

## Imaging in Schizophrenia: Looking Back and Peering Ahead

Christos Pantelis,<sup>1</sup>*MD, MRCPsych, FRANZCP*, Stephen J Wood,<sup>1</sup>*PhD*

Clearly, schizophrenia does not readily lend itself to finding simple answers. As well as being clinically heterogeneous, it is not a disorder of one brain region or even one network of regions. Findings from brain imaging studies are varied, and while consistent patterns are apparent (e.g. structural abnormalities in frontal cortex, temporal lobe, and subcortical regions),<sup>1-3</sup> these are not always observed at earlier illness stages and may not be apparent pre-psychosis onset.<sup>4,5</sup>

In the third of their series of papers entitled, '*Schizophrenia, "Just the Facts": What we know in 2008*', Keshavan and colleagues<sup>6</sup> review the extant findings on this issue from the fields of neuroimaging, electrophysiology, and neuropathology. They conclude that no definitive diagnostic markers have emerged, and that intermediate phenotypes may be promising as ways to examine aetiological factors or evaluate treatments. They call for novel integrative models to test hypotheses and predictions. Their conclusions clearly demonstrate the complexity we face and their analysis highlights the issue of heterogeneity of findings that have proved difficult to reconcile with existing hypotheses and approaches.

While necessarily complicating the interpretation of findings, this heterogeneity of findings in schizophrenia also provides, perhaps, the most consistent clue to the disorder, a fact that has been repeatedly stated but generally ignored. Thus, most often the aims of research studies are to identify a consistent pattern of abnormalities that exist at all illness stages. This continues to thwart progress. This heterogeneity was exemplified in an early PET study from our group, in which activation of the anterior cingulate cortex was associated with significant variability in the location of peak activation within the ACC;<sup>7</sup> the approach needed was to assess this variability directly as between-subject variability in the pattern of activation meant that a group average of the data under-estimated the degree of activation in schizophrenia. Such variability is also observed across a range of measures, particularly at the earliest illness stages, when the disorder is less differentiated (and therefore less homogeneous), and occurs during a dynamic period of brain maturation.<sup>4,5,8</sup> Interestingly, such

heterogeneity is also observed in recent genetic studies identifying increased mutations widely across the genome, though a relevant finding is that these increased mutations are more highly represented in genes coding for neurodevelopment.<sup>9</sup>

While the early 'neurodevelopmentalists' proposed that schizophrenia results from a lesion or insult in the second trimester,<sup>10,11</sup> the available evidence does not support such a contention, with insults at all stages of development being relevant.<sup>12</sup> Indeed, we proposed that interpretation of the evidence should be 'flipped on its head'.<sup>12</sup> Thus, while studies have sought to identify how brain changes in schizophrenia were a consequence of an insult in the 2<sup>nd</sup> trimester of pregnancy, the evidence points to a simpler hypothesis; namely, that an insult at different developmental stages results in (and potentially explains) the heterogeneity in the pattern and extent of abnormalities observed. Thus, an insult in the 1<sup>st</sup> trimester would have more extensive consequences than 2<sup>nd</sup> or 3<sup>rd</sup> trimester lesions, versus insults in childhood or adolescence. This points to an interaction between stage of neurodevelopment and the particular aetiological insult relevant to later illness onset, an interaction that may be complicated by specific gene variants. For example, risk for psychosis has been associated with the use of cannabis, but this risk is modified by the age of initiation of use.<sup>13,14</sup> Furthermore, this risk is dependent on a functional polymorphism of the catechol-O-methyltransferase (COMT) gene.<sup>15</sup> Thus, the heterogeneity observed in the imaging literature may reflect interactions both with the temporal dimension and genetic variation.

### The Way Forward: Mapping Trajectories of Development Using Multimodal Imaging Techniques

Contrary to the early neurodevelopmental hypothesis that has dominated our thinking and studies over the last two decades, schizophrenia is characterised by a range of structural brain abnormalities that are not observed in every individual, which differ at different illness stages, and that do not represent stable markers of the illness.<sup>4,5,16</sup> It is likely that the varied genetic markers so far identified also contribute to this heterogeneity. What is required is a

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<sup>1</sup> Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne & Melbourne Health, Australia  
Address for Correspondence: Prof Christos Pantelis, National Neuroscience Facility (NNF), Level 3, 161 Barry Street, Carlton South, Vic 3053, Australia.  
Email: cpant@unimelb.edu.au

multimodal longitudinal approach to neuroimaging research in the disorder. While longitudinal studies to date have assessed patients over a relatively brief period with two or at most three scans, it is now necessary more accurately to assess the neurodevelopmental trajectories of brain structure and function from before illness onset. In particular, we need to expand our focus from the structural integrity of grey matter to white matter tracts (using diffusion tensor and magnetisation transfer imaging), as well as assessing in vivo chemistry, function and connectivity (for example, see<sup>17,18</sup>). Such an approach is also exemplified in recent studies detailing trajectories of brain development in normal childhood and adolescence,<sup>19,20</sup> and in childhood-onset schizophrenia,<sup>21</sup> as well as the interaction of maturational trajectories with genetic variation.<sup>22</sup> This effort will help to reconcile anomalies in the findings in psychotic disorders and schizophrenia as well as other psychiatric disorders developing at this time.

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