Multimodal 7T Imaging reveals enhanced functional coupling between Salience and Frontoparietal networks mediating aberrant intertemporal choice but intact microstructural architecture and diffusion connectivity in young adult tobacco cigarette smokers.

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Research Article

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Abstract

BACKGROUND:

Deficits in intertemporal choice (ITC) are an important predictor of tobacco use and relapse rates. Cigarette smoking is associated with disrupted brain network dynamics in cognitive resting networks including the Salience (SN) and Fronto parietal (FPN). Unified multimodal methods [Resting state connectivity analysis, Diffusion Tensor Imaging (DTI), neurite orientation dispersion and density imaging (NODDI), and cortical thickness analysis] were employed to test the hypothesis that smokers have deficits in inter temporal choice and these deficits may be due to alterations in white matter (WM) microstructure and connectivity, functional connectivity and cortical thickness (CT).

METHODS:

Multimodal analyses of previously collected 7 Tesla MRI data via the Human Connectome Project were performed on 22 smokers (average number of daily cigarettes was 40 ± 4) and 22 age- and sex-matched nonsmoking controls. First, subjects scores on the delay discounting test were analyzed. Functional connectivity analysis was used to examine SN-FPN interactions between smokers and nonsmokers. The anatomy of these networks was then assessed using DTI and CT analyses while microstructural architecture of WM was analyzed using NODDI.

RESULTS:

Smokers scored significantly lower on all the items within delay discounting task (DD)) except for tasks: subjective value for $4K at 6 months and subjective value for $4K at 1-year tasks where we observed a trend. Seed-based connectivity analysis revealed significantly enhanced within network [p = 0.001 FDR corrected] and between network functional coupling of the salience and R-FP networks in smokers [p = 0.004 FDR corrected]. Functional coupling scores were inversely correlated with DD scores in nonsmokers. The total number of cigarettes smoked strongly correlated with Fagerström Test for Nicotine Dependence scores. Whole brain diffusion analysis revealed no significant differences between smokers and nonsmokers in Fractional Anisotropy, and Mean diffusivities and in neurite orienting and density. There were also no significant differences in CT in the hubs of these networks.

CONCLUSIONS:

Our results demonstrate that tobacco cigarette smoking is associated with steeper devaluation of delayed rewards mirrored in enhanced functional connectivity, but anatomy is largely intact in young adults. Whether these reductions are pre-existing, transient or permanent is not known. The observed
disrupted salience in resting state networks may be the reason for steeper discounting in smokers which may contribute to difficulties in quitting and/or facilitating relapse.

**Introduction**

Tobacco cigarette smoking is a major cause of preventable death in the US accounting for more than 480,000 deaths every year, or about 1 in 5 deaths (USDHHS report). The time between smoking initiation and its effects on health is a key factor in nicotine addiction reaching epidemic proportions (Menossi et al, 2013). The neuroadaptation created by chronic nicotine exposure promotes continued nicotine use. Attempts at smoking cessation causes disruption of homeostasis leading to withdrawal and craving that is reflective of a neurochemical imbalance (Menossi et al, 2013). This imbalance creates a bias towards impaired decision making (DM) leading to smoking relapses. The role of DM and inhibitory control (IC) in nicotine dependence has been a much-debated issue (Kraplin et al, 2019). The key questions are whether DM is a general characteristic of nicotine dependence or whether DM is particularly impaired in addiction disorder related contexts (Goschke, 2014).

Impaired DM and IC are risk factors preceding nicotine dependence and in turn nicotine use can also impair decision making and inhibitory control. Impaired DM and IC have been associated with smoking relapses (Froeliger et al, 2017; Kronke et al, 2015). Bickel et al, (2014, 2017) conceptualized nicotine dependence as a reinforcer pathology which is a persistently high valuation of a reinforcer (cigarettes) and an excessive preference for immediate consumption. Cigarette demand acts synergistically with delay discounting (DD) which lead to the severity of nicotine dependence (Weidberg et al, 2018). While the neural correlates of DD in nicotine dependence are still a matter of debate, altered activity in executive networks may relate to impaired delayed gratification.

Cigarette smoking has been linked to altered brain functional network topology in the SN and FPN (Janes et al, 2009; Breckel et al, 2013). Examining functional connectivity of DD in a group of smokers and a comparison group of nonsmokers, Clewett et al, (2014) found the degree of functional connectivity between the left fronto-parietal network and left fronto-insular cortex was significantly correlated with individual differences in discounting. They proposed that greater functional coupling between the anterior insula and left fronto-parietal network as a candidate neural substrate linking smoking and impulsivity. A study by Chen et al, (2018) found that enhanced connectivity between Fronto parietal network (FPN) and Salience network (SN) was predictive of performance in inter temporal DM. The SN, which is centered in the anterior insula (AI) and the dorsal anterior cingulate cortex (dACC), is involved in detecting, integrating, and filtering interoceptive, autonomic and emotional information (Menon, 2011). The FPN centered in the dorso lateral prefrontal cortex, and the posterior parietal cortex is involved in attention and processing of external stimuli (Janes et al, 2009). Connectivity changes in the FPN, thought to support task switching, have been linked to learning and decision making (Chand & Dhamala, 2017, Cooper et al, 2018).
The primary question we investigated was given smokers showed aberrant intertemporal choices as recorded by several studies, how is this reflected in functional connectivity? Our first objective therefore, was to test resting state coupling strength, which is thought to represent inherent brain organization, which in turn influences brain function (Menon and Uddin, 2010). We aimed at testing between network (SN-FPN) and within-network coupling strength (FPN: Posterior Parietal Cortex – Rostral Prefrontal Cortex [PPC-RPFC]). We hypothesized that in smokers, craving for cigarettes would enhance salience processing possibly engaging brain activity patterns associated with behavioral responding to such salient stimuli. At the between-network level, preoccupation with smoking related thoughts would lead to decrements in total network connectivity in smokers. To date, there have been no studies on this aspect of resting state interactions between young adult smokers and nonsmokers.

A second aim was to assess anatomic connectivity in the white matter of these two networks using diffusion tensor imaging (DTI), to determine if structural connectivity between these regions mirrored functional connectivity. A commonly used metric in DTI studies is fractional anisotropy (FA), which is a measure of white matter connectivity between regions of the brain (Basser and Pierpaoli, 1996). Hudkins et al, (2012) compared FA between young adult smokers and adolescents and nonsmokers. They found that FA may be higher in adolescence in several networks but declines with continued smoking in adulthood. A recent study by Baeza-Loya et al (2016), found smokers had reduced FA in the right cingulum in comparison with nonsmokers while the left cingulum FA correlated negatively with number of cigarettes per day. Yu et al, (2015) found increased FA in the right posterior limb of the internal capsule, the right external capsule and the right superior corona radiata in young smokers relative to non-smokers. In sum, although it is clear that smoking affects FA, the direction and specificity of these effects is still a matter of debate.

We also examined the effects of smoking on neurite density and orientation dispersion estimates. High-angular-resolution 7T scans allows for the examination of microstructural architecture using the NODDI method (Zhang et al, 2012). Neurite orientation dispersion and density imaging (NODDI) applies a multicomartment model to separate contributions of neurite density and fiber orientation (Rae et al, 2017). These permit detailed characterization of white matter integrity and can shed light on the effects of addictive substances on WM. NODDI allows a deeper characterization of WM than FA or MD by providing measures of tissue microstructure that are much more direct and hence more specific. To date, there have been no studies that have looked at neurite density and orientation dispersion estimates in smoking populations.

FA alterations are complemented in cortical thickness alterations. In line with this, our fourth approach was to examine cortical thickness (CT) in the nodes of these three networks. The nodes we examined were Anterior Insula – Dorsal Anterior cingulate cortex (AI – DACC), Dorso lateral prefrontal cortex – Inferior parietal cortex (DLPFC- IPC), Anterior cingulate cortex – Posterior cingulate cortex (ACC- PCC), Precuneus. Young adult smokers showed reduced CT compared to non-smokers in the left caudal anterior cingulate cortex (ACC), right lateral orbitofrontal cortex (OFC), left insula, left middle temporal gyrus, right inferior parietal lobule, and right parahippocampus reductions (Li et al, 2015). Other studies have
documented that CT of the right anterior insula is negatively correlated with cigarette dependence and urge to smoke (Morales, 2014). The left insula cortical thickness was also negatively correlated with the number of cigarettes per day (Stoeckel et al, 2015). In sum, although some of the nodes of these three resting networks have been shown as being altered in cigarette smokers, it is still unknown whether these are the only regions that show reductions, if some or all of the nodes of these networks are altered, and whether they relate to alterations in functional and structural connectivity.

While each of these studies using rsfMRI, DTI, and CT have provided insights into individual aspects of cigarette smoking, there have been no published studies that have integrated all four methods. The advantage of a unified approach is that we obtain not only separate system-wise understanding of group differences, but also at the complex interplay between structure and function. We used a staged approach that consisted of utilizing rsfMRI, DTI, NODDI and CT analyses. We investigated the following hypotheses:

1. Smokers would score significantly lower on the DD tasks reflective of higher delay discounting and lower response inhibition.
2. The within network interactions of the FPN and the between network interactions of the SN-FPN would be altered in smokers.
3. Smokers would have reduced FA in the regions associated with the SN-FPN.
4. Smoking would adversely impact neurite density and orientation dispersion as shown by the parameter maps.
5. The cortical thickness of concomitant regions of the 2 resting state networks would be reduced in smokers.

**Methods**

**Participants**

The Human Connectome Project (HCP) was the source of the study data: WU-Minn Consortium (see http://www.neuroscienceblueprint.nih.gov/connectome). Subjects for the present study were chosen from the HCP subject website (from a total database of 184 subjects scanned on the 7T scanner). Inclusion in the smoking group was based on SSAGA measurement of daily smoking. Smoking frequency was quantified with self-report measures using the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) (Hesselbrock et al, 1999; Bucholz et al, 1994). The Fagerström Test for Nicotine Dependence (FTND), a standard instrument for assessing the intensity of physical addiction to nicotine was used to quantify nicotine dependence (Fagerström K. 2012). On this basis, we carefully selected 22 tobacco cigarette smokers and 22 nonsmokers (matched for sex and age). The neuroimaging processing and analyses thus consisted of 44 total participants.

**Demographic Information and Cognitive Status**
Demographic variables including age, sex, race and education were collected. 22 smokers and 22 nonsmokers between the ages of 22 and 37 (mean 30.3 ± 3.3 years) with an average of 14 years of education (± 4.4) were assessed. Smokers reported smoking an average of 40 cigarettes (2 packets) /day (± 4.4; range: 6–20). Nonsmoking subjects did not have a history of using tobacco.

Image Acquisition Detailed information on image acquisition and pre-processing pipelines of the HCP datasets has been previously published (Van Essen et al, 2013; Glasser et al, 2013). Briefly, scans were acquired on a customized Siemens 7T Magnetom Terra system with a 32-channel receive coil arrays (Vu et al, 2015). 3D multi echo multi-planar rapidly acquired gradient echo-structural images (MPRAGE) were acquired with the following parameters: resolution = 224 x 320 x 256 mm, repetition time (TR) = 1000 ms, echo time (TE) = 2.14 ms, slices = 256, matrix = 320, flip angle = 8 degrees. Participants completed two resting state fMRI runs for the present analysis, each lasting 15 minutes; oblique axial acquisitions were phase encoded in both directions. Participants were asked to relax with their eyes open and were presented with a bright fixation cross on a dark background. All data were acquired using multi-band acceleration with the following parameters: TR = 720 ms, TE = 33.10 ms, flip angle = 52 degrees, slices = 72, voxel size = 1.0 x 1.0 x 1.0 mm isotropic.

Diffusion MRI acquisition:
The images were acquired using spin-echo EPI, with 7000 ms TR, and a TE of 71.2ms, flip angle was 90deg, refocusing flip angle180 deg. A FOV of 210x210 (RO x PE) was used, matrix was 200x200 (RO x PE), slice thickness was 1.05 mm, 132 slices, 1.05 mm isotropic voxels. A multiband factor 2, image acceleration factor (iPAT) 3 was used, including echo spacing 0.82 ms, BW 1388 Hz/Px Phase partial Fourier 6/8, b-values 1000, 2000 s/mm².

Multimodal Neuroimaging Analysis

Four separate analyses were applied to the 44 participants from both groups

Spatially preprocessed resting state functional connectivity data was analyzed using the CONN toolbox (MIT/BU Boston Whitfield-Gabrieli S, Nieto-Castanon A. 2012) running on MATLAB v2018. The toolbox uses a component-based noise correction method (Behzadi, Restom, Liau, & Liu, 2007) to reduce physiological and extraneous noise, providing interpretative information on correlated and anticorrelated functional brain networks. BOLD data were bandpass filtered (0.008–0.09 Hz) to reduce low-frequency drift and noise effects. We generated seed-to-voxel connectivity maps for each individual for the following reproducibly demonstrated functional networks: the default mode, salience and fronto-parietal attention. These networks were chosen as they have been intimately associated with aspects of cognitive functioning disrupted in addiction. (Menon, 2015; Janes et al, 2015) Seeds were 10-mm-diameter spheres. These seeds are provided in the CONN toolbox, and represent core and reproducibly demonstrated topological nodes within each resting-state network. The reasoning for identification and use of these seeds is described in greater detail by the designers of CONN (Whitfield-Gabrieli et al., 2011). We investigated functional networks generated from individual seeds separately (i.e., not averaged over
seed regions within a given network); this resulted in 6 analyses (two seeds each for default mode (Medial Prefrontal cortex (MPFC), and posterior cingulate cortex (PCC) and fronto-parietal networks [Posterior parietal cortex (PPC) and Dorsolateral prefrontal cortex (DLPFC), two seeds for the salience network Anterior cingulate cortex (ACC) and Insula. We used family wise error correction (FWE) to correct for multiple comparisons.

DTI analysis was done using FSL v 5.0.10 (FMRIB, Oxford, UK). We began with preprocessing that included denoising, eddy correct and B1 field inhomogeneity corrections. Tract Based Spatial Statistics (TBSS) was done on metrics FA, AD, RD and MD with Randomise using 10,000 permutations. We used the whole brain FA analysis map to examine SN-FPN ROIs. Stringent whole brain FWE corrected p was used in the analysis.

Whole brain microstructural integrity was examined using the NODDI toolbox (Zhang et al, 2012) (Imperial College, London) running on MATLAB v2018. Briefly, this toolbox estimates the following microstructure information: the intra-cellular volume fraction referring to the space bounded by the membranes of neurites, and their orientation dispersion.

Finally, cortical thickness analysis of the nodes of the SN – FPN was done using FreeSurfer 5.3 pipeline (MGH, Boston).

Statistical analysis was performed on the 44 subjects using IBM SPSS version 25. A Shapiro Wilks test examined group differences in socio demographics of both groups.

**Results**

The groups were equally matched in age, sex and educational level (Table 1). Smokers revealed steeper discounting in the delay discounting tasks with the exception of subjective value_10yr_200 and subjective value_6mo_40K tasks, while subjective Value_5yr_40K and subjective value_10yr_40K tasks showed a trend (Table 2).

Seed based resting state functional connectivity analysis revealed significantly enhanced coupling in the smokers in comparison to non-smokers within the nodes of the R-FPN and between the Salience and the Right fronto parietal networks (See Fig. 1) (see Table 3). The functional coupling of the left FPN revealed no significant difference between the groups.

Pearson’s correlations showed that the increased coupling between the SN_FPN networks and scores on the delay discounting task were negatively correlated with the Area under the curve AUC_40 \([r = -0.451 p = 0.03]\) and AUC_200 \([r = -0.521 p = 0.01]\) in nonsmokers but not smokers.

The total number of cigarettes smoked was strongly correlated with the FTND score \([r (44) = 0.582 p = 0.004]\). Delay discounting Area Under Curve AUC_200 was positively correlated with DSM criteria for nicotine tolerance \([r = 0.43 p = 0.04]\) and with the number of cigarettes smoked \([r = 0.63 p = 0.001]\).
DTI analysis did reveal white matter differences between the two groups but were washed away for all metrics when FWE multiple comparison correction was applied. Whole brain analysis of the neurite orientation and density microstructure also revealed differences but failed multiple comparison's correction.

Cortical thickness of the hubs of the salience network and the FPN namely the bilateral Medial Prefrontal, Angular, Supramarginal, dorsal anterior cingulate and Insular cortices showed that although the smokers had thinner cortices in comparison to nonsmokers, they were not statistically significant.

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>Smokers (22)</th>
<th>Nonsmokers (22)</th>
<th>Test statistic</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean or N</td>
<td>SD or %</td>
<td>Mean or N</td>
<td>SD or %</td>
</tr>
<tr>
<td>Age, Years</td>
<td>28.85</td>
<td>3.7</td>
<td>28.81</td>
<td>3.6</td>
</tr>
<tr>
<td>Sex, Male</td>
<td>22</td>
<td>50%</td>
<td>22</td>
<td>50%</td>
</tr>
<tr>
<td>Education, Years</td>
<td>14.7</td>
<td>1.85</td>
<td>15</td>
<td>1.76</td>
</tr>
<tr>
<td>Age at Nicotine 1st use</td>
<td>19</td>
<td>9.4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SSAGA FTND score</td>
<td>2.78</td>
<td>1.678</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 1
Socio-demographic and clinical characteristics of the study sample:
### Table 2
Delay Discounting test

<table>
<thead>
<tr>
<th>DD Test</th>
<th>Smokers (22)</th>
<th>Nonsmokers (22)</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Subjective value_1mo_200</td>
<td>122.9</td>
<td>50.7</td>
<td>157.2</td>
<td>34</td>
</tr>
<tr>
<td>Subjective Value_6mo_200</td>
<td>59.7</td>
<td>39.3</td>
<td>112.4</td>
<td>61.8</td>
</tr>
<tr>
<td>Subjective Value_1yr_200</td>
<td>41.2</td>
<td>48.7</td>
<td>93.6</td>
<td>67.5</td>
</tr>
<tr>
<td>Subjective Value_3yr_200</td>
<td>30.6</td>
<td>29.3</td>
<td>58.02</td>
<td>55.5</td>
</tr>
<tr>
<td>Subjective Value_5yr_200</td>
<td>23.8</td>
<td>29.3</td>
<td>57.2</td>
<td>49.05</td>
</tr>
<tr>
<td>Subjective Value_10yr_200</td>
<td>22.7</td>
<td>42.6</td>
<td>33.8</td>
<td>48.4</td>
</tr>
<tr>
<td>Subjective Value_1mo_40K</td>
<td>29429.35</td>
<td>11062.1</td>
<td>35190.2</td>
<td>8150</td>
</tr>
<tr>
<td>Subjective Value_6mo_40K</td>
<td>26494.6</td>
<td>12168.5</td>
<td>30462</td>
<td>11333.7</td>
</tr>
<tr>
<td>Subjective Value_1yr_40K</td>
<td>19809.8</td>
<td>14389.1</td>
<td>29048.9</td>
<td>13771.8</td>
</tr>
<tr>
<td>Subjective Value_3yr_40K</td>
<td>14266.3</td>
<td>12217.9</td>
<td>22201.1</td>
<td>13543</td>
</tr>
<tr>
<td>Subjective Value_5yr_40K</td>
<td>12201.1</td>
<td>10694.7</td>
<td>18777.2</td>
<td>13918.7</td>
</tr>
<tr>
<td>Subjective Value_10yr_40K</td>
<td>7853.3</td>
<td>9292.9</td>
<td>14212</td>
<td>12810.4</td>
</tr>
<tr>
<td>Area Under Curve_200</td>
<td>.15794</td>
<td>.1510</td>
<td>.30765</td>
<td>.23352</td>
</tr>
<tr>
<td>Area Under Curve _40K</td>
<td>.34089</td>
<td>.23693</td>
<td>.51547</td>
<td>.29710</td>
</tr>
</tbody>
</table>

Table 3
Resting State Seed based functional connectivity analysis of the Salience and RFPN.

<table>
<thead>
<tr>
<th>Network</th>
<th>SEED ROI</th>
<th>Target ROI</th>
<th>Beta</th>
<th>T (44)</th>
<th>P uncorrected</th>
<th>p -FDR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salience - R.FPN</td>
<td>Right FPN</td>
<td>Dorsal ACC</td>
<td>0.17</td>
<td>3.59</td>
<td>0.0008</td>
<td>0.019*</td>
</tr>
<tr>
<td></td>
<td>Right FPN</td>
<td>Left Anterior Insula</td>
<td>0.11</td>
<td>2.29</td>
<td>0.027</td>
<td>0.145</td>
</tr>
<tr>
<td></td>
<td>Right FPN</td>
<td>Right Anterior Insula</td>
<td>0.15</td>
<td>2.93</td>
<td>0.005</td>
<td>0.144</td>
</tr>
<tr>
<td>Within Network</td>
<td>Right FPN</td>
<td>Left Rostral PFC</td>
<td>0.18</td>
<td>3.78</td>
<td>0.0004</td>
<td>0.03*</td>
</tr>
<tr>
<td></td>
<td>Right FPN</td>
<td>Right Rostral PFC</td>
<td>0.23</td>
<td>4.54</td>
<td>0.00004</td>
<td>0.007*</td>
</tr>
</tbody>
</table>

*-corrected for False discovery rate

Examining correlations between subjects scores on the delay discounting tasks, we found that functional coupling affected smokers and nonsmokers differently. In the graphs 1 & 2 we examined DD - Area under...
the curve 40 in the two groups.

Figure 1 shows that the higher the coupling between R-FP and Salience, the lower the score on the DD test in nonsmokers. This implies greater network control over impulsive decision making which is observed in controls. Figure 2 shows this pattern, but the association is non-significant implying that the coupling may not be influencing scores on the DD test.

Figure 3 shows a similar pattern with fig 1. Higher coupling between R-FP and Salience correlates with lower scores on the DD test (AUC 200) in nonsmokers. This again implies greater network control over impulsive decision making. Figure 4, however, shows a different pattern where higher coupling is associated with higher discounting.

Figure 5 shows that longer (in years) one has smoked the higher the coupling in R-FP-ACC network.

Figures 6, 7 and 8 show the relationship between age at first cigarette use and functional coupling in 3 networks: 1. R-FP – DACC, R-FP – L-RPFC, R-FP – R-RPFC. All 3 figures show that the higher the network coupling, the earlier the onset.

Finally, examining the relationship of network connectivity and difficulty quitting smoking as measured by the Diagnostic and Statistical Manual (DSM -V), we found that enhanced connectivity between these 2 networks is related to a greater degree of difficulty in quitting smoking.

**Discussion**

In the present study the principal question was: Are there significant differences in intertemporal decision-making scores between smokers and nonsmokers? If so, how are these differences biologically expressed? We employed a four-method multimodal image analysis on high dimensional 7 tesla MRI images examining functional connectivity, white matter microstructure and gray matter thickness in a group of cigarette smokers and nonsmokers. This is the first time a study such as this has been undertaken.

First, Smokers’ performance on the delay discounting task was significantly lower than nonsmokers (NS) implying that smokers exhibit aberrant inter temporal choices and lower response inhibition than NS. This finding is in line with a meta-analysis by Amlung et al, (2017) who showed that DD is strongly correlated with continuous measures of addiction severity and quantity-frequency in several drugs of abuse. The delay discounting AUC task also correlated with the number of cigarettes smoked.

Seed-based connectivity analysis revealed significantly increased functional coupling within the nodes of the Right FPN: [R-PPC and R-RPFC and Right PPC and L-RPFC] and also between the SN and right fronto-parietal networks in smokers. This finding is similar to Clewett et al, (2014) study who showed increased functional coupling between the Left FPN and Salience networks to be a predictor of performance on the delay discounting test. Another study found enhanced mPFC-left fronto-parietal coupling in smokers suggestive of cue exposure may increase communication between cue-evaluative and action planning
brain regions (Janes et al, 2012). While the fronto parietal network is anatomically similar in smokers and non-smokers, amplitude within this network is enhanced in smokers. Resting state amplitude is thought to reflect neuronal activity, whereby an increase in amplitude may indicate greater local neuronal activity (Yang et al., 2007). The relationship between resting state amplitude and neuronal activity suggests that, compared to non-smokers, smokers may have greater intrinsic neuronal activity in the fronto parietal and salience network. This enhancement is consistent with preclinical studies that show nicotine inducing a persistent increase in the baseline sensitivity of brain reward systems (Kenny and Markou, 2006; Kenny et al, 2008).

Functional Connectivity and Delay discounting: Pearson's correlations of subjects scores on DD tasks area under curve (AUC) and SN-FPN coupling showed that non-smokers were significantly correlated with the connectivity strength between SN-FPN (Figs. 1 & 3). This indicates that the greater the coupling strength, the more robust the cognitive control and the less impulsivity in making intertemporal choices in nonsmokers. Thus, stronger coupling predicted scores on the DD in nonsmokers. This key association was non-significant in smokers (Fig. 2) and reversed (Fig. 4). – a key difference that could plausibly be the reason for sustained use and abuse.

This finding is in line with several studies that have shown that cognitive control plays an important role in inter temporal DM (Luo et al, 2009, Figner et al, 2010). Stronger between and within network coupling in the SN-FPN lead to enhanced cognitive control which in turn lead to greater impulse control.

Functional connectivity and Age at first cigarette: Chen et al (2018) showed that stronger SN-FPN coupling mediates the higher discounting which in turn leads to cigarette smoking. This is shown in the present study (see graphs 6, 7 and 8). Three separate networks showed higher functional coupling being inversely correlated with age at first cigarette initiation. The implication of this is that the earlier the exposure to cigarettes, the higher the functional coupling in these networks’ indicative perhaps of a greater difficulty in quitting.

Functional connectivity and years of cigarette smoking: Fig. 5 showed that the longer one smoked tobacco cigarettes, the stronger the functional coupling between the R-FP and the salience networks. The strengthening of this association over time implies that quitting smoking may be harder for those who have been smoking for many years.

Functional connectivity and difficulty quitting (DSM- V): In line with the above statement, the present study showed the stronger the functional coupling between R-FP and Salience, the harder it is to quit smoking as measured by the DSM scale on quitting (Fig. 9).

DD correlated with DSM criteria for nicotine tolerance and with the number of cigarettes smoked indicating that inter temporal choices play a crucial role in both these aspects of nicotine addiction.

Examining the white matter correlates of this DD deficit, DTI analysis showed that there were no significant differences between the groups in fractional anisotropy, radial, axial and mean diffusivities.
This is indicative of fairly intact structural connectivity in the WM of smokers. A review of WM integrity in young tobacco users (Gogliettino et al, 2016) showed FA increases in corpus callosum (genu, body and splenium), internal capsule and superior longitudinal fasciculus. The reason we did not find this difference may be due to a limitation of the FSL DTI method of FWE correction that was used. Examining whole brain WM intracellular neurite orientation and dispersion (NODDI), no significant differences were observed between the groups. This indicates that even in the multi compartment model of WM integrity, the effects of tobacco may be less pronounced. This may again be a limitation of the multiple comparison correction methods that we used. Another possible explanation for the lack of a difference in WM integrity between the groups in both models may be the degree of chronicity. Several studies have shown that subjects with chronic cigarette smoking habits having WM alterations (Baeza-Loya et al, 2016; Hudkins et al, 2010). Subjects in the present study had an average 7 years of use and incipient WM changes may be fallen below the multiple comparisons threshold.

The cortical thickness differences between the groups in the hubs of the salience network and FPN were also not significant. This is in line with Morales et al (2014) who did not find any differences in the thickness of the insula. Thickness deficits were however found in rodents (Zhu et al, 2012) and only one study found CT deficits in the medial orbitofrontal cortex (MOFC) in humans (Kuhn et al, 2010). The MOFC was not part of the regions that we investigated. Again as with WM, the reason for this lack of a difference could be chronicity of cigarette use.

Finally, the total number of cigarettes smoked was strongly correlated with the FTND score (which is a scale denoting nicotine dependency) implying that that the level of nicotine addiction was proportional to the number of cigarettes smoked.

In sum, tobacco cigarettes appear to affect cognition (inter temporal choices) and dynamic networks mediating cognition as shown by the present study. The underlying white matter appears to be largely spared but this may be due to shorter exposure to the effects of tobacco smoke. These key associations imply that higher discounting and greater functional coupling in smokers may be alterations that arise as independent developments lead to cigarette initiation and smoking dependence.

**Conclusions**

The present study used high dimensional 7T data to report significant alterations in delay discounting mirrored in enhanced functional connectivity of in the SN-FPN networks. Functional connectivity was also shown as being significantly associated with clinical features like Age at 1st cigarette use, tobacco – years, and DSM difficulty quitting score. Results of this study should be interpreted cautiously. First, as with all cross-sectional studies, effects described could have been pre-existing, a result of smoking, or a combination of both.

There were some methodological limitations to this study (e.g., the analysis could not control for all brain inhomogeneity artifacts). Furthermore, future research can also extend investigations to other regions to more thoroughly understanding the impact of nicotine exposure on the human brain and its potential
effects on cognitive processing. Finally, DD has been proposed as a trait marker for addiction (Odum 2011a).

**Declarations**

**Ethical Approval**

This study was approved by the Internal Review Boards at Washington university at Saint Louis University of Minnesota.

**Competing interests**

The authors have no financial disclosures to declare.

**Authors' contributions**

Dr. Francis designed the study, performed the neuroimaging and statistical analysis, and wrote the manuscript. Dr. Sebille was involved in programming for the NODDI analysis, and manuscript editing. Dr Gabrieli and Dr. Camprodon provided guidance in analysis, manuscript composition and revised it with critically important intellectual content in the submitted version of the manuscript.

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**Availability of data and materials**

Not applicable.

**References**


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Figures
Correlation: Area under Curve 40 - R-Fronto-Parietal – Salience coupling in nonsmokers.
Correlation: Area under Curve 40 - R-Fronto-Parietal – Salience coupling in smokers.
Figure 3

Correlation: Area under Curve 200 R-Fronto-Parietal – Salience coupling against Delay Discounting in nonsmokers.
Figure 4

Correlation: Area under Curve 200 R-Fronto-Parietal – Salience coupling against Delay Discounting in smokers.
Figure 5

Years of tobacco smoking and functional connectivity: Next we looked at years of tobacco use and its association with dynamic networks.
Figure 6

Functional connectivity and Age of onset of cigarette smoking - network 1
Figure 7

Functional connectivity and Age of onset of cigarette smoking – network 2
Figure 8

Functional connectivity and Age of onset of cigarette smoking – network 3
Figure 9

Functional connectivity and difficulty quitting smoking (DSM score)