Modulation of functional connectivity in the resting brain by typical and atypical antipsychotic drugs

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Introduction: Low frequency (< 0.1 Hz) oscillations in resting state BOLD signal have been studied for some years, and are now attracting interest in terms of their relationship to the so-called 'default-mode' of the brain. Previous studies have identified the posterior cingulate, medial, prefrontal, inferior parietal and anterior cingulate cortices as elements of the default-mode network [1-3]. The network is believed to be important in environmental surveillance, and it may become perturbed in psychotic illness, leading to misinterpetation of internal brain activity as external. Antipsychotic drugs, e.g. risperidone, improve the positive symptoms of schizophrenia by blocking dopamine D2 receptors in the striatum. Atypical antipsychotic drugs can treat the positive symptoms of schizophrenia whilst having a very low propensity to produce the possible side effects caused by normal antipsychotic drugs such as extrapyramidal symptoms and reward disturbances[4]. The newest of these atypical antipsychotic drugs is aripiprazole. Here we test the hypothesis that these two drugs, aripiprazole (partial agonist) and risperidone (D2 antagonist/5HT2A antagonist) will have direct effects on functional connectivity within the default-mode network.

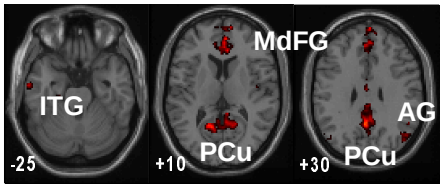


Figure 1 Default-mode component from pre-drug scan: ITG – Inferior Temporal Gyrus, PCu – Precuneus, MdFG – Medial Frontal Gyrus and AG – Angular Gyrus.

Table 1 Significant areas within default mode component

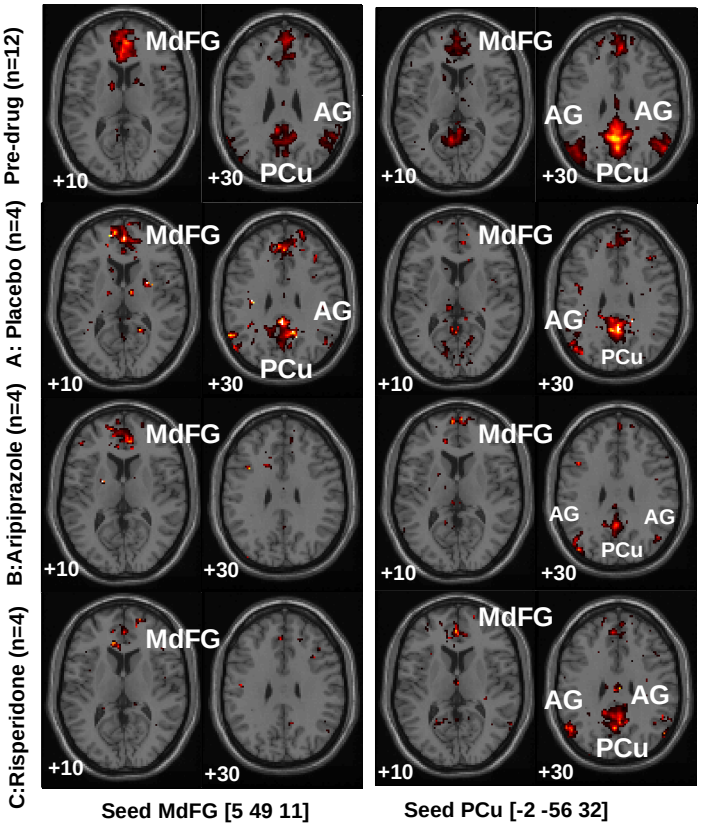
Area	k_E	MNI
PCu_L	92	-2 -56 32
PCu_R	168	4 -47 18
MdFG_L	61	0 41 28
MdFG_R	77	5 49 11
AG_R	91	41 -63 35
ITG_L	12	-59 -5 -28

Methods: Three groups of 4 male healthy subjects were randomised to receive a single oral dose of 5 mg aripiprazole, 1mg risperidone or placebo. Each participant had a pre- and post-drug scan. After the pre-drug scan the participant took the prescribed drug and waited 3.5 hours to allow for drug absorption and then the post-drug scan was carried out. Subjects were instructed to keep their eyes closed for 5 minutes in both scans. Whole brain images were acquired on a 3T Philips *Achieva* scanner with gradient-echo echo-planar imaging with the following parameters: FOV = 230mm, acquisition matrix = 128x128, TR/TE 2000/35 msec, voxel size=1.8x1.8x3.0mm, 0.5mm slice gap, 34 slices. fMRI data were processed using SPM2.

The default-mode network was identified by using independent component analysis (ICA) of the pre-drug scan. The group ICA of fMRI toolbox (GIFT) (http://icatb.sourceforge.net/) was carried out to perform group ICA on the resting state data. The data were decomposed into 20 components by independent component estimation with the infomax algorithm [5]. The default mode component was identified as that which correlated most significantly with a predefined mask of the default-mode network, generated by using the WFU_pickatlas. This mask contained the previous reported default-mode areas: posterior cingulate and precuneus; medial frontal pole; angular gyrus; and anterior cingulate cortex. The selected default mode component from each subject was then loaded into SPM2 to perform a second level group analysis on the pre-drug scan.

Seed ROIs ($5mm^3$) consistent with the pre-drug scan default-mode map were selected. The time courses from individual ROIs in the resting-state data were then globally scaled, averaged, and band-pass filtered $0.008<f<0.15$ Hz. The resulting time series were then used as linear regressors in a whole-brain SPM analysis to form individual functional connectivity correlation maps. Group functional connectivity maps were then obtained from a random effects analysis across all subjects and drug conditions.

Figure 2 Connectivity maps from seed regions



Results: Fig. 1 shows the group default-mode component from the pre-drug data (n=12) superimposed on the canonical anatomical images supplied with SPM. Table 1 shows the most significant clusters in the default-mode component, labeled with cluster size (k_E), and MNI coordinates in mm. The medial frontal gyrus ([5 49 11]) and precuneus ([-2 -56 32]) were selected as seed regions for the connectivity analysis. Maps of the resting-state connectivity for the seed areas are shown in Fig. 2, in four categories: pre-drug, placebo, aripiprazole and risperidone. The numbers below each image refer to the z plane MNI coordinates. The left hemisphere of the brain corresponds to the left side of the image. Extent thresholds were set to $p_{FWE}<0.05$ at height threshold $p_{unc}<0.01$. As expected, the connectivity maps of the pre-drug control data and placebo data show a number of identical nodes of the default-mode network. However, fewer regions were found to be connected with the seed regions in both of the drug-treatment groups. In the connectivity maps seeded from the medial frontal gyrus, connections to the posterior cingulate/precuneus and angular areas were significantly attenuated by the drugs.

Conclusion: The resting state regions revealed in the pre-drug baseline scans include a number of key nodes of the reported default-mode network. Altered functional connectivity following antipsychotic drug administration has been demonstrated, despite the small numbers presently scanned. A significant decrease in the anterior to posterior connection was observed for both drugs suggesting that these antipsychotic drugs may play an important role in modulating connections from the prefrontal cortex. This may give insight into the pathology of schizophrenia and the mode of action of antipsychotic drugs. It is notable that drugs with different mechanisms of action (D2-antagonism vs partial agonism) seem to have similar effects on connectivity, though increasing the subject numbers, as planned, to 12 per group should allow these effects to be discriminated.

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