Prefrontal and frontal functional connectivity increases in current smokers versus non-smokers

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Target Audience Researchers using resting state fMRI functional connectivity to study addiction, especially in the context of nicotine effects and tobacco cigarette smoking. This presentation demonstrates the use of multi-echo fMRI towards studying resting-state seed-based functional connectivity differences between nicotine addicted individuals and healthy controls, and will be informative to researchers considering advanced fMRI methods to study other disease and drug conditions.

Purpose Despite now decades of research and health education on the severe health risks of tobacco cigarette smoking, smoking addiction still represents the greatest source of toxic chemical exposure to humans worldwide [1]. This is in large part because, for addicted individuals, smoking cessation is notoriously difficult due to the addictive properties of nicotine. In this study we assess the functional connectivity differences between current smokers and nonsmokers to elucidate the neural networks underlying the state of nicotine addiction. This research is especially novel for its use of advanced functional connectivity estimation techniques based on multi-echo fMRI for probing connectivity differences between normative and addicted conditions. The multi-echo approach is relevant for being robust to type I error in statistical inference on functional connectivity, which is associated with subject motion and other nuisance effects [2], as especially relevant for patient study.

Methods Subjects were recruited in accordance with the Local Ethical Research Committee of the University of Cambridge, including 20 current smokers (mean age 28y, std. 9y, 7 females) and 21 never-addicted non-smokers (mean age 33, std. 11y, 6 females). Subjects underwent scanning in a 3T Siemens Trio MRI scanner equipped with a 32-channel receive-only head coil (Siemens, Erlangen, Germany) using an anatomical MPRAGE sequence (76 × 240 FOV; 1-mm in-plane resolution; inversion time, 1100 ms) and multi-echo EPI fMRI sequence (TEs=12,28,44,60ms, TR=2.5s, 240mm FOV, 64x64 in-plane resolution, GRAPPA 3, BW=1698 Hz/pixel, 240 volumes). Anatomical and functional images were processed using the AFNI tool *meica.py*, which conducts multi-echo independent components analysis (ME-ICA), involving: slice timing and motion correction, T_2* weighted anatomical-functional coregistration and nonlinear standard space normalization to an MNI template, T_2* weighted optimal combination of echoes, ME-PCA for joint BOLD and non-BOLD dimensionality estimation (i.e. MR signal versus thermal noise), ME-ICA for BOLD vs. non-BOLD component differentiation and non-BOLD component removal for denoising. Notably, no bandpass filtering or FWHM spatial smoothing was applied. Seed-based connectivity analysis was conducted using AFNI *3dGroupInCorr*, based on Pearson correlation of denoised time series, regularized by the canonical standard error term: Z=arctanh(R)*sqrt(df_e), where sqrt(df_e) is the standard error for correlation. df_e of denoised BOLD time series is approximated as the number of BOLD independent components [1,3], as this reflects the dimensionality of denoised BOLD time series. This approach to connectivity analysis has been shown to control for type I error for seed-connectivity in conditions with significant variation in BOLD acquisition sensitivity or functional variability such as associated with subject motion [1].

Results From the multi-seed analysis based on AFNI *3dGroupInCorr*, the connectivity patterns showing greatest difference between smokers and non-smokers corresponded to seeds in right dorsolateral prefrontal cortex (DLPFC) and pre-supplementary motor area (pre-SMA) (Figure 1). Smokers showed increased connectivity of the right DLPFC to: left dorsolateral prefrontal cortex (-45,43,13), middle frontal (-23,8,47), bilateral insula (R:-37,8,2 L:48,8,1), fusiform gyrus (-21,-58,-12), subthalamic nucleus (-10,-19,-6), and striatum (-20,0,2). Increases were also found for the pre-SMA seed to: bilateral premotor cortex (R:33,-11,52 L:-32,-11,52), medial dorsal nuclei of thalamus (i.e. prefrontal correlate 11,-19,5) and subthalamic nucleus. Seed regions including primary visual and motor cortex did not show significant connectivity differences between smokers and non-smokers. Altogether these connectivity patterns are consistent with cholinergic and dopaminergic pathways, which are activated by nicotine.

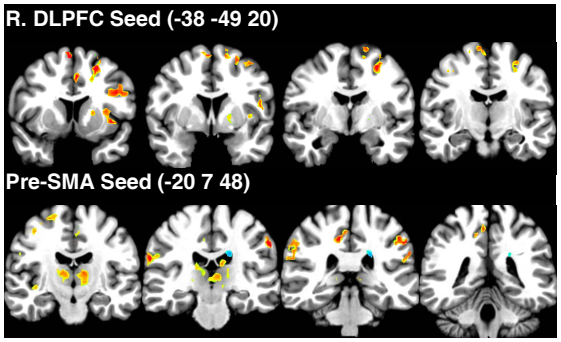

Figure 1 Seed-based functional connectivity maps for seeds with respective locations given in MNI coordinates. Maps are thresholded at p<0.01 (uncorrected).

Discussion and Conclusion In this study on resting state functional connectivity we report several prefrontal and frontal regions associated with greater inter-regional seed-based functional connectivity in smokers versus non-smokers. These findings are consistent with previous findings showing that nicotine, the primary psychoactive component cigarette smoke, augments several aspects of higher-order cognition including working memory, attention, arousal, and motivation, through the action of increasing neurotransmission on cholinergic pathways [4]. These findings suggest that future studies on neuropsychological effects of cigarette smoking and cessation give particular focus to prefrontal and frontal connectivity within cortex and to subcortex.

References

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