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# Multimodal functional imaging investigation before and after the onset of psychosis



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Mr A. was a 20-yr-old white male with no medical history of note. His GP, who was concerned about his poor psychosocial functioning, referred him to a specialist service offering advice and support for young people at risk for psychosis.

On assessment he reported daily paranoid experiences such as 'sensing' the thoughts of strangers passing him on the street, next-door-neighbours and family members. He also reported occasional visual and tactile hallucinations. The frequency and severity of these symptoms did not reach DSM-IV criteria for schizophrenia or other psychotic disorders [Positive and Negative Symptoms Scale (PANSS) scores: positive 16, negative 8, general 35; Global Assessment of Functioning (GAF) scale total score 55]. These attenuated psychotic symptoms met operationalized criteria for an 'at risk mental state' (ARMS) assessed using a validated structured assessment (Yung et al., 2002). People with an ARMS have a very high risk of developing a psychotic disorder in the next 1–2 yr (Yung et al., 2003). Mr A.'s overall level of function was low, as scored on the GAF scale (GAF 55; highest function 100). Neuropsychological assessment indicated a normal level of performance in all cognitive domains tested with the exception of verbal learning (as indexed by the Auditory Verbal Learning Test). Over the ensuing 17 months Mr A.'s psychotic symptoms became more severe, with the emergence of frank persecutory delusions and marked formal thought disorder (and increased PANSS scores: positive 43, negative 18, general 22), and a further decline in his psychosocial function (GAF score fell by 20 points to 35). The clinical picture at this point met DSM-IV criteria for schizophrenia. He was admitted to an in-patient ward and treated with oral aripiprazole (15 mg o.d.). Although his symptoms subsequently improved, residual symptoms and functional impairment prevented him from returning to work.

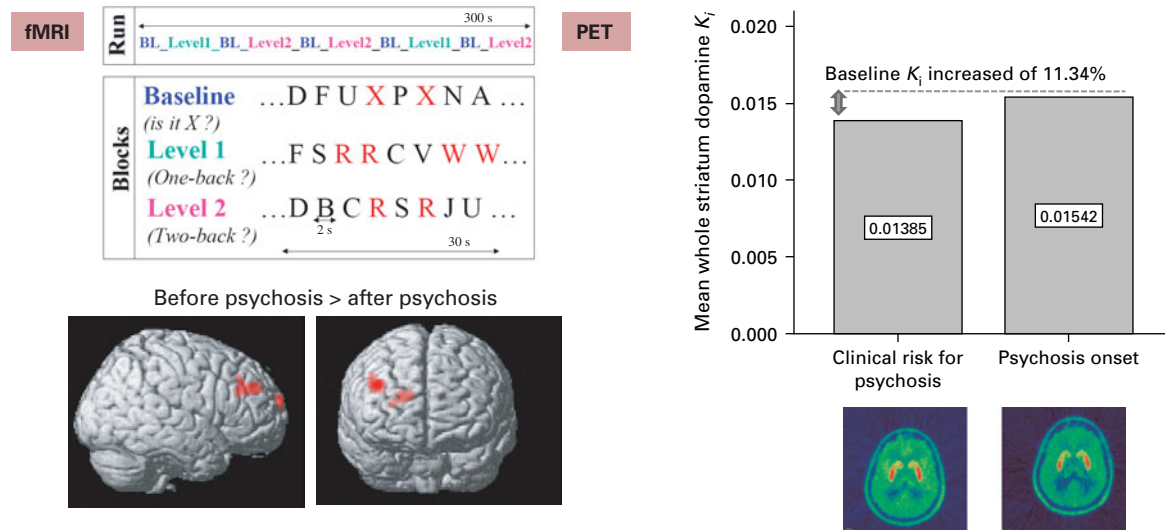
Mr A. underwent fluoro-dopa (F-DOPA) positron emission tomography (PET) when he first presented

with an ARMS and was scanned again shortly after he developed schizophrenia. The PET scanning was carried out using a 3D PET scanner (ECAT/EXACT 3D; Siemens/CTI, Knoxville, TN, USA), which has a spatial resolution of  $4.8 \pm 0.2$  mm and a sensitivity of 69 cps/Bq.ml. The subject received 150 mg carbidopa and 400 mg entacapone orally 1 h prior to scanning to reduce the formation of radiolabelled metabolites. A 5-min transmission scan was carried out before radiotracer injection using a 150-MBq  $^{137}\text{Cs}$  rotating point source to correct for attenuation and scatter. Approximately 150 MBq of F-DOPA were administered by intravenous injection immediately following a 30-s background frame. The region-of-interest (ROI) analysis was carried out blind to clinical status by one investigator. A graphical analysis was used to calculate influx constants ( $K_i$  values) for the whole striatal ROI. The cerebellum was used as the reference region as this has been shown to have the lowest F-DOPA uptake in the brain.

We also examined Mr A.'s frontal lobe function using functional magnetic resonance imaging (fMRI) in conjunction with a working-memory task at the same time-points (before and after the onset of psychosis). Images were acquired on a 1.5 T Signa (GE) system at the Maudsley Hospital, London.  $T_2^*$ -weighted images were acquired with a TR of 2000 ms and TE 40 ms, with a 0.3 mm gap in 14 axial planes parallel to the intercommissural (AC–PC) line. During the working-memory (n-back) task the subject is presented with series of letters that are viewed using a prismatic mirror and is required to move a joystick to the left when the letter 'X' appears (o-back) or when the currently presented letter is the same as that presented n trials (n-back) previously. Images were analysed with SPM5. The onset times (in seconds) for each trial were convolved with a canonical haemodynamic response function. Active task condition (n-back) was then contrasted against the baseline condition ('is it X?'). To test our hypothesis that there were differences between the two time-points reflecting the development of acute psychosis, the activation for the task (n-back > baseline) was then compared between the two time-points (ARMS and psychosis onset). Whole-brain voxel-wise threshold was set at  $p < 0.05$  family-wise error (FWE)-corrected.

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**Figure 1.** Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) in the same subject before and after the onset of psychosis. Left of the picture: n-back working-memory task (above) and fMRI (below); brain activity in the prefrontal cortex during the mnemonic task (one-back and two-back > baseline) over time (before > after the onset of psychosis) in a within-subject design (voxel  $p > 0.05$  family-wise error). Right of the picture: PET, [ $^{18}\text{F}$ ]fluoro-DOPA images which evidence an increase of striatal dopamine from the prodromal phases (pre) to the onset of psychosis (post). Influx constants ( $K_i$ ) were calculated from region-of-interest (ROI)-derived time-activity curves using Patlak analysis with a cerebellar reference region following frame-by-frame movement correction.

The PET scans showed that following the development of schizophrenia there was an increase in striatal dopamine function, from baseline values (Figure 1) to a level similar to that seen in established schizophrenia (Howes et al., in press; McGowan et al., 2004). Previous molecular-imaging studies indicate that schizophrenia is associated with increased striatal pre-synaptic dopaminergic function, and elevated synaptic levels and release of dopamine in the striatum (reviewed in McGuire et al., 2008). The observed dopamine abnormalities may underlie the phenomenology of the prodromal symptoms (McGuire et al., 2008).

However, the increase in this case was within the test-retest variability of [ $^{18}\text{F}$ ]DOPA 3D PET  $K_i$  values, reported to be 2–4% in the putamen and 0–11% in the caudate (Weinhard, 1998). Longitudinal studies of a group of ARMS subjects will be required to determine if there is a statistically significant increase in  $K_i$  value. A power calculation using the data reported here indicates that a sample size of at least 7 is required for future longitudinal studies.

Mr A. had received 4 wk treatment with 15 mg/d aripiprazole prior to the follow-up PET scanning. A few days of treatment with antipsychotic drugs increases F-DOPA uptake but 5 wk treatment with haloperidol has been found to decrease F-DOPA uptake (Grunder et al., 2003; Vernalaken et al., 2006), suggesting that if we had been able to measure the

$K_i$  value immediately before treatment commenced it may have been higher.

The fMRI scans showed that transition to psychosis was associated with a longitudinal reduction of the task-related activation in the right dorsolateral prefrontal cortex (DLPFC), a cortical region which is normally engaged during this task. Reduced activation in the prefrontal cortex has been widely observed in patients with schizophrenia and is thought to underlie the pervasive cognitive impairment seen in the illness (Fusar-Poli et al., 2007). The disruption of prefrontal functioning may reflect a meso-cortical modulation of neural activity in this region by striatal dopamine (Floresco and Magyar, 2006). In particular, there is evidence that the associative part of the striatum is connected with the DLPFC and that dopamine levels in such striatal regions are associated with/related to cognitive functioning (Cropley et al., 2006), and specifically with working memory (Tanaka, 2006).

This case study indicates that the pathophysiology of developing psychosis involves the progression of striatal hyperdopaminergia, working-memory dysfunction and prefrontal cortical dysfunction. Although conclusions are methodologically limited by it being a single within-group case and despite the test-retest liability in functional imaging indicating that larger samples are needed to obtain reliable results, this report suggests that future studies should investigate

the relationship between these factors. Furthermore, it shows that it is possible to conduct multimodal imaging during the prodromal first psychotic phases of schizophrenia, and that the combination of imaging techniques has the potential to delineate the causal relationships between key pathophysiological processes in the evolution of schizophrenia. The observation that transition to psychosis is associated with abnormalities of prefrontal function and striatal dopamine raises the possibility that multimodal neuroimaging techniques could be used to identify the core pathophysiological changes underlying the disorder onset. The PET fMRI evidence that presynaptic striatal dopamine and working-memory function is perturbed in the prodromal phase of schizophrenia provides a biological rationale to support the introduction of anti-dopaminergic preventive intervention in people at high risk of psychosis (McGlashan et al., 2006; McGorry et al., 2002).

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### Statement of Interest

None.

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