

## Brain Structure and Function Changes During the Development of Schizophrenia: The Evidence From Studies of Subjects at Increased Genetic Risk

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**This article reviews the evidence for changes in the structure and function of the brain in subjects at high risk of schizophrenia for genetic reasons during the genesis of the disorder. We first highlight the structural and functional abnormalities in schizophrenia and whether any similar or lesser abnormalities are apparent in unaffected relatives. There is good evidence for subtle abnormalities of hippocampal and ventricle volume in relatives that are not as marked as the deficits in schizophrenia. In addition, the functional imaging literature suggests that prefrontal cortex function may deteriorate in those at risk who go on to develop the disorder. We then review the findings from longitudinal imaging studies of those at high risk, particularly the Edinburgh High-Risk Study, which report gray matter density reductions in medial and lateral temporal lobe because people develop schizophrenia, as well as functional abnormalities which precede onset. We conclude by quoting our own and others' imaging studies of the associations of genetic and other risk factors for schizophrenia, including stressful life events and cannabis use, which provide mechanistic examples of how these changes may be brought about. Overall, the literature supports the view that there are measurable changes in brain structure and function during the genesis of the disorder, which provide opportunities for early detection and intervention.**

*Key words:* high risk/structural MRI/functional MRI

### Introduction

Schizophrenia is known to be a highly genetic disorder<sup>1</sup> and to be associated with abnormalities of brain structure and function.<sup>2</sup> Controversy remains as to whether or not there are progressive aspects to these abnormalities, and,

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if so, what causes them. Part of the difficulty in answering these questions is that the time at which these abnormalities are first evident is unknown. Further, the time course and extent of any structural and functional changes have to be distinguished from developmental, maturational, or other age-related effects, and it has to be established that apparent progression is not simply attributable to prescribed medication and/or substance misuse. Clearly, the measurement techniques must have sufficient sensitivity to change.

The ideal study design—a prospective study of people from early life to the onset of schizophrenia and beyond—is impractical for a variety of technological, clinical, and epidemiological reasons. An alternative method is to study at-risk populations leading up to and during the time period of maximum risk of onset of the disorder. These studies are themselves expensive and prey to changes in technology and potentially biased by participant drop-out. More practical, but generally less reliable, case-control studies have sought to relate various exposures (eg, family history, substance abuse, stress) to neuroimaging indices and to the development of schizophrenia. Combining the evidence from these studies with what is known from animal in vivo and molecular biology in vitro studies could build a cohesive account and perhaps even a compelling case for or against progression at various stages of the disorder.

This article will review the available evidence, from clinical, epidemiological, and imaging studies, for pre-morbid changes in subjects at high risk for genetic reasons as they develop schizophrenia. Before considering these, it is necessary to highlight the anatomical and functional abnormalities in schizophrenia that require explanation, which can now be done from systematic reviews and meta-analyses, and then the evidence that exists for similar abnormalities in well relatives, most of whom will not become ill.

### The Structural and Functional Deficits of Schizophrenia

Computerized tomography (CT) demonstrated ventricular enlargement and a generalized loss of brain tissue in patients with schizophrenia as compared with healthy controls (CONs), albeit in one composite area

measure—the ventricular:brain ratio (VBR).<sup>2–4</sup> Structural magnetic resonance imaging (sMRI) has replicated those findings and convincingly shown additional volume deficits in the prefrontal and temporal lobes, particularly the medial temporal lobe (MTL) and superior temporal lobe.<sup>2,5–8</sup> The thalamus is also reduced in volume.<sup>9</sup> These findings are further supported by postmortem and computational morphometry studies.<sup>10–12</sup> It is still controversial whether or not some of these changes are progressive, and, if so, whether differential changes are evident according to medication status and type (see the other articles in this issue). Two recent reviews of the first-episode sMRI literature have found evidence for abnormalities of a similar magnitude to those found in chronic cases, suggesting that significant structural abnormalities are present from the onset of the illness.<sup>13–15</sup>

The early emphasis on “hypofrontality” in the functional imaging literature on schizophrenia has been refined over time. It is now appreciated that relative underactivation in patients who have difficulties performing a task may reflect a deficit in underlying processes related to that task but could also reflect a lack of engagement.<sup>15–17</sup> Certainly, positron emission tomography (PET) and functional MRI (fMRI) studies that balance performance between patients and healthy CONs often find no hypofrontality or even hyperfrontality. The overall picture is however more complex still and probably includes task effects and regional effects. In 2 recent systematic reviews, 12 N-back (working memory) fMRI studies and 18 episodic memory studies with PET or fMRI found hypofrontality in dorsolateral and inferolateral prefrontal cortex (PFC), respectively.<sup>18,19</sup> Glahn et al<sup>18</sup> also reported hyperfrontality in medial areas including (dorsal) anterior cingulate. In the temporal lobe, there is fairly consistent evidence for increased cortical activity while Achim and Lepage<sup>19</sup> have convincingly demonstrated bilateral reductions in perfusion in the MTLs.

One possible synthesis of this literature is that schizophrenia is characterized by abnormal PFC interactions with other cortical areas. Such a synthesis is at least in keeping with the disconnectivity hypothesis of schizophrenia, which posits a general reduction in coherent activity in distributed neuronal networks. This is usually measured as interregional cross-correlations in functional imaging time series, such as in replicated findings of reduced frontotemporal and frontoparietal functional connectivity.<sup>20,21</sup> PET, single photon emission computed tomography (SPECT), and fMRI studies of disconnectivity are also supported by accounts of reduced frontotemporal coherence and gamma asynchrony in schizophrenia on electroencephalogram (EEG) and magnetoencephalogram.<sup>22</sup> Where medial regions have been invoked in such systems, it has usually been in terms of medial frontal regions modulating lateral frontotemporal interactions.<sup>20,21</sup> Overall, the structural and functional imaging literature in schizophrenia consistently implicates the prefrontal and temporal lobes.

## Anatomical and Functional Differences in Relatives

The underlying rationale of examining brain structure and function in the unaffected first-degree relatives of patients with schizophrenia is that they share approximately 50% of their genome. Given that schizophrenia is usually reckoned to have approximately 70%–80% heritability, with relatively small unique and familial environment effects,<sup>1,23</sup> differences in patients and relatives vs CONs probably reflect shared genetic risk factors for the disorder. In addition, studying unaffected relatives has the important advantage that any abnormalities cannot be attributed to secondary effects of the illness or its treatment.

### *Structural Neuroimaging in Relatives*

Most of the structural imaging studies have hand-traced regions of interest (ROIs) on MRI scans to examine the volumes of the lateral ventricles (LVs) and/or the amygdalo-hippocampal complexes (AHCs) in first-degree relatives (usually sibs and/or offspring) and healthy CONs. Few studies have reported significantly enlarged LVs in relatives as compared with CONs, although most of the studies give results in that direction (see Lawrie<sup>24</sup> for a detailed review). The fewer comparisons of patients and sibs are almost universally significant,<sup>24</sup> suggesting notable changes as people move from being at risk to ill. This pattern of results is reversed in studies of the third ventricle. Almost all the available ROI literature suggests third ventricle increases and/or thalamus reductions in relatives compared with CONs, while patient-relative differences are consistently reported as trends.<sup>24–27</sup> Similar results for the LVs have been obtained with the VBR on CT.<sup>24</sup> Although the increased VBR on CT could reflect a greater reduction in brain volume than increase in ventricular size, the whole-brain volume literature in relatives with sMRI is equivocal.

The relatives' studies are very clear that reductions in the AHC or its component structures are evident in relatives but less marked than those found in patients. In terms of statistical significance, relatives have consistently been shown to have smaller AHCs than CONs and schizophrenics have smaller AHCs than relatives.<sup>24,27–29</sup> In terms of relative (%) differences, patients are generally found to have smaller AHCs than their unaffected relatives and relatives are generally found to have smaller AHCs than healthy CONs.<sup>24</sup> There is also specific evidence for bilateral hippocampal differences as well.<sup>30–33</sup> A recent meta-analysis convincingly demonstrated hippocampal volume reductions in relatives that are not as marked as in patients with schizophrenia itself (see table 1).<sup>34</sup>

The evidence from relatives' studies is inconclusive for most other brain regions, in some cases because of insufficient studies and in others due to low power. There is however a fair degree of agreement among the automated

**Table 1.** Effect Sizes (Cohen *d*) of Relatives Vs Controls and Relatives Vs Patients Group Differences, Where Calculated and Not Limited by Statistical Heterogeneity in the Meta-analyses of Boos *et al.*,<sup>34</sup> With Comparable Results for First-Episode Patients Vs Controls From the Meta-analysis by Vita *et al.*<sup>13</sup>

Region	Effect Size (95% CI) for Relatives Vs Controls	Effect Size (95% CI) for Patients Vs Relatives	Effect Size (95% CI) for First-Episode Patients Vs Controls
Hippocampus	-0.47 (-0.34 to -0.61)	-0.29 (not given)	-0.66 (-0.45 to -0.87) [left side]
Gray matter	-0.18 (-0.02 to -0.33)	Not examined	Not examined
Third ventricle	-0.21 (-0.03 to -0.40)	Not examined	-0.59 (-0.38 to -0.80)

studies for some differences between patients and their relatives and CONs.<sup>35</sup> Such “computational morphometry” techniques average the neuroanatomy in subject groups, with reference to a standardized brain template. Because each brain is fitted to this template, any volume or shape differences between groups tend to be rendered as differences in tissue density or concentration (although newer techniques are moving back toward volume comparisons). Both Job *et al.*<sup>36</sup> and Diwadkar *et al.*<sup>37</sup> found reduced gray matter (GM) density in PFC in relatives at high risk for schizophrenia. In addition, reductions in the thalamus have been replicated as a measure of genetic liability to psychosis.<sup>38,39</sup> Most of these analyses have confined themselves to looking at GM, but many researchers are now turning their attention to white matter densities.

#### *Functional Neuroimaging in Relatives*

There are far fewer functional than structural imaging studies of patients with schizophrenia, and the functional imaging literature in relatives is also smaller than the amount of structural imaging. The individual studies tend also to include fewer participants, and there are very few direct comparisons with patients. Moreover, the interpretation of results is critically influenced by the type, difficulty, and performance of the task. All that being said, sufficient studies have examined PFC function for some consistent findings to emerge.

Early PET and SPECT studies tended to report hypo-frontality but were potentially confounded by poor task performance.<sup>35</sup> Four subsequent fMRI studies have reported hyperactivation of the right dorsolateral PFC (DLPFC) on *working memory* tasks in relatives vs CONs<sup>40–43</sup>—whereas only one small study of unaffected twins has not.<sup>44</sup> In 3 of the studies, there were no significant performance differences observed between the study groups, although relatives performed significantly worse than CONs in the other study and controlling for this resulted in the hyperfrontality being nonsignificant.<sup>41</sup> In contrast, 1 PET<sup>45</sup> and 3 fMRI studies<sup>46–48</sup> have used *language* tasks in relatives, and the only one to detect any PFC abnormality found a (right-sided) hyperfrontality<sup>48</sup>

that was only apparent when linguistic and nonlinguistic elements of the task were combined.

Three studies have examined responses to longer term (verbal) memory tasks in high-risk (HR) relatives. Two of them reported increased activity in the right inferior frontal gyrus in relatives vs CONs during an encoding task, against a background of similar task performance.<sup>49,50</sup> A third did not<sup>51</sup>—although it did find differences in the MTL. It is also worth noting from these studies that other regions have also been repeatedly implicated, particularly abnormal activation of parietal cortex,<sup>40,42–44,46,48</sup> medial PFC (including anterior cingulate),<sup>40,41,46,52</sup> and the thalamus and cerebellum.<sup>40,46,49</sup>

Although it is too early to draw firm conclusions about the nature of PFC functioning in HR relatives, let alone whether or not there is any progression, there is consistent evidence to suggest right-sided hyperfrontality on at least 2 tasks in those at high genetic risk for the disorder. These findings are generally interpreted as a functional inefficiency of this region in relatives during task performance.<sup>40</sup> This in turn could necessitate the recruitment of bilateral prefrontal regions in tasks where predominantly left-sided activation is usually seen in normal CONs,<sup>48</sup> perhaps as part of a general compensatory response to maintain adequate performance.<sup>52</sup> There are also indirect replicated accounts of PFC disconnectivity on PET,<sup>45</sup> fMRI,<sup>53</sup> and EEG<sup>54</sup> in relatives. The best replicated electrophysiological abnormality in relatives is of abnormal P300 amplitude and latency—but this shows almost equivalent differences from CONs in both relatives and patients, suggesting limited opportunity for change around onset.<sup>2,15</sup>

In summary, there is good evidence for structural and functional abnormalities of at least parts of the PFC and temporal lobes in schizophrenia, with reasonably strong evidence for abnormalities of a similar nature but unknown extent in relatives. The clearest evidence for differences between subjects at genetic high risk and patients is in the volumes of the MTL and LVs, and these and perhaps PFC functional abnormalities would therefore appear to be the most appropriate areas on which to concentrate the search for progressive changes related to the onset of schizophrenia.

## Prospective Studies of High-Risk Populations

There have been several prospective longitudinal studies of people at genetic high risk of schizophrenia, but only a small number has included imaging measures.

### *Copenhagen High-Risk Project*

The Copenhagen High-Risk Project was the first HR study to include brain imaging, although the scans were not repeated over time. The researchers initially examined 34 offspring of mothers with schizophrenia, 10 of whose fathers also had a spectrum disorder. Widened fissures and sulci and an increased VBR appeared to relate to a gene-environment interaction,<sup>55–57</sup> but only the schizophrenics had enlarged ventricles.<sup>58</sup> Obstetric complications are the most plausible environmental factor. In the 27 HR subjects who were scanned and whose midwife records were available, birthweight was inversely correlated (0.6) with the VBR. There were weaker correlations with duration of labor and length at birth.<sup>59</sup> Those with relatively lower weight (and those with signs of prematurity) were more likely to have VBRs above the group median, with stronger correlations in those who had subsequently developed schizophrenia (0.77) than those who had not.<sup>60</sup> On stepwise regression, birthweight accounted for 22% of the variance in VBR in the HR group but 64% in a “superhigh risk” group with schizotypal fathers,<sup>61</sup> with no apparent effect of either genetic risk alone, maternal illness, or maternal neglect.<sup>62</sup> Further analysis revealed that increased VBR (and third ventricle width) was particularly related to an interaction between the level of genetic risk and the severity of delivery complications, with a smaller effect of low birthweight and no significant effect of total pregnancy complications.<sup>55</sup>

### *Edinburgh High-Risk Study*

In Edinburgh, we have examined subjects with at least 2 close relatives (parents and/or sibs) with schizophrenia. A total of 229 suitable HR subjects were identified; 162 provided some clinical, neuropsychological, and/or imaging data; and 150 had one or more sMRI scans between 1994 and 1999. Groups of similarly aged healthy CONs and first-episode schizophrenia (FES) patients were also examined. Most of the HR subjects and CONs returned for at least one further sMRI and a fMRI scan between 2000 and 2005, when data collection was stopped.

*sMRI in the Edinburgh High-Risk Study.* Our preliminary ROI findings on sMRI, in the first 100 HR subjects,<sup>28</sup> were that the AHC was significantly smaller (by about 4%) than in CONs but about 4% larger (effect size about 0.3 of a standardized difference) than in FES. Reductions in the volume of the thalamus were only evident in the HR vs CONs contrast. An increase in third ventricular volume in the FES group was not significant

after controlling for intrafamilial clustering (reduced variance) in the full HR sample.<sup>29</sup> The main findings were replicated on voxel-based morphometry (VBM) analysis,<sup>28,63</sup> which also showed anterior cingulate and medial prefrontal reductions in GM density with an FES < HR < CON pattern. PFC, thalamus, and whole-brain volumes, but not those of the AHC, were associated with the strength of genetic liability to schizophrenia.<sup>29</sup> The apparent absence of a relationship between AHC volume and genetic liability may reflect the relatively narrow range of liability in the Edinburgh High-Risk Study (EHRS).

Psychotic symptoms were elicited with the Present State Examination, and isolated or transient symptoms were found in more than half of the sample—many more than we had expected. In those with psychotic symptoms at any point in the first 5 years of the study, the whole-brain volume at study entry was reduced (after controlling for age, sex, paternal social class, height, and handedness) compared with those did not have psychotic symptoms over this time.<sup>29</sup> No other brain volumes at intake were related to a liability to psychotic symptoms. Those with psychotic symptoms, and 2 or more sMRI scans over approximately 18 months, had significant reductions in the (right) temporal lobes and nonsignificant reductions in whole-brain and (left) AHC volume over that time.<sup>64</sup>

Twenty-one subjects (13%), 20 with complete clinical data, developed schizophrenia by the close of the study.<sup>65</sup> Sixteen of these participants had at least 1 sMRI scan, 8 had 2 or more, and 4 also had an fMRI scan, before becoming ill. Preliminary results suggested that relatively large brains (and relatively small thalami in women) predicted the onset of psychosis within the first 5 years of the study.<sup>66</sup> Subsequent, complete analyses have however found little more than weak predictive utility of reduced AHC or thalamus volume,<sup>65,67</sup> and it seems that any predictive effect of regional brain volumes or GM densities for the subsequent development of schizophrenia is at most weak.<sup>68</sup> Baseline measures of cortical folding, particularly in PFC, may however be relatively strong predictors,<sup>69–71</sup> even though this measure may be primarily driven by the amount of gray matter in that region.<sup>71</sup>

Job et al<sup>67</sup> extended the earlier findings of reductions in temporal lobe volume over approximately 18 months in those with psychotic symptoms by using VBM. All HR subjects had distributed changes in GM concentration in the prefrontal and temporal lobes as compared with healthy CONs, but these were more marked in those who had psychotic symptoms at one or both assessments. Moreover, there were additional GM density reductions in left (para) hippocampal uncus, fusiform gyrus, and right cerebellar cortex in the 8 individuals at high risk who subsequently developed schizophrenia ( $z > 4$ , corrected for multiple comparisons) compared with

10 who also had psychotic symptoms but did not make the transition over an average 2.5 years after the first of the 2 scans (or indeed subsequently). This makes it clear that such changes may occur years prior to diagnosis. They cannot be attributable to medication because none of the participants were medicated until after their second scan. We have since evaluated the diagnostic properties of these reductions in GM density and shown positive predictive values of around 60% for these regional reductions individually and about 70% in combination.<sup>72</sup> These figures can be contrasted with much lower values for even the most predictive clinical or behavioral measures. These latter measures, of memory impairment and schizotypy, were more strongly associated with other aspects of the schizophrenia imaging phenotype—gray matter density in thalamic nuclei and the superior temporal gyrus.<sup>73</sup>

*fMRI in the EHRS.* Our fMRI studies were able to demonstrate a compatible picture of trait-related deficits in PFC, thalamus, and cerebellum using a sentence completion task.<sup>46</sup> We also found increased parietal lobe activity in those with isolated or transient symptoms at the time of the scan. This was accompanied by an increased frontoparietal connectivity, presumably to compensate for genetically related PFC dysfunction.<sup>53</sup> A comparable picture of symptom-related exaggerations of trait deficits in PFC and cerebellum was evident on another 2 tasks.<sup>49,74</sup> HR subjects who became ill demonstrated increased activation of the parietal lobe, decreased activation of the anterior cingulate, and smaller increases in activation with increasing sentence completion difficulty in the right lingual gyrus and bilateral temporal regions. Although these findings have to be considered cautiously, because only 4 subjects who had an fMRI scan subsequently became ill, they suggest functional abnormalities are present in HR subjects who later became ill, which distinguish them not only from normal control subjects but also from those at high risk who do not develop the disorder.<sup>75</sup> We have since looked at the associations of delusions and hallucinations, in particular, and have found associations in the temporal lobes and cerebellum, similar to those noted in patients, suggesting perhaps less of a qualitative than a quantitative change with the development of schizophrenia itself.<sup>76</sup>

The overall pattern of results from the EHRS therefore suggests genetically mediated structural and functional deficits in PFC, MTL, thalamus, and cerebellum, with additional volume decrements in the MTL and lateral temporal lobe being related to the onset of more severe symptomatology and frank psychosis. These results find support from the studies published by researchers in Melbourne who have examined groups of people at “ultra-high risk.” Recruited as clinic attenders, they tend to be young people (usually 15–30 years old) with mainly “attenuated” psychotic symptoms over up to 5 years

or transient symptoms of less than 1-week duration in the past year. A few had a family history and a worsening in mental state or general functioning in the past year. The results of this study are described in another article in this issue, but it is here worth noting one particular point of agreement. Pantelis *et al.*<sup>77</sup> reported on their VBM findings in a sample of 75 people with these prodromal symptoms, of whom 23 (31%) developed a psychotic disorder, with roughly equal numbers of schizophrenia and affective psychoses. Twenty-one subjects had a repeat scan after 1–2 years—10 of whom had become psychotic (5 with schizophrenia). They showed reductions over time in (left) parahippocampal, fusiform, orbitofrontal, and cerebellar gray matter density, while those who did not become psychotic only exhibited cerebellar reductions.

Thus, both the currently available studies suggest gray matter density reductions in the left parahippocampal and fusiform gyri in the run up to psychosis. This begs the question—which of the many putative risk factors for schizophrenia are responsible?

### **Brain Imaging and Risk Factors for Schizophrenia**

The strongest known risk factor for schizophrenia is family history, which increases the risk of the disorder by about 5–50 times depending on the degree of genetic association.<sup>1,78</sup> Even the strongest other risk factors that could impact on brain structure and function (ie, stressful life events and cannabis use<sup>78</sup>) have comparatively weak effects but may be more likely to act nearer to the time of onset.

#### *Family History and Specific Genetic Effects*

Family history is of course essentially a proxy for genetic effects. Given that brain growth is maximal prenatally and for 1–2 years thereafter, it is likely that genetic factors play an important part in the patterns of abnormality we have already described in unaffected relatives. These and other genetic risk factors could however also be expressed later in development and lead to the additional changes of greatest interest here. We will therefore now concentrate on the brain imaging studies comparing affected and unaffected twins and the emerging literature on the imaging associations of particular risk genes in unaffected relatives and patients.

*sMRI Studies of Twins.* Suddath *et al.*<sup>79</sup> found that the affected people in 15 pairs of discordant monozygotic (MZ) twins had reduced left temporal lobe gray matter and bilaterally smaller hippocampal volumes, as well as larger ventricular structures, with no such differences in the frontal lobe or in white matter. They subsequently examined an extended sample of 22 discordant MZ twin pairs and found that those with schizophrenia and large

ventricle volumes were more likely to have had labor and neonatal problems, as well as a prolonged labor.<sup>80</sup> They also reported that intrapair differences in hippocampal volumes between discordant MZ twins were related to a prolonged labor. Baare et al<sup>81</sup> examined 15 MZ and 14 dizygotic (DZ) twin pairs discordant for schizophrenia and 29 healthy twin pairs. The affected twins had smaller brains, more cerebrospinal fluid (CSF), and larger LVs.

van Erp et al<sup>82</sup> examined 7 MZ twin pairs concordant for schizophrenia and 16 MZ and 32 DZ twin pairs discordant for schizophrenia, ascertained so as to be representative of all such probands in a Finnish birth cohort, along with 28 MZ and 26 DZ healthy comparison twin pairs. They found that although hippocampal volume in healthy individuals is largely affected by genetic factors, it is subject to substantially greater modulation by environmental factors in schizophrenic patients and their relatives. Styner et al<sup>83</sup> found in contrast that the genetic influences on the LVs are stronger on shape than volume and stronger than the disease-related effects of schizophrenia. Rijdsdijk et al<sup>84</sup> examined MZ twin and sib pairs concordant and discordant for schizophrenia and found significant familial effects for hippocampus and third ventricle but could not resolve whether these were genetic or environmental in origin. Subsequent twin studies have demonstrated substantial genetic contributions to medial (orbito)-frontal<sup>85</sup> and thalamus<sup>86</sup> volume, as in the EHRS.

Cannon et al<sup>87</sup> constructed probabilistic cortical surface maps in MZ and DZ discordant twins and control twins. Twin group effects (as MZ > DZ > control twin differences) and highlights apparently genetic deficits in GM density at the poles of the frontal and temporal lobes, the DLPFC, and Broca and Wernicke areas. MZ affected status contrasts, and findings of higher intraclass correlation coefficients in healthy than diseased pairs suggested environmental effects in DLPFC and parts of the temporal lobe (including Heschl gyrus), which were correlated with symptom severity (especially negative) and cognitive dysfunction (especially on memory tasks). Others have used a similar technique to map hippocampal surface morphology in the same twin groups and found both schizophrenia and genetic liability effects.<sup>88</sup>

These rather inconsistent findings on sMRI—as with the earlier CT literature<sup>24</sup> can perhaps be best summarized as indicating that most volumetric reductions represent both genetic and environmental effects. The few fMRI studies of twins are even less conclusive due to their small size.<sup>35</sup>

*Imaging Specific Gene Effects.* Egan et al<sup>89</sup> were the first to relate a genetic risk factor for schizophrenia to its imaging phenotype. They showed that CONs, sibs, and patients all had greater activation of DLPFC if they were homozygotes for the relatively more efficient Val allele at codon 108/158 of the catechol-O-methyl-

transferase (COMT) gene. This result has been well replicated. Several groups have also related COMT Val status to reduced volumes of the PFC and temporal lobes (see especially Ohnishi et al<sup>90</sup>). Intriguingly, Ho et al<sup>91</sup> found a tendency to a gene-by-group interaction in prefrontal lobe CSF volumes, and Ohnishi et al<sup>90</sup> found a significant group-by-gene interaction in that those with the Val/Val genotype had greater reductions in PFC and MTL volumes if they were patients than if they were CONs. These results may point to particularly strong effects in particular genetic and/or environmental backgrounds.

*Imaging Genetic Effects in the EHRS.* In the EHRS data set, we have initially examined the genetic associations of the first-round imaging data and our results suggest distinguishable trait and state effects. Our neuregulin1 (NRG1) publication was the first to relate brain imaging measures to a variant in that very plausible candidate gene.<sup>92</sup> Genotype information was available for 79 HR subjects. There was a highly significant effect of SNP8NRG243177 genotype on the development of psychotic symptoms—auditory hallucinations or persecutory ideas—over the course of the study. Individuals homozygous for the risk allele (T/T) also showed significantly decreased activation of right medial PFC (and right posterior medial temporal gyrus, as a failure of deactivation) relative to those without the risk allele in the contrast of sentence completion vs rest, even though there was no difference between groups in behavioral measures on this task. This study therefore demonstrated that a specific genetic variant in the NRG1 gene was associated with the development of psychotic symptoms—rather than syndromal schizophrenia—and abnormalities in cortical function suggesting that variation in NRG1 may contribute risk for an intermediate phenotype, which only in some individuals translates into schizophrenia.<sup>93,94</sup> These findings have recently been reinforced by our demonstration, in healthy CONs, of the effects of SNP8NRG243177 on the density and integrity of white matter tracts of relevance to psychosis.<sup>97</sup>

Examination of the effects of the COMT Val158Met polymorphism in the EHRS delivered a complimentary picture.<sup>95</sup> We examined the effects of the COMT Val158-Met polymorphism on brain structure, function, and risk of developing schizophrenia in the 78 people at high genetic risk of schizophrenia who provided all the necessary data. Intriguingly, and somewhat unexpectedly given the relatively small sample size (at least for a genetic association study), the COMT Val allele increased the risk of schizophrenia in this cohort in a dose-dependent manner. Subjects with the COMT Val allele had reduced GM density in anterior cingulate cortex on sMRI. In addition, there was evidence of increased activation on fMRI in lateral PFC and anterior and posterior cingulate, with increasing sentence difficulty on the Hayling task, in

those with the COMT Val allele despite a similar level of performance. At least in the EHRS, therefore, the COMT Val allele is associated with an increased risk of schizophrenia in subjects at increased familial risk, in whom it has demonstrable effects on prefrontal brain structure and function. We are currently addressing whether or not this and other variants is associated with the progressive reductions in hippocampal volume and possible changes in PFC function because those at high risk develop schizophrenia.

#### *Possible Effects of Stress and Cannabis*

Similar changes in cortical GM density have also been shown in children in the earliest stages of childhood-onset schizophrenia (COS), which is likely to be a highly genetic variant of the disorder. The fact that many such changes are also shared by healthy full siblings of COS probands reinforces suggestions of genetic influences on these abnormalities of brain development.<sup>96</sup> These reductions, perhaps particularly those which are near to the time of onset in young people, could however also represent the effects of environmental triggers or gene-environment interactions. Various illegal drugs and social difficulties are thought to increase the risk of schizophrenia,<sup>78</sup> although the evidence is nothing like as strong as it is for genetic effects and it is much more difficult separating cause from effect. Even so, the amount of direct evidence linking these putative etiological factors to the possible pathophysiological processes indexed by brain imaging is surprisingly slight.

There is actually quite strong evidence for abnormalities of the stress response in schizophrenia. Advances in the understanding of the neurobiology of the stress cascade in both animal and human studies can be used to construct a plausible model by which this interaction may occur.<sup>97</sup> There is a substantial literature to suggest that sustained stress is associated with altered adrenocortical function and high levels of corticosteroids. Hypercortisolemia has been repeatedly described in schizophrenic patients and been related to the severity of psychotic symptoms in several studies.<sup>98</sup> There are also several suggestions that hypercortisolemia is linked with brain disturbances compatible with our previous findings of hippocampal volume deficits and the likely underlying neuropathology of reduced neuronal size and dendritic arborization. In particular, stress has been shown to have a number of effects on the glucocorticoid receptor-rich hippocampus (and PFC), including potentially reversible processes, such as the atrophy of dendrites on excitatory pyramidal neurons and the reduced expression of neurotrophic factors such as brain-derived neurotrophic factor, as well as the perturbation of *N*-methyl-D-aspartic acid-dependent synaptic plasticity in the hippocampus.<sup>97,98</sup>

A number of studies in anxiety and depression suggest that predisposing and precipitating stressors are associ-

ated with reduced volumes of the hippocampus.<sup>99</sup> It is therefore intriguing to note that independent life events (and cannabis use) were associated with both “neurotic” and psychotic symptoms in the EHRS<sup>100</sup> and that symptoms of anxiety preceded the development of frank psychotic symptoms in those who went on to develop schizophrenia.<sup>101</sup> Further, in a study we have commenced of those at high risk of schizophrenia because of low IQ, we have found an association between the increasing severity of anxiety symptoms and reduced hippocampal gray matter density.<sup>102</sup> Two recent reports are also noteworthy in this regard. Pariante *et al*<sup>103</sup> have shown that the first episode of a psychotic disorder is associated with a larger pituitary gland, independently of the presence of antipsychotic treatment, and Marcelis *et al*<sup>104</sup> demonstrated that lower gray and white matter volumes in schizophrenia are associated with a dysregulated dopaminergic/noradrenergic mediated stress response. There are however no direct demonstrations that life stressors can be related to the characteristic imaging findings in schizophrenia.

In contrast to the stress literature, the neurobiological effects of cannabis use are relatively poorly defined but there are consistent imaging associations in patients with schizophrenia. Quickfall and Crockford<sup>105</sup> recently reviewed this literature. They found that structural abnormalities generally have not been identified with chronic cannabis use. Regular users demonstrate reciprocal changes in brain activity in cerebellar and frontal regions—abstinence results in decreases and administration results in increases correlating with subjective intoxication. Chronic use and cannabis administration have repeatedly been shown to result in attenuated brain activity in task-activated regions (or activation of compensatory regions).

#### **Conclusions**

Genetic liability to schizophrenia may be inherited as reduced volumes of MTL structures and a tendency to PFC dysfunction. There is fairly persuasive evidence that labor complications and hypoxia interact with genetic risk for schizophrenia to produce larger LVs and smaller hippocampi. These abnormalities are likely to be observable at birth, although there is no direct evidence for this. Relatively little is known about brain development in childhood and adolescence, in health and schizophrenia, but inference from the degrees of abnormality found in relatives as compared with first-episode patients and direct evidence from the very few prospective studies of HR populations are at least consistent. These studies suggest that there are further changes in frontal and especially temporal lobe structure and function, and perhaps particularly in coherent frontotemporal connectivity, in the year or two before the onset of psychosis. There is an emerging literature to suggest that genetic effects,

stress, and cannabis may mediate these apparent changes but as yet no direct empirical demonstrations.

It will be some time before these and other developments lead to a sophisticated understanding of the time course of subregional anatomical and functional abnormalities in schizophrenia. The EHRS has however already demonstrated that brain imaging predictors of psychosis provide a means of identifying subjects at very high risk of transition. This might justify early interventions to reduce stress or cannabis use, and perhaps to prescribe antipsychotics or neuroprotective drugs, which could ameliorate or even prevent the devastating effects of schizophrenia. More speculatively still, given that most of any changes probably occur within a few years of diagnosis and the neuropathology of schizophrenia appears to essentially consist of small poorly connected neurones—but no actual cell death—it is conceivable that some or all of these changes could at least in principle be reversed.

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