

## Neuroimaging of Schizophrenia: What it Reveals About the Disease and What it Tells us About a Patient

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### Abstract

**Neuroimaging in psychiatry, and in schizophrenia in particular, moves ahead at a rapid pace delivering new insights into the nature of the illness and its intriguing symptoms via technologies such as MRI, fMRI, PET, and SPET scanning. How do these impact on understanding the patient in front of us? What do they mean for the busy clinician in clinic? We outline some of the recent findings in neuroimaging research of schizophrenia and consider their potential application in clinical practice.**

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**Key words:** Functional magnetic resonance imaging (fMRI), Positron emission tomography (PET), Psychosis

Neuroimaging promises much in the age of modern technology driven medicine to both patient and clinician. Its immediate and vivid images of the living brain help discover the neural bases of subjective psychiatric symptoms and help bring psychiatry closer to mainstream medicine. But how does it inform day-to-day clinical treatment?

It has been over 3 decades since the demonstration of enlarged ventricles via computed tomography (CT) scanning confirmed the biological basis of schizophrenia.<sup>1</sup> Since then a host of structural neuroimaging studies have demonstrated grey matter loss in areas relevant to disease: the hippocampus and parahippocampal gyrus, cingulate gyrus, insula, thalamus, and prefrontal and temporal cortices.<sup>2</sup> These findings have been extended to first-episode groups, high-risk groups and schizotypal disorder and have been integrated in a stage-based disease model.<sup>3</sup> The severity of these structural abnormalities at first presentation and their subsequent rate of progression<sup>4</sup> have been linked to long-term outcome<sup>5</sup> and have been used to demonstrate a progressive component to what was thought to be primarily a static neurodevelopmental disorder.<sup>6</sup> This has helped build the case for early detection and intervention, where it is thought that vigorous treatment prior to the onset of frank psychosis may ameliorate disease progression and poorer long-term outcomes.<sup>7,8</sup>

Neurochemical imaging has also made great contributions to our understanding of disease mechanisms in

schizophrenia as well as informed treatment. Positron emission tomography (PET) and single photon emission tomography (SPET) use radioactive ligands to generate images reflecting the distribution of specific molecules in the brain, while magnetic resonance spectroscopy (MRS) uses magnetic resonance imaging (MRI) images. PET and SPET studies have shown increased presynaptic striatal dopamine synthesis and storage in schizophrenia<sup>9</sup> and in high-risk subjects<sup>10</sup> as well as increased striatal dopamine release following amphetamine challenge<sup>11</sup> thus helping build a clearer picture of the dopamine dysregulation in schizophrenia.<sup>12</sup> These findings have re-established dopamine dysregulation as central in the disorder, further underpinned by the demonstration of D2 blockade as critical to effective anti-psychotic action.<sup>13</sup> Neurochemical imaging studies have also helped demonstrate early effects of antipsychotic action explored mechanisms of action of so-called “atypical” antipsychotics<sup>14</sup> and helped determine the optimal range of D2 blockade required for antipsychotic effect avoiding hyperprolactinemia and extrapyramidal side effects – between 65% and 72%.<sup>15,16</sup> This facilitates optimal dose selection, encourages the use of low-dose antipsychotics, and allows the calculation of approximate dose equivalence between different antipsychotics.<sup>17</sup> Other neurochemical imaging studies have supported the implication of neurotransmitter systems such as glutamate and GABA in schizophrenia and led to speculations on the

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interactions of such systems with dopamine in disease development.<sup>18</sup>

Studies using these and other functional imaging modalities, particularly functional magnetic resonance imaging (fMRI) have explored the underpinnings of specific symptoms, such as thought disorder, passivity phenomena and auditory verbal hallucinations. In one study, Shergill et al<sup>19</sup> demonstrated lateral temporal cortex activity during the perception of auditory hallucinations and somatosensory activation during tactile hallucinations. In another, Kirchner et al<sup>20</sup> elicited formal thought disorder (FTD) by asking subjects to describe ambiguous pictures and found severity of FTD inversely correlated with activity in the left superior temporal cortex, an area critical to healthy speech processing. Using these symptom based approaches may facilitate the development of a new categorisation of schizophrenia informed by symptom specific neuro-cognitive deficits.<sup>21</sup> Other theoretical models of illness can also be explored and developed using neuroimaging, such as those suggesting disintegration or dysconnectivity between different cognitive processes and brain regions.<sup>22</sup> Using PET for example, functional fronto-temporal dysconnectivity has been shown in subjects with schizophrenia compared to controls during verbal fluency tasks.<sup>23</sup> This “functional dysconnectivity” can be then explored structurally using other methodologies such as diffusion tensor imaging (DTI) that reflects the integrity of long white matter tracts in the brain.<sup>24</sup> Integrating this imaging data with experimental animal and cognitive modelling and phenomenological work allows the development of promising new translational conceptions of disease that integrate chemical, structural and functional anatomical abnormalities through to symptoms and the effects of treatment.<sup>25</sup> Thus neuroimaging has contributed much to our current and evolving understanding of disease in schizophrenia and related disorders. How applicable is this now in the clinical setting?

The most usual reason for requesting a brain scan in first-episode psychosis is to “exclude organic causes” and it has been estimated that up to 5-10% of cases may show some abnormalities.<sup>26</sup> There has been some considerable debate over the cost-utility of such investigations however,<sup>27</sup> and while some authorities recommend scanning all patients presenting with psychosis for the first time,<sup>28,29</sup> others do not.<sup>30</sup>

It therefore remains uncertain for most practising psychiatrists what benefit a brain scan will provide for the individual patient. While neuroimaging research findings such as those sketched above have informed diagnosis, disease course and outcome, symptom and disease mechanisms, treatment dose, response and side effects these are evident only at the group level – no findings have

yet been reliably extended to the individual in the clinic. Why is this so?

Simply because statistically significant differences are not always or even often clinically significant. In order for group level findings to be translated to the bedside, they need to be converted into specific tests with specific predictive value. For the clinician trying to confirm a putative diagnosis of schizophrenia what matters is this positive and negative predictive value of each test. That is to say, how many of those with a positive finding on a brain scan will have the diagnosis confirmed (positive predictive value, PPV) and how many of those with a negative result are excluded (negative predictive value, NPV). At present the PPV and NPV of neuroimaging tests for schizophrenia are unfeasibly low. This may be due to a number of reasons, including the small and heterogeneous effects found, differences in clinical subjects groups used, confounding effects of medication and the small samples used so far in most studies.<sup>31</sup>

While we have not as yet reached useful PPV and NPV there are several developments that look hopeful. First, finding reliable and meaningful differences will require large co-ordinated efforts – several recent multi-centre initiatives unify imaging protocols and analysis methods to harness greater statistical power.<sup>32,33</sup> Second, it will require the development multivariate techniques (i.e. techniques that look at more than one region and their correlations simultaneously) and neuroimaging meta-analyses methods.<sup>34</sup> To this end Kawasaki et al<sup>35</sup> used a multivariate analysis technique on standard clinical MRI brain scans to separate patients with schizophrenia from healthy controls with a sensitivity of over 80%. Comparing the size and shape of specific target regions such as the hippocampus also improves the rate of detection<sup>36</sup> particularly in combination with other regions such as the thalamus.<sup>37</sup>

Third, it will require conjunction with other clinical information – while imaging may be of limited use as a primary screening tool, it may be more useful for the more focused questions of secondary prevention. Structured clinical screening instruments such as the Comprehensive Assessment of the At Risk Mental State (CAARMS)<sup>38</sup> incorporate clinical and genetic risk data to detect subjects with a 25-41% chance of developing psychosis within the following 12 months.<sup>39</sup> Determining which subjects will do so, however, is difficult, and does not reliably relate to presenting symptoms or other baseline clinical factors. Amongst such subjects however those who later develop psychosis differ from those who do not in having reduced grey matter volume in prefrontal, cingulate and medial temporal cortices.<sup>40</sup> Using these and other structural and functional imaging findings alongside cognitive and clinical data to develop reliable predictors of transition to psychosis

is an important and evolving project.<sup>41</sup>

Neuroimaging promises much and has already delivered many insights into our understanding of schizophrenia and related disorders. For the clinician faced with a patient with psychosis, direct applications of neuroimaging remain limited. However it increasingly holds the potential to guide accurate diagnosis, help predict who will develop the disorder and monitor its course, and provide a rationale to guide treatment selection and further drug discovery.

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