

EFFECTS OF NICOTINE WITHDRAWAL AND TREATMENT ON RESTING-STATE NETWORK DYNAMICS

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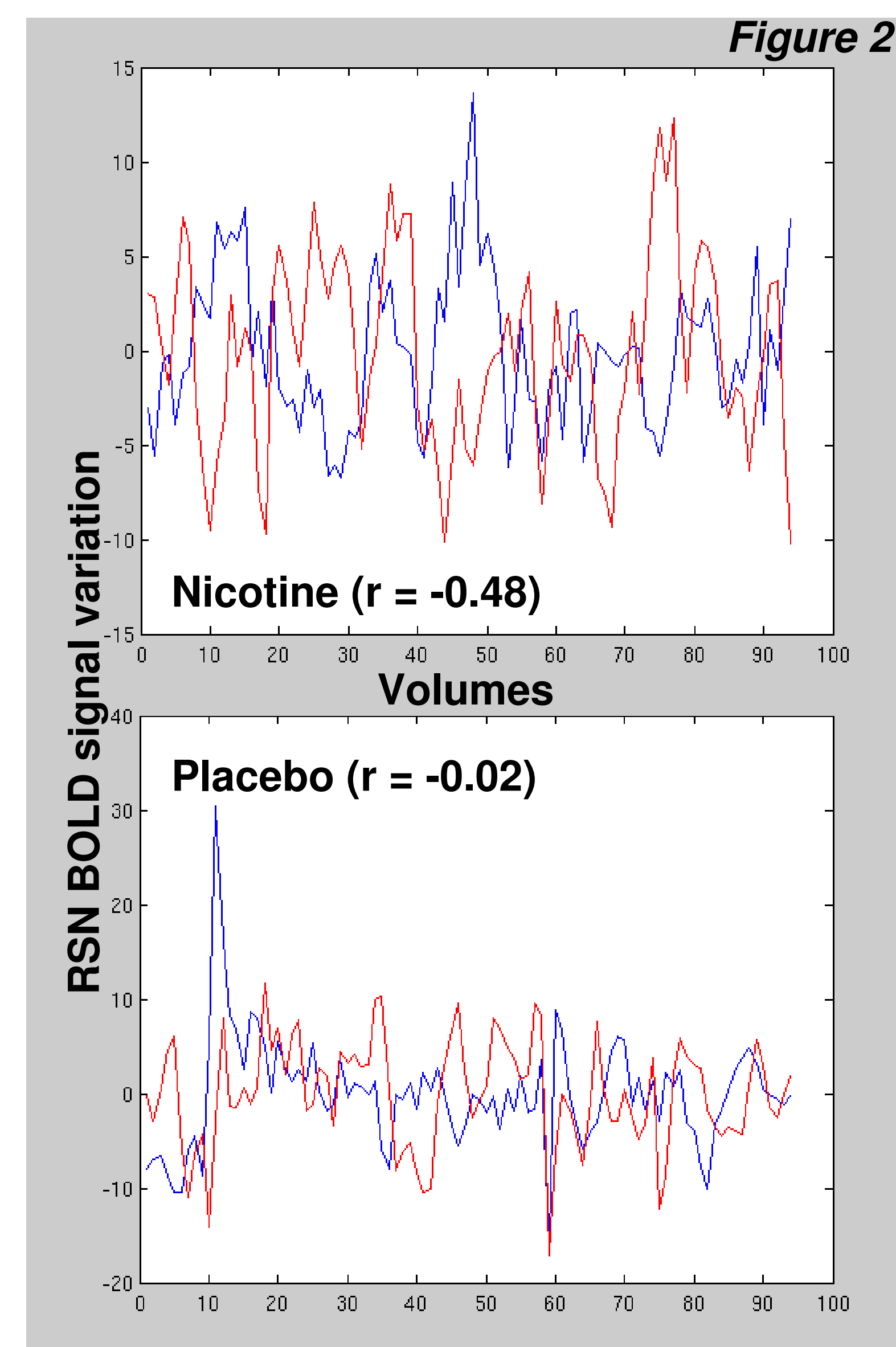
INTRODUCTION

- Nicotine withdrawal is associated with a number of symptoms (e.g. cravings, irritability, impaired cognition) which may be ameliorated by nicotine replacement.
- Symptom severity and treatment efficacy can vary across smokers.
- Using fMRI, we compared the effects of nicotine replacement and placebo on resting-state network (RSN) connectivity dynamics in smokers during withdrawal. We also examined the relationship between RSN dynamics and individual differences in withdrawal symptom severity and cognitive performance.
- We focussed on 'default mode' and 'executive control' networks (DMN and ECN, respectively). Prior research suggests that reduced negative connectivity between these two RSNs may exist in disorders associated with cognitive impairments (e.g. Alzheimer's disease; Wang et al, 2007).

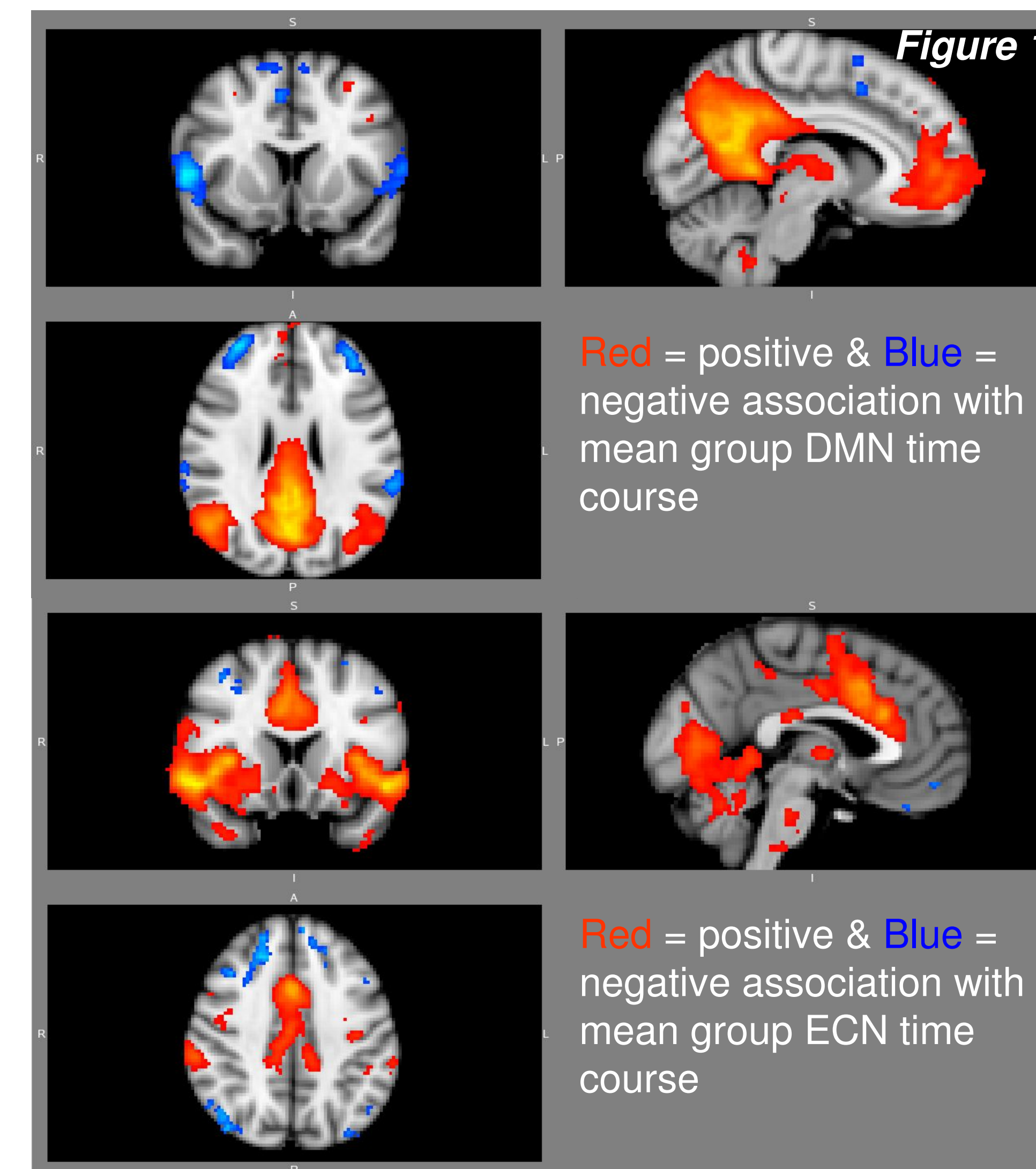
METHODS

- 17 smokers underwent 5 minutes of EPI scanning during rest following 8hr abstinence periods in a Nicotine lozenge x Placebo crossover design.
- RSNs were identified with group probabilistic independent component analysis (ICA) as implemented in FSL MELODIC.
- Individual subject maps were estimated for each session by entering group IC maps into a linear model fit, to derive subject-specific sets of IC time courses. Each set of IC time courses was then regressed against each subject's corresponding fMRI data set.
- This dual linear regression approach provided spatial maps representing the functional connectivity of each RSN, within each treatment, for each subject. Voxel-wise random-effects testing was carried out to compare treatment effects at the group level.
- Withdrawal symptom severity (as measured by the Modified Minnesota Withdrawal Symptom (MMWS) scale) and cognitive performance (measured in a separate rapid visual information processing (RVIP) task) variables were included as regressors of interest. Within-session DMN and ECN time courses were correlated to compare with individual differences in these measures across drug conditions.

RESULTS: Negative Coupling between RSNs. Group ICA generated 14 IC maps, of which eight corresponded to typical RSNs (Damoiseaux et al, 2006), including the Default Mode Network (DMN; i.e. bilateral posterior cingulate cortex (PCC), precuneus, inferior parietal (IPC) and ventromedial prefrontal cortices (PFC)); and the Executive Control Network (ECN; i.e. bilateral anterior cingulate, insulae, IPC and dorsolateral PFC (dlPFC)). In line with previous research, DMN & ECN appeared negatively functionally connected (*Figure 1*).



Comparison of treatment effects. There were no significant differences in global DMN-ECN negative coupling across subjects explained solely by treatment. Dual regression and subsequent paired group comparison revealed several localised drug effects, with nicotine reducing within-RSN network functional connectivity (**p<0.05, local FDR corrected**).



Relationship between RSN dynamics, withdrawal symptom severity and cognitive performance. Individual differences in the degree to which nicotine improved concentration, as measured by the MMWS scale (relative to placebo), significantly predicted functional connectivity between DMN & ECN (**R=0.62, p<0.01**). *Figure 2* shows an example subject in whom improved concentration following nicotine was associated with a strong negative correlation between DMN & ECN time courses (red & blue, respectively). Finally, we found that changes in connectivity between the ECN & DMN were strongly correlated with total MMWS scores and RVIP accuracy, as were alterations in the RSN connectivity of other brain regions implicated in nicotine addiction (*Figure 3*; **p<0.05, local FDR corrected**).

DISCUSSION: In line with prior evidence that withdrawal severity and treatment responsiveness vary across smokers, we found that individual subjects' improvements in concentration correlated with the degree to which nicotine induced negative coupling between the DMN and ECN. Further, we were able to conduct a data-driven, fine-grained spatial analysis of RSN connectivity across the whole brain at the group level. Brain regions displaying strong reductions in connectivity with the DMN, associated with improvements in withdrawal and cognitive performance, matched circuitry involved in reward-based learning and self-referential processing. Concomitant decreases in ECN connectivity of regions implicated in interoceptive awareness and monitoring the immediate environment were also associated with symptom improvements. Our results demonstrate the importance of individual differences in the negative relationship between two RSNs in nicotine withdrawal symptom amelioration.

