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Nicotine acutely alters temporal properties of resting brain states

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ABSTRACT

Background: Nicotine-dependent individuals have altered activity in neurocognitive networks such as the default mode (DMN), salience (SN) and central executive networks (CEN). One theory suggests that, among chronic tobacco smokers, nicotine abstinence drives more DMN-related internal processing while nicotine replacement suppresses DMN and enhances SN and CEN. Whether acute nicotine impacts network dynamics in non-smokers is, however, unknown.

Methods: In a randomized double-blind crossover study, 17 healthy non-smokers (8 females) were administered placebo and nicotine (2-mg lozenge) on two different days prior to collecting resting-state functional magnetic resonance imaging (fMRI). Previously defined brain states in 462 individuals that spatially overlap with well-characterized resting-state networks including the DMN, SN, and CEN were applied to compute state-specific dynamics at rest: total time spent in state, persistence in each state after entry, and frequency of state transitions. We examined whether nicotine acutely alters these resting-state dynamics.

Results: A significant drug-by-state interaction emerged; post-hoc analyses clarified that, relative to placebo, nicotine suppressed time spent in a frontoinsular-DMN state (posterior cingulate cortex, medial prefrontal cortex, anterior insula, striatum and orbitofrontal cortex) and enhanced time spent in a SN state (anterior cingulate cortex and insula). No significant findings were observed for persistence and frequency.

Conclusions: In non-smokers, nicotine biases resting-state brain function away from the frontoinsular-DMN and toward the SN, which may reduce internally focused cognition and enhance salience processing. While past work suggests nicotine impacts DMN activity, the current work shows nicotinic influences on a specific DMN-like network that has been linked with rumination and depression.

1. Introduction

Nicotine, the main psychoactive ingredient in tobacco cigarettes, impacts large-scale neurocognitive networks such as the default mode (DMN), salience (SN), and central executive networks (CEN; for review see Sutherland et al., 2012). For example, in chronic smokers, nicotine abstinence enhances DMN-SN functional connectivity and reduces CEN-SN functional connectivity (Lerman et al., 2014). In contrast, nicotine replacement mitigates such connectivity changes (Sutherland et al., 2012), leading to improved cognition and reduced craving (Lerman et al., 2014; Cole et al., 2010). Collectively, these studies highlight nicotine's influence on the *static* dimensions of network functioning (e.g., overarching functional connectivity across the entire duration of the function magnetic resonance imaging [fMRI]scan). While such studies clarify specific aspects of how the brain is functionally organized on average, what remains relatively underexplored is how nicotine impacts the time-varying or *dynamic* functions of these resting-state networks.

The brain at rest has been shown to vary both its functional connectivity and activation patterns across time (Allen et al., 2014). During the course of a fMRI scan, the brain transitions between a number of states, staying in one for some time period before transitioning out of that state and into another. Newer methods have emerged to capture these dynamic properties (for review see Hutchison et al., 2013), including co-activation pattern (CAP) analysis (Liu et al., 2018, 2013; Kaiser et al., 2019; Chen et al., 2015). Using a fully data-driven approach, CAP analysis temporally segregates the brain into distinct

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spatial activation patterns—or states—to measure time-dependent *dynamic* properties such as total time spent in each state (i.e., time in state), total number of transitions into each state (i.e., frequency), and time spent in the state during each transition (i.e., persistence). These *dynamic* properties are beginning to provide novel insights about neural systems underlying psychological/biological constructs; for instance, rumination and depression have been linked to increased time spent in a frontoinsula-DMN state (Kaiser et al., 2019), and we have recently shown that in nicotine-dependent individuals, spending more time in the DMN state at rest positively predicts greater brain reactivity to smoking cues and a subsequent rise in cue-induced craving (Wang et al., 2020a). Whether nicotine acutely impacts resting-state network dynamics in non-smoking individuals, however, remains unclear. Answering this question will enhance the field's understanding of how nicotine's early influence on brain function may contribute to continued use.

To fill this gap, the current study used a double-blind crossover design to examine the effect of acute nicotine administration, relative to placebo, on state dynamics during resting-state fMRI. We applied state definitions from a large healthy sample (N = 426) from the Human Connectome Project (Janes et al., 2020; Van Essen et al., 2013) to divide the brain into eight states that spatially overlap with well-defined resting state networks (e.g., DMN, SN, CEN). CAP analysis was used to investigate how nicotine selectively changed the dynamic properties of resting-state networks in non-smokers, which mimics the initial stages of nicotine use. Thus, we are able to assess nicotine's acute impact on dynamic resting-state properties and hypothesize that nicotine would suppress the DMN while enhancing the CEN and SN.

2. Material and methods

2.1. Participants

Seventeen (8 females) participants (mean age: 26.06 +/− 6.09) were recruited for the healthy control group in previously published work (Janes et al., 2018; Wang et al., 2020b). Participants self-described as non-smokers with no nicotine use within the past 12 months, no more than 20 lifetime nicotine-use instances, and had an expired carbon monoxide (CO) level of <5 ppm at time of scan. The structured clinical interview for DSM-IV-TR (First et al., 2002) was used to rule out lifetime history or current diagnosis of any of the following psychiatric illnesses: organic mental disorder, schizophrenia, schizoaffective disorder, delusional disorder, psychotic disorders not otherwise specified, bipolar disorder, attention deficit hyperactivity disorder (ADHD), mood congruent or incongruent psychotic features, generalized anxiety disorder and social anxiety disorder. Participants were also excluded if they met any of the following criteria: failure to meet MRI safety requirements, lifetime history of electroconvulsive therapy, anticholinergic drug use in the past week, history or current cardiac problems such as arrhythmia, acute coronary syndromes, or ischemic heart disease, seizure disorder, psychotropic medication or illicit substance use, or breath blood alcohol levels greater than zero on both study days. During each study visit, participants tested negative for both pregnancy and recent drug use via a urine sample. Participants received a complete description of the experiment and provided written informed consent in accordance with the protocol approved by the Partners HealthCare Institutional Review Board.

2.2. Study drug

On separate study visits approximately one week apart, participants were administered either 2-mg nicotine (Nicorette Lozenge, GlaxoSmithKline, Brentford London) or placebo (Tums antacid, GlaxoSmithKline, Brentford London) lozenges. A 2-mg dose of nicotine was used because it delivers the total amount of nicotine typically received from smoking a single cigarette (Benowitz, 1997; Benowitz et al., 1988; Benowitz and Jacob, 1984). Lozenges were administered in a randomized, counterbalanced, and double-blind manner. An hour before entering the scanner, participants placed the lozenge inside their mouth, next to their cheek, and allowed it to dissolve completely without chewing. We measured cotinine to confirm the presence and absence of nicotine absorption on nicotine and placebo study days respectively (Ziegler et al., 2004).

2.3. Neuroimaging

Resting-state data were collected on a Siemens Trio 3 T scanner (Erlangen, Germany) using a 32-channel head coil. Multiecho multiplanar rapidly acquired gradient echo-structural images (MPRAGE) were acquired with the following parameters (TR = 2.1 s, TE =3.3 ms, slices = 128, matrix = 256, 256, flip angle 7°, resolution 1.0 × 1.0 × 1.33 mm).

Gradient echo-planar images were collected during a 6-min resting state scan where slices were acquired aligned to the anterior and posterior commissures and the phase encode direction was set from the posterior to anterior direction to minimize prefrontal signal loss. A multi-band acquisition sequence was used with the following parameters: TR = 0.72 s, TE = 0.32 s, multi-band acceleration factor = 8, flip angle 66°, slices = 64, voxel size = 2.5 × 2.5 × 2.5 mm. During the resting-state scan, participants were presented with a dark blank screen and instructed to keep their eyes open.

Images were processed using fMRI of the Brain (FMRIB) Software Library (FSL; www.fmri-b.ox.ac.uk/fsl) with a pre-processing pipeline that included brain extraction, motion correction with MCFLIRT, slice time correction, spatial smoothing at full-width half-maximum of 6 mm, and high-pass temporal filtering. Regarding motion influences across study visits, we compared the absolute mean displacement under nicotine (mean: 0.29 mm +/− 0.20) and placebo (mean: 0.23 mm +/− 0.12) and found no significant difference due to the onboarding of nicotine compared to placebo ($t(16) = 1.13$, $p = 0.28$). To further reduce motion-related artifacts, resting-state data were subsequently denoised using independent component analysis with the FSL tool for Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC). Each participant's data were visually inspected to identify and remove noise-related components (e.g., motion and physiological signals).

2.4. Resting-state coactivation pattern analysis

In a previously-published analysis using the resting-state data of 462 individuals from the Human Connectome Project (HCP; Janes et al., 2020), *k*-means clustering identified eight co-activation patterns or states. Here, we applied the HCP-derived state maps to the present data. The states (Supplementary Fig. 1) overlapped with resting-state networks including DMN-like (states 1 and 7), CEN (state 2), DMN (state 3), dorsal attention (state 4), SN (state 5), sensorimotor network (state 6) and SN-like (state 8), These states were used to compute state-specific dynamic measures including the total time spent in each state (total proportion of scan time spent in a particular state), persistence during each transition into a state (average time spent in a particular state during each transition into that state), and frequency of transitions into each state (total number of entries into each particular state). All CAP analyses were performed using the open-source "capcalc" package (Frederick, B, capcalc [Computer Software] 2017; https://github.com/bbfrederick/capcalc).

2.5. Data analysis

To examine whether nicotine acutely altered resting-state dynamics in healthy non nicotine-dependent individuals, we performed a repeated-measure ANOVA on the *total time in state* metric considering drug (i.e., placebo vs nicotine), state (i.e., eight total CAP-derived neural

maps), and their interaction. Given that *total time in state* comprises two other state-specific metrics (i.e., frequency and persistence), we investigated how these two factors drove changes in total time in state. We applied Benjamini/Hochberg false-discovery rate corrections for all *post-hoc* pairwise comparisons.

3. Results

3.1. Total time in state

In a repeated-measure ANOVA with the total time spent in each state as the dependent variable, we found a significant interaction of drug (i.e., placebo vs nicotine) by state ($F(7,112) = 3.27$, $p_{corr} = 0.019$, generalized $\eta^2 = 0.053$) and a significant main effect of state ($F(7,112) = 34.35$, $p_{corr} < 0.001$, generalized $\eta^2 = 0.61$ but not visit ($F(1,16) = -12.83$, $p_{corr} = 1.00$). Greenhouse-Geisser correction for *p*-values was applied due to the violation of sphericity for repeated-measure ANOVA. *Post-hoc pairwise* tests comparing nicotine and placebo for each state revealed that participants spent significantly less total time in a frontoinsular-DMN state (state 1), which included regions of the canonical DMN (e.g., posterior cingulate cortex and medial prefrontal cortex) as well as frontoinsular regions, under nicotine compared to placebo (Fig. 1A; $t(16) = -2.88$, $p_{corr} = 0.043$, Bias-corrected Hedges' g $= -0.63$) while they spent significantly more total time in the SN state (state 5) under nicotine compared to placebo (Fig. 1A; $t(16) = 2.89$, $p_{corr} = 0.043$, Bias-corrected Hedges' g $= 0.52$; states visually represented in Fig. 1B). Given that DMN and SN activity have been shown to anti-correlate (Zhou et al., 2018), we evaluated the relationship between the two states and found that the total time spent in frontoinsular-DMN (state 1) and SN (state 5) were significantly anti-correlated during the nicotine visit ($r = -0.49$, $p = 0.048$) but not significantly anti-correlated following placebo ($r = -0.44$, $p = 0.075$). However, these drug-specific relationships were not significantly different $z = 0.16$, $p = 0.86$.

3.2. Frequency of transitions into frontoinsular-DMN (state 1) and SN (state 5)

A repeated-measure ANOVA for frequency of transitions into frontoinsular-DMN (state 1) and SN (state 5) states revealed a non-significant interaction of state by drug (Fig. 2A; $F(1,16) = 3.48$, $p = 0.080$, generalized $\eta^2 = 0.018$) and a significant main effect of state ($F(1,16) = 422.67$, $p < 0.001$, generalized $\eta^2 = 0.64$) but not drug ($F(1,16) = 0.036$, $p = 0.85$). Pairwise *post-hoc* comparisons on the main effect of state showed that there were significantly fewer transitions into the frontoinsular-DMN (state 1) than the SN (state 5; $t(16) = -20.56$, $p < 0.001$) irrespective of drug administration.

3.3. Persistence in frontoinsular-DMN (state 1) and SN (state 5)

A repeated-measure ANOVA of persistence for frontoinsular-DMN (state 1) and SN (state 5) states revealed a significant interaction of state by drug (Fig. 2B; $F(1,16) = 6.20$, $p = 0.024$, generalized $\eta^2 = 0.050$) and a significant main effect of state ($F(1,16) = 89.66$, $p < 0.001$, generalized $\eta^2 = 0.44$) but not drug ($F(1,16) = 0.75$, $p_{corr} = 0.40$). Pairwise *post-hoc* comparisons did not reveal any significant difference between placebo and nicotine for either state. However, the non-significant *post-hoc* effects suggest a directional effect for the interaction, where nicotine may reduce persistence in the frontoinsular-DMN (state 1; $t(16) = 2.08$, $p_{corr} = 0.11$) while enhancing persistence in the SN (state 5; $t(16) = -1.30$, $p_{corr} = 0.21$).

4. Discussion

Using a double-blind crossover design, we found that acute nicotine administration in healthy, non-smokers significantly increased the time spent in the SN state while decreasing the time spent in the frontoinsular-DMN state at rest. Although we did not observe a nicotine effect on the CEN, we did find that nicotine reduced DMN and enhanced SN function, which aligns with our hypothesis. As discussed in detail below, our findings expand beyond our initial conjecture by showing that nicotine specifically impacts a complex DMN state that also includes frontoinsular brain regions.

Prior work in chronic nicotine-dependent individuals showed that acute nicotine impacts neurocognitive networks. For example, nicotine reduced activity in key DMN regions (i.e., the medial prefrontal cortex and posterior cingulate cortex) during both resting-state (Tanabe et al., 2011) and attention-demanding tasks (Thiel and Fink, 2008; Hahn et al., 2007). While these prior studies largely reported nicotine's effect on the DMN in nicotine-dependent individuals, our study—conducted in *non-smokers*—extended these findings to show that a single acute dose of nicotine suppressed the functioning of a frontoinsular-DMN state that is distinct from the canonical DMN. This suggests that nicotine has immediate, task-independent, suppressive effects on a transient frontoinsular-DMN state. This frontoinsular-DMN state overlaps with the canonical DMN but also includes regions such as the anterior insula, striatum, anterior cingulate and orbitofrontal cortex. Prior work employing *dynamic* methods has not only identified such a frontoinsular-DMN state but also showed that increased time spent in

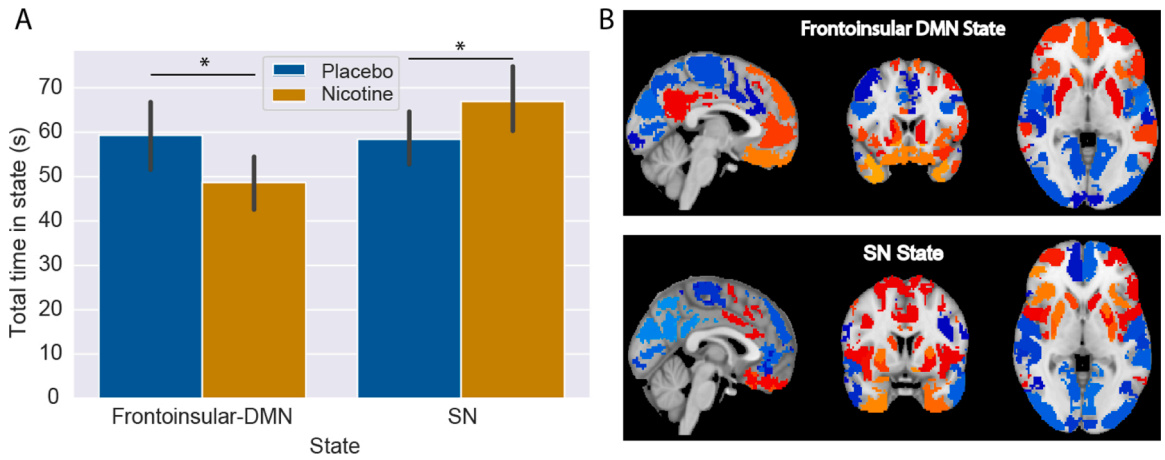

Fig. 1. Influence of nicotine on total time in state. (A). Nicotine, compared to placebo, selectively decreased total time spent in frontoinsular-DMN (state 1) and increased total time spent in SN (state 5). Error bars represent bootstrapped (N = 1000) 95th confidence interval. * indicates $p < 0.05$. **(B).** Spatial representations for the frontoinsular-DMN and SN states. The CAP derived frontoinsular-DMN (state 1) and SN (state 5) states were projected back into anatomical space for visualization. Hot (red to yellow) colors indicate relative (above-mean) activation and cool (blue) colors indicate relative (below-mean) deactivation.

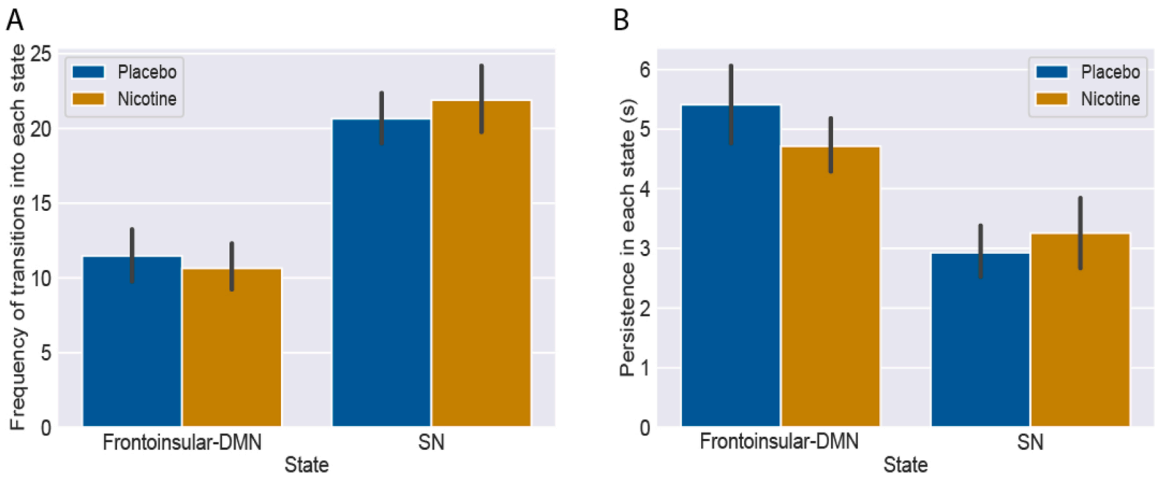

Fig. 2. Influence of nicotine on frequency and persistence in state. (A). Nicotine did not significantly changed frequency of transitions into either frontoinsular-DMN (state 1) or SN (state 5). **(B).** Although a significant interaction of state by visit was noted, nicotine did not significantly alter the persistence in either frontoinsular-DMN (state 1) or SN (state 5). Error bars represent bootstrapped (N = 1000) 95th confidence interval.

this frontoinsular-DMN state is associated with enhanced rumination in those with major depressive disorder (Kaiser et al., 2019) and increased psychotic symptoms in those with psychosis (Bolton et al., 2020). Thus, the current findings provide evidence that nicotine suppresses time spent in a network that supports a ruminative internal focus, which fits with the theory that nicotine biases brain function away from internal information processing (Sutherland et al., 2012). Our findings further showed that the suppression of the time spent in the frontoinsular-DMN state at rest was accompanied by an increase in the time spent in the SN state. This suggests that nicotine shifts the brain away from the frontoinsular-DMN state and self-referential thoughts and toward being in a state where the brain can flexibly monitor for salient internal and external events, a function subserved by the SN (Menon and Uddin, 2010). It is plausible that this shift in temporal dominance, suppressing the frontoinsular-DMN state and enhancing the SN state, would contribute to improved cognition that requires a suppression of internal focus (Chand et al., 2017; Li et al., 2019). This mechanism may contribute to nicotine's cognitive-enhancing effects (Beer, 2016; Warburton, 1992; Myers et al., 2012), which warrants further investigation into how the observed change in resting temporal dynamics relates to cognition and behavior.

While our findings enhance the field's understanding of nicotine's impact on brain dynamics, the current work has several limitations of note. The primary limitation was its small sample size and thus our reported observations certainly warrant future replication in a larger sample, which will also allow the findings to be extended into domains such as sex differences. A larger sample size may also clarify our finding that persistence showed a significant drug by state interaction, thus confirming whether nicotine's impact on total time spent in state is driven by a change in persistence. A second limitation was that we measured brain activity during the anticipated peak nicotine levels estimated across population (Choi et al., 2003). This does not preclude the possibility that nicotine's acute impact on large-scale networks may differ based on individual differences in rates of nicotine metabolism (Falcone et al., 2016). In the same vein, nicotine consumption methods (e.g., smoked, vaped, oral) could also influence the observed changes in time spent in the different states. As such, future studies will benefit from investigating how nicotine metabolism and pharmacokinetics impact the dynamic properties of the resting-state networks. A third limitation is that our current study design only captured nicotine's acute effects when administered in lozenge form, and the impact of physically smoking may potentially lead to other dynamic features. We cannot and do not discount other factors (e.g., social factors and mean age of initial nicotine use) that likely also contribute to how nicotine can alter brain temporal dynamics. As such, more work in naturalistic settings is needed to further explain nicotine's initial effects on brain dynamics. Despite these limitations, our current work employed a rigorous design and data-driven approach and thereby provided strong preliminary evidence that an acute dose of nicotine in non-smoking individuals induced a decrease in time spent in the frontoinsular-DMN state and a simultaneous increase in time spent in the SN state at rest.

5. Conclusions

We showed that nicotine acutely reduces time spent in the frontoinsular-DMN state and increases time spent in the SN state at rest. Our findings add to the growing literature that seeks to understand nicotine's effect on brain function from a network-level perspective (Koob and Volkow, 2016; Zhang and Volkow, 2019). Our work provides novel insights into how initial nicotine exposure influences large-scale network function, which likely impact cognition in a manner that leads to continued nicotine use.

Clinical trial registration

This study was registered on ClinicalTrials.gov with the title "Effects of Nicotine on Brain Reward Pathways" and identifier NCT02346539. More information on https://clinicaltrials.gov/ct2/show/NCT02346539?term=Effect+of+Nicotine+on+Brain+Reward+Pathways&draw=2&rank=1.

Contributors

ACJ conceptualized and designed the study with DAP. KSW conducted all analyses and wrote the initial draft with ACJ and KB. LVM and DO provided clinical expertise and served as study physicians. BBF and RHK provided technical expertise on methodology and wrote scripts for analyses. All authors reviewed and edited the final manuscript.

Declaration of Competing Interest

Over the past 3 years, DAP has received consulting fees from BlackThorn Therapeutics, Boehringer Ingelheim, Compass Pathway, Concert Pharmaceuticals, Engrail Therapeutics, Otsuka Pharmaceuticals, and Takeda Pharmaceuticals; one honorarium from Alkermes, and research funding from Millennium Pharmaceuticals, for activities unrelated to the current work. In addition, he has received stock options from BlackThorn Therapeutics. ACJ and BBF are consultants for Axial

Biotherapeutics for activities unrelated to this work. All other authors declare no competing financial interests.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2021.108846.

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