21 nicotine dependent individuals (6 women, 15 men) were enrolled from a smoking cessation clinical trial (MGH; [NCT01480232](#)). Smokers met DSM-IV criteria for current nicotine dependence, reported smoking 5 cigarettes per day within the last six months and had expired air carbon monoxide (CO) 10ppm at screening (Bedfont Micro IV Smokerlyzer, Bedfont Scientific, Kent, England). Participants were excluded for current unstable medical illness, substance-use disorder other than nicotine in the prior 6 months, positive ten-panel urine screen for recent use of addictive drugs (Medimpex United Inc.), current major depressive disorder, lifetime diagnosis of bipolar disorder or schizophrenia, self-reported use of psychotropic medications, or positive pregnancy test. This study was approved by the Partners Human Subjects Committee. All participants were consented and compensated.

2.1 Assessments

Baseline smoking behavior was characterized by measuring expiratory CO levels, urine cotinine levels, and assessing pack-years of tobacco smoking, and severity of nicotine dependence (Fagerstrom Test for Nicotine Dependence (FTND); Heatherton et al., 1991) and craving (Tiffany Questionnaire of Smoking Urges (TQSU). The ASRS was evaluated during the screening visit approximately 1–2 weeks before the scanning visit.

2.2 Acquisition of Neuroimaging Data

All smokers were permitted to smoke prior to the scan to minimize withdrawal and scanning occurred approximately 1–1.5 hours after the last cigarette. They were scanned using a 3 T Siemens (Erlangen, Germany) Skyra scanner with a 32-channel head coil at the Martinos Center for Biomedical Imaging. Whole-brain T1-weighted 1 mm isotropic structural scans were collected using a 3D multiecho MPRAGE sequence (176 sagittal slices, 256 mm FoV, TR 2530 ms, TI 1200 ms, 2x GRAPPA acceleration, TE 1.64/3.5/5.36/7.22 ms). Functional scans were collected using a 2D gradient echo EPI sequence (31 slices, 3 mm thick, 0.6 mm gap, TR 3 s, TE 30 ms).

2.3 Resting State Analysis

Functional MRI analysis was implemented using software from the fMRI of the Brain (FMRIB) Software Library (FSL: www.fmrib.ox.ac.uk/fsl). Data were pre-processed using motion correction with MCFLIRT, brain extraction using BET, slice timing correction, spatial smoothing with a Gaussian kernel of full-width half-maximum 6mm, and high-pass temporal filtering with Gaussian weighted least squares straight-line fitting with $\sigma = 100$ s. Functional MRI data were registered to the MNI 152 standard space template with a $2 \times 2 \times 2$ resolution.

To prevent motion and other sources of noise from influencing the resting state connectivity measures, each subject's data were denoised using FSL's multivariate exploratory linear decomposition into independent components (MELODIC). The time courses of all independent components (ICs) were visually inspected and those representing noise were identified and regressed out (Kelly et al., 2010, Janes et al., 2015). After this de-noising, but prior to resting state analysis, we performed dynamic global signal regression (dGSR) on each subject's data to remove blood-borne systemic low frequency noise (Erdogan, 2016). dGSR regresses out systemic noise which can lead to inflated (or spurious) correlations between brain regions after correcting for blood arrival time in each voxel. This significantly reduces spurious correlations between regions without generating the spurious negative correlations which necessarily arise from standard (or static) global signal regression.

Time courses for the dACC and AI regions-of-interest (ROIs) were extracted from the denoised resting state data following dGSR. The bilateral AI ROI was used in our prior work assessing dACC-AI coupling (Janes et al., 2015) and was comprised of two 5-mm spheres located at MNI coordinates ($x = \pm 34$, $y = 26$, $z = 2$). While there are other insula subregions, the anterior insula is functionally connected with the dACC while mid/posterior insula regions are functionally connected with more posterior regions of the cingulate (Taylor et al., 2009). Furthermore, connectivity between this specific insula subregion and

the dACC showed an association with brain reactivity to smoking cues while the connectivity of other insula regions to the dACC did not (Janes et al., 2015). The dACC ROI also has been used to evaluate dACC-AI coupling (Janes et al., 2015) and was comprised of two 5-mm spheres located at MNI coordinates (0,32,20) and (0,24,26). The ROIs for the SN, ECN, and DMN were taken from Smith et al., 2009. The average time course for each ROI were demeaned, detrended, Hamming windowed (Oppenheimer and Shafer, 1975, page 242) and correlated resulting in one correlation value (r) per individual. Maximal correlation values were calculated allowing for a possible time lag between signals, thus allowing for the detection of correlated yet temporally offset signals (Janes et al., 2015). This differs from the Pearson correlation approach that calculates relationships with a zero-time delay between signals, which may miss identifying true associations. To calculate RAI, correlations were calculated between the SN-DMN and SN-ECN. These values were then z transformed and RAI was calculated by: $RAI = (SN, ECN \text{ coupling}) - (SN, DMN \text{ coupling})$ (Lerman et al., 2014). Since the ECN separates into a right and left lateralized network two RAI scores were calculated involving the right or left ECN individually.

3. Results

3.1 Demographics

Smokers and non-smokers did not differ in age ($p = 0.4$) or education level ($p = 0.1$) but did differ on expired CO ($p < 0.001$). See Table 1 for demographic information.

3.2 Brain Coupling

There were no group differences in RAI when considering either RAI scores incorporating the right ($p = 0.84$) or left lateralized ($p = 0.68$) ECN along with the SN and DMN. Smokers had significantly greater dACC-AI coupling relative to healthy controls (smokers: 0.53 ± 0.175 , healthy controls: 0.33 ± 0.30 , $p = 0.013$, Figure 1), a finding that was still significant when Bonferroni correcting for multiple comparisons accounting for the three total measures of intra-and inter-SN coupling. Given the significant group difference in inter-SN coupling, subsequent analyses focused on dACC-AI coupling and not RAI scores.

3.3 ASRS

In comparison to healthy controls, smokers reported more ADHD symptoms as indicated by greater ASRS score (smokers: 2.8 ± 1.8 ; healthy controls: 0.71 ± 1.3 , $p < 0.001$). Specifically, 90% of smokers reported at least one symptom on the ASRS, with 47.6% reporting a score of 4 or greater. In comparison, 25% of healthy controls reported at least one symptom on the ASRS and only one non-smoker reported a score of 4.

3.4 ASRS and Intra-SN Coupling

Independently evaluating groups showed that this correlation was significant in smokers ($r = 0.58$, $p < 0.01$, Figure 2) but not healthy controls ($r = 0.24$, $p = 0.35$). The lack of a stronger association between ASRS and intra-SN coupling in healthy controls appears to be driven by a floor effect in ADHD symptoms for the non-smoking cohort.

dACC-insula coupling and ASRS showed no association with FTND ($r=0.21$, $p=0.6$, $r = 0.05$, $p = 0.84$ respectively), pack-year ($r = -0.26$, $p = 0.26$, $r = -0.22$, $p = 0.34$) or cigarettes smoked per day as reported over the last week ($r = -0.11$, $p = 0.6$, $r = -0.06$, $p = 0.8$). Given the prior report showing dACC-AI coupling is associated with the number of cigarettes smoked in the last 60 days, this value was estimated based on the 7-day self-report and no significant relationship was found between intra-SN coupling and 60-day cigarette use ($r = -0.28$, $p = 0.2$).

4. Discussion

The SN, along with networks such as the ECN and DMN are implicated across neuropsychiatric disorders (Menon, 2011). The current findings fit within this framework as smokers, relative to controls, showed significantly greater intra-SN connectivity. Somewhat surprisingly, there were no group differences in RAI score, which is a measure of SN interactions with the DMN and ECN, indicating that inter-network interactions did not differ based on smoking status. This lack of difference may be due to nicotine dependent individuals being allowed to smoke prior to scanning (~1–1.5 prior), as others reported that RAI is higher in sated vs. overnight abstinent smokers (Lerman et al., 2014), suggesting that nicotine abstinence may reveal additional group differences. In relation to dACC-AI coupling, our prior work showed that coupling strength in smokers was not influenced by exposure to smoking cues or following an hour delay since smoking, suggesting that dACC-AI strength is stable during early abstinence. The idea that acute changes in nicotine do not influence intra-SN connectivity is supported by Moran et al. (2012) who showed no change in intra-SN coupling strength following nicotine administration. Whether dACC-AI connectivity changes over longer-term abstinence is still unclear. However, the prior literature showing dACC-AI stability suggests that intra-SN connectivity may be a trait difference between smokers and non-smokers. Collectively, our findings indicate that intra- but not inter-SN connectivity differs between non-smokers and smokers who recently smoked.

The present work also found group differences in ASRS scores, with nicotine dependent individuals reporting significantly greater ADHD symptoms during their screening visit following smoking as usual. These symptoms positively correlate with dACC-AI coupling strength suggesting that intra-SN communication may contribute to these symptoms. This association was significant in the nicotine dependent group. It is likely that the low level of ADHD symptoms in the non-smokers diminished the ability to see an association in this group alone, and assessing non-smokers with more pronounced ADHD symptoms may reveal a significant correlation in nonsmokers as well. Thus, it is plausible that dACC-AI coupling may be associated with ADHD symptoms more broadly and not only in those who smoke. However, this hypothesis is speculative and requires further testing. Despite this, when evaluating smokers and non-smokers lacking a formal ADHD diagnosis, the significantly higher ADHD symptoms and dACC-AI coupling in smokers fits with the existent literature and supports the idea that these factors contribute to nicotine dependence.

Defining a single, specific role to the SN is difficult as the dACC and AI co-activate across a wide range of tasks, indicating that these regions play a ubiquitous role in cognitive and

emotional processes. One theory is that these regions form a system pertaining to self-awareness and related responses. Awareness of cognitive, affective, and physical state is thought to be integrated by the AI, which projects to the dACC leading to response selection (Dosenbach et al., 2006). This hypothesis fits with Posner's (1988) claim that the ACC plays a specific role in "attention for action" as well as the idea that the dACC and AI are involved in attentional direction and salience processing (Seeley et al., 2007). These processes are disrupted by damage to either SN node as stroke damaging the insula reduces motivation and drive (Manes et al., 1999), including the motivation to smoke (Naqvi et al., 2007) and cingulotomy patients note impairments in the initiation of behavior and formation of intentions (Cohen et al., 1999). It is plausible that optimal dACC-AI communication falls along a continuum with too little communication resulting in the deficits noted above while enhanced connectivity results in aberrant SN function contributing to greater reactivity to salient external stimuli such as smoking cues (Janes et al., 2015) and neurocognitive symptoms associated with ADHD.

Emerging literature suggests a link between disrupted SN connectivity and ADHD. Relative to healthy adolescents, those with ADHD show reduced RAI scores and decreased SN-ECN connectivity (Cai et al., 2015; von Rhein et al., 2017). One hypothesis suggests that individuals with ADHD have an immature SN which may contribute to both a lack of proper task preparation and over-activation of the SN resulting in impulsivity (Aboitiz et al., 2014), which is a common trait noted in those with a substance abuse disorder (Belin et al., 2008). Further, adults with ADHD have been found to have enhanced SN connectivity with other brain regions such as the putamen, which the author interprets as contributing to enhanced sensitivity to external stimuli (Dongchuan, 2013). This theory fits with the idea that individuals with ADHD are more susceptible to interfering irrelevant stimuli (Lopez et al., 2006). In relation to nicotine dependence, interference from external, irrelevant smoking stimuli predicts relapse vulnerability (Janes et al., 2010; Waters et al., 2003). Such behavioral interference is associated with the function and neurochemistry of the SN nodes (Luijten et al., 2012; Janes et al., 2010; Janes et al., 2013) and individuals with stronger dACC-AI connectivity at rest show greater brain reactivity to smoking cues (Janes et al., 2015). Collectively this suggests that greater dACC-AI connectivity may influence neurocognitive properties leading to enhanced interference and behavioral reactivity to external stimuli contributing to both ADHD and nicotine dependence. This conjecture is supported by recent work showing that moment-to-moment changes in arousal is associated with changes in SN connectivity (Young et al., 2017). Specifically, inter-SN connectivity linearly increases with arousal, while SN-ECN connectivity shows an inverted-U shape pattern of connectivity, peaking at moderate arousal levels before dropping off at higher levels of arousal. While arousal was not measured directly in this study, it is plausible that the group differences and association with ADHD scores may map to differences in response to arousing stimuli. However, this hypothesis requires more direct testing.

While dACC-AI coupling was significantly greater in smokers, coupling strength was not associated with any smoking-related clinical variable (i.e., FTND, pack-year, CO). Prior reports have shown a weak negative association between dACC-AI coupling and number of cigarettes smoked over the past 60 days (Wilcox et al., 2017). However, the association we report in the current work ($r = -0.28$) was not statistically different ($z = 0.32$, $p = 0.75$) from

the value reported by Wilcox et al. 2017 ($r = -0.21$, $p < 0.05$) who reported a significant association due to their larger sample size ($N = 144$). Nevertheless, the similar correlation values between studies suggests dACC-AI coupling may contribute in a small way to the variance in cigarettes smoked per day. It is possible that more posterior regions of the ACC and insula play a stronger role in this aspect of smoking behavior, as weaker connectivity between more caudal regions of the ACC and posterior insula is associated with nicotine addiction severity (Moran et al., 2012). In line with this, poorer cessation outcome has been associated with weaker posterior insula connectivity to primary somatosensory regions (Addicott et al., 2015). Nicotine dependence severity also has been associated with weaker coupling between the dACC-dorsal striatum (Hong et al., 2009). The dorsal striatal activation reported by Hong did show slight overlap with the ventral posterior region of the insula, mirroring findings reported by Moran above. Collectively, these studies suggest that weaker dACC communication with regions beyond the dorsal anterior sub region of the insula studied here may be associated with dependence severity. The strong involvement of the currently studied dACC and insula regions is supported by the vast findings that these regions co-activate during smoking cue-exposure across studies (Englemann et al., 2012; Franklin et al., 2007; McClernon et al., 2005; Brody et al., 2002; Claus et al., 2013) and during cue-exposure the insula shows enhanced connectivity with brain circuits involved in motivated behavior (Claus et al., 2013). Thus, enhanced communication within the SN may not ubiquitously contribute to nicotine dependence but, as discussed above, this network may play a specific role in those aspects of nicotine dependence related to the function of this circuit such as reactivity to salient stimuli.

The current work has several limitations including our inability to define causality as our work relied on correlations to identify relationships between dACC-AI coupling and ASRS symptoms. Whether dACC-AI coupling strength changes along with a reduction in ADHD symptoms in those receiving effective treatment may provide a more causal link. The limited sample size also restricts our ability to identify the interaction of our main variables with other pertinent biological variables such as sex, which is relevant given sex differences in nicotine dependence (Dumais et al., 2017; Wetherill, et al., 2016). Despite these limitations, our work not only supports prior findings that ADHD symptoms contribute to nicotine dependence, but this work strengthens the idea of SN involvement in nicotine dependence. The current findings further the field by linking ADHD symptoms with intra-SN coupling, which may explain the high rates of smoking in those with ADHD and suggests a neurobiological treatment target that may aid both disorders.

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References

Aboitiz F, Ossandón T, Zamorano F, Palma B, Carrasco X, 2014 Irrelevant stimulus processing in ADHD: catecholamine dynamics and attentional networks. *Front. Psychol* 5, 183. [PubMed: 24723897]

- Addicott MA, Sweitzer MM, Froeliger B, Rose JE, McClernon FJ, 2015 Increased functional connectivity in an insula-based network is associated with improved smoking cessation outcomes. *Neuropsychopharmacol.* 40, 2648–2656.
- Belin D, Mar AC, Dalley JW, Robbins TW, Everitt BJ, 2008 High impulsivity predicts the switch to compulsive cocaine-taking. *Science* 320, 1352–1355. [PubMed: 18535246]
- Brody AL, Mandelkern MA, London ED, Childress AR, Lee GS, Bota RG, Ho ML, Saxena S, Baxter LR Jr., Madsen D, Jarvik ME, 2002 Brain metabolic changes during cigarette craving. *Arch. Gen. Psychiatry* 59, 1162–1172. [PubMed: 12470133]
- Bush G, 2011 Cingulate, frontal, and parietal cortical dysfunction in attention-deficit/hyperactivity disorder. *Biol. Psychiatry* 69, 1160–1167. [PubMed: 21489409]
- Cai W, Chen T, Szegletes L, Supekar K, Menon V, 2015 Aberrant cross-brain network interaction in children with attention-deficit/hyperactivity disorder and its relation to attention deficits: A multisite and cross-site replication study. *Biol. Psychiatry*
- Claus ED, Blaine SK, Filbey FM, Mayer AR, Hutchison KE, 2013 Association between nicotine dependence severity, BOLD response to smoking cues, and functional connectivity. *Neuropsychopharmacol.* 38, 2363–2372. 10.1038/npp.2013.134
- Daigre C, Ramos-Quiroga JA, Valero S, Bosch R, Roncero C, Gonzalvo B, Nogueira M, 2009 Adult ADHD self-Report scale (ASRS-v1.1) symptom checklist in patients with substance use disorders. *Actas Esp. Psiquiatr.* 37, 299–305. [PubMed: 20066581]
- Dakwar E, Mahony A, Pavlicova M, Glass A, Brooks D, Mariani JJ, Grabowski J, Levin FR, 2012 The utility of attention-deficit/hyperactivity disorder screening instruments in individuals seeking treatment for substance use disorders. *J. Clin. Psychiatry* 73, 1372–1378.
- Dias ND, Peechatka AL, Janes AC, 2016 Insula reactivity to negative stimuli is associated with daily cigarette use: A preliminary investigation using the Human Connectome Database. *Drug Alcohol Depend.* 159, 277–280. [PubMed: 26748411]
- Dongchaun Y, 2013 Additional brain functional network in adults with attention-deficit/hyperactivity disorder: A phase synchrony analysis. *PLoS One* 8, e54516. [PubMed: 23382908]
- Dosenbach NU, Visscher KM, Palmer ED, Miezin FM, Wenger KK, Kang HC, Burgund ED, Grimes AL, Schlaggar BL, Petersen SE, 2006 A core system for the implementation of task sets. *Neuron* 50, 799–812. [PubMed: 16731517]
- Dumais KM, Franklin TR, Jagannathan K, Hager N, Gawrysiak M, Betts J, Farmer S, Guthrie E, Pater H, Janes AC, Wetherill RR, 2017 Multi-site exploration of sex differences in brain reactivity to smoking cues: Consensus across sites and methodologies. *Drug Alcohol Depend.* 178, 469–476. [PubMed: 28711813]
- Engelmann JM, Versace F, Robinson JD, Minnix JA, Lam CY, Cui Y, Brown VL, Cinciripini PM, 2012 Neural substrates of smoking cue reactivity: A meta-analysis of fMRI studies. *NeuroImage* 60, 252–262. [PubMed: 22206965]
- Erdo an SB, Tong Y, Hocke LM, Lindsey KP, Frederick BD, 2016 Correcting for blood arrival time in global mean regression enhances functional connectivity analysis of resting state fMRI-BOLD signals. *Front. Hum. Neurosci* 10, 253. [PubMed: 27313521]
- Forget B, Pushparaj A, Le Foll B, 2010 Granular insular cortex inactivation as a novel therapeutic strategy for nicotine addiction. *Biol. Psychiatry* 68, 265–271. [PubMed: 20299008]
- Franklin TR, Wang Z, Wang J, Sciortino N, Harper DLY, Li Y, Ehrman R, Kampman K, O'Brien CP, Detre JA, Childress AR, 2007 Limbic activation to cigarette smoking cues independent of nicotine withdrawal: A perfusion fMRI study. *Neuropsychopharmacol.* 32, 2301–2309.
- Hong LE, Gu H, Yang Y, Ross TJ, Salmeron BJ, Buchholz B, Thaker GK, Stein EA, 2009 Association of nicotine addiction and nicotine's actions with separate cingulate cortex functional circuits. *Arch. Gen. Psychiatry* 66, 431–441. [PubMed: 19349313]
- Janes AC, Farmer S, Peechatka AL, Frederick B, Lukas SE, 2015 Insula-dorsal anterior cingulate cortex coupling is associated with enhanced brain reactivity to smoking cues. *Neuropsychopharmacol.* 40, 1561–8. 10.1038/npp.2015.9
- Janes AC, Gilman JM, Radoman M, Pachas G, Fava M, Evins AE, 2017 Revisiting the role of the insula and smoking cue-reactivity in relapse: A replication and extension of neuroimaging

findings. *Drug Alcohol Depend.* 179, 8–12. 10.1016/j.drugalcdep.2017.06.012 [PubMed: 28735078]

Janes AC, Pizzagalli DA, Richardt S, Frederick B. deB., Chuzi S, Pachas G, Culhane MA, Holmes AJ, Fava M, Evins AE, Kaufman MJ, 2010 Brain reactivity to smoking cues prior to smoking cessation predicts ability to maintain tobacco abstinence. *Biol. Psychiatry* 67, 722–729. 10.1016/j.biopsych.2009.12.034 [PubMed: 20172508]

Janes AC, Jensen JE, Farmer SL, Frederick B, Pizzagalli DA, Lukas SE, 2013 GABA levels in the dorsal anterior cingulate cortex associated with difficulty ignoring smoking-related cues in tobacco-dependent volunteers. *Neuropsychopharmacol.* 38, 1113–1120.

Janssen TWP, Heslenfeld D, van Mourik R, Logan GD, Oosterlaan J, 2015 Neural correlates of response inhibition in children with attention-deficit/hyperactivity disorder: A controlled version of the stop-signal task. *Psychiatry Res. Neuroimag* 233, 278–284. 10.1016/j.psychresns.2015.07.007

Kelly RE, Alexopoulos GS, Wang Z, Gunning FM, Murphy CF, Morimoto SS, Kanellopoulos D, Jia Z, Lim KO, Hoptman MJ, 2010 Visual inspection of independent components: Defining a procedure for artifact removal from fMRI data. *J. Neurosci. Methods* 189, 233–245. [PubMed: 20381530]

Kessler RC, Adler M, Ames M, Demler O, Faraone S, Hiripi E, Howes MJ, Jin R, Secnik K, Spencer T, Ustun TB, Walters EE, 2005 The world organization adult ADHD self-report scale (ASRS): A short screening scale of use in the general population. *Psychol. Med* 35, 245–266. [PubMed: 15841682]

Kollins SH, McClernon J, Fuemmeler BF, 2005 Association between smoking and attention-deficit hyperactivity disorder symptoms in a population based sample of young adults. *Arch. Gen. Psychiatry* 62, 1142–7. [PubMed: 16203959]

Lambert MM, Hartsough CS, 1998 Prospective study of tobacco smoking and substance dependencies among samples of ADHD and non-ADHD participants. *J. Learn Disabil* 31, 533–544. [PubMed: 9813951]

Lerman C, Gu H, Loughhead J, Ruparel K, Yang Y, Stein EA, 2014 Large-scale brain network coupling predicts acute nicotine abstinence effects on craving and cognitive function. *JAMA Psychiatry* 71, 523–30. [PubMed: 24622915]

López V, López-Calderón J, Ortega R, Kreither J, Carrasco X, Rothhammer P, Rothhammer F, Rosas R, Aboitiz F, 2006 Attention-deficit hyperactivity disorder involves differential cortical processing in a visual spatial attention paradigm. *Clin. Neurophysiol* 117, 2540–2548. 10.1016/j.clinph.2006.07.313 [PubMed: 17000133]

Luijten M, Veltman DJ, Hester R, Smits M, Peppinkhuizen L, Franken IHA, 2012 Brain activation associated with attentional bias in smokers is modulated by a dopamine antagonist. *Neuropsychopharmacol.* 37, 2772–2779.

Manes F, Springer J, Jorge R, Robinson RG, 1999 Verbal memory impairment after left insular cortex infarction. *J. Neurol. Neurosurg. Psychiatry* 67, 532–534. 10.1136/jnnp.67.4.532 [PubMed: 10486407]

McClernon FJ, Hiott FB, Huettel SA, Rose JE, 2005 Abstinence-induced changes in self-report craving correlate with event-related fMRI responses to smoking cues. *Neuropsychopharmacol.* 30, 1940–1947. 10.1038/sj.npp.1300780

Moran LV, Sampath H, Stein EA, Hong LE, 2012 Insular and anterior cingulate circuits in smokers with schizophrenia. *Schizophrenia Res.* 142, 223–229.

Menon V, 2011 Large-scale brain networks and psychopathology: A unifying triple network model. *Trends Cogn. Sci* 15, 483–506. [PubMed: 21908230]

Menon V, Uddin LQ, 2010 Saliency, switching, attention and control: A network model of insula function. *Brain Struct. Funct* 214, 655–667. 10.1007/s00429-010-0262-0 [PubMed: 20512370]

Naqvi NH, Rudrauf D, Damasio H, Bechara A, 2007 Damage to the insula disrupts addiction to cigarette smoking. *Science* 315, 531–534. 10.1126/science.1135926 [PubMed: 17255515]

NIMH, 2016 Attention Deficit Hyperactivity Disorder. <https://www.nimh.nih.gov/health/topics/attention-deficit-hyperactivity-disorder-adhd/index.shtml> (retrieved 8/17/17)

Oppenheim AV, Schaffer RW, 1975 Digital Signal Processing. Prentice-Hall International London pp. 242.

- Pomerleau OF, Downey KK, Stelson FW, Pomerleau CS, 1995 Cigarette smoking in adult patients diagnosed with attention deficit hyperactivity disorder. *J. Subst. Abuse* 7, 373–8. [PubMed: 8749796]
- Posner MI, Petersens P, Raichle M, 1988 Localization of cognitive operations in the human brain. *Science* 240, 1627–31. [PubMed: 3289116]
- Pushparaj A, Hamani C, Yu W, Shin DS, Kang B, Nobrega JN, Le Foll B, 2012 Electrical stimulation of the insular region attenuates nicotine-taking and nicotine-seeking behaviors. *Neuropsychopharmacology* 38, 690–8. [PubMed: 23249816]
- Seeley WW, Menon V, Schatzber AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD, 2007 Dissociable intrinsic connectivity networks for salience processing and executive control. *J. Neurosci* 27, 2349–2356. [PubMed: 17329432]
- Smith SM, Fox PT, Miller KL, 2009 Correspondence of the brain's functional architecture during activation at rest. *Proc. Natl. Acad. Sci. U.S.A* 106, 13040–13045. [PubMed: 19620724]
- Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality, 2013 The NSDUH Report: Adults With Mental Illness or Substance Use Disorder Account for 40 Percent of All Cigarettes Smoked [PDF–563 KB]. Rockville, MD
- Taylor KS, Seminowicz DA, Davis KD, 2009 Two systems of resting state connectivity between the insula and cingulate cortex. *Hum. Brain Mapp* 30, 2731–2745. [PubMed: 19072897]
- von Rhein D, Beckmann CF, Franke B, Oosterlaan J, Heslenfeld DJ, Hoekstra PJ, Hartman CA, Luman M, Faraone SV, Cools R, Buitelaar JK, Mennes M, 2017 Network-level assessment of reward-related activation in patients with ADHD and healthy individuals. *Hum. Brain Mapp* 38, 2359–2369. [PubMed: 28176434]
- Waters AJ, Shiffman S, Sayette MA, Paty JA, Gwaltney CJ, Balabanis MH, 2003 Attentional bias predicts outcome in smoking cessation. *Health Psychol.* 22, 378–387. [PubMed: 12940394]
- Wetherill RR, Franklin TR, Allen SS, 2016 Ovarian hormones, menstrual cycle phase, and smoking: A review with recommendations for future studies. *Curr. Addict. Rep* 3, 1–8. [PubMed: 27134810]
- Wilbertz G, Delgado M, Van Elst Tebartz L, Maier S, Philippsen A, Blechert J, 2017 Neural response during anticipation of monetary loss is elevated in adult attention deficit hyperactivity disorder. *World J. Biol. Psychiatry* 18, 268–278. 10.3109/15622975.2015.1112032 [PubMed: 26508322]
- Wilcox CE, Calhoun VD, Rachakonda S, Claus ED, Littlewood RA, Mickey J, Arenella PB, Hutchison KE, 2017 Functional network connectivity predicts treatment outcome during treatment of nicotine use disorder. *Psychiatry Res.* 265, 45–53. 10.1016/j.psychresns.2017.04.011
- Young CB, Raz G, Everaerd D, Beckman CF, Tendolkar I, Hendler T, Gernandez G, Hermans EJ 2017 Dynamic shifts in large-scale brain network balance as a function of arousal. *J. Neurosci* 37, 281–290. [PubMed: 28077708]

Highlights

- Salience network (SN) coupling is greater in tobacco smokers vs. non-smokers.
- Relative to healthy controls, smokers have more Attention Deficit Hyperactivity Disorder (ADHD) symptoms.
- Intra-SN connectivity is positively associated with ADHD symptoms.

Figure 1. Relative to healthy controls, nicotine dependent tobacco smokers have significantly greater dACC-AI coupling at rest.

Figure 2. ASRS symptoms are positively correlated with dACC-AI coupling at rest. This association was significant in those with nicotine dependence.

Table 1.

Demographics comparing smokers to healthy controls. Smokers did not differ on age, or education but a significant difference was found in expired carbon monoxide levels. Information also is reported for specific smoking variables within the nicotine dependent cohort.

	Healthy Controls <i>n</i> = 17	Smokers <i>n</i> = 21	<i>P</i>
Age (years)	43.6 ± 11.3	39.9 ± 12.0	0.4
Education (years)	15.41 ± 2.2	14.4 ± 1.6	0.1
Cigarettes per day	0	19.0 ± 9.8	--
Expired CO (ppm)	2.29 ± 1.26	23.1 ± 15.1	0.000
FTND	0	5.3 ± 2.6	--
Total Craving Score (TQSU)	0	41.6 ± 13.9	--