Callosal morphology in schizophrenia: what can shape tell us about function and illness?†

Mark Walterfang and Dennis Velakoulis

Summary
Examination of the corpus callosum provides a window to cortical brain change in brain disorders. Combining volumetric with microstructural analysis allows a greater understanding of the biology underpinning change, and examining callosal structure alongside the structure of the cortical regions it interconnects may allow us to understand the true significance of callosal change in psychiatric disorders.

Declaration of interest
None.

Callosal morphology in schizophrenia
With the advent of modern neuroimaging techniques, the callosum became an attractive candidate for analysis via structural imaging: an obviously bright structure on sagittal images, it is readily segmented from surrounding structures; its unique shape lends itself to a range of morphological descriptors, such as area, thickness and curvature. Unlike other brain structures, the callosum does not lend itself to anatomically meaningful volume estimations because of the absence of clear lateral boundaries; researchers have thus relied on estimates of area or shape. Its topographical fibre organisation – where anterior segments connect anterior cortical regions and posterior segments connect posterior cortical regions – suggests that regional cortical alterations may be detectable as subtle regional changes in callosal shape or thickness. In this way, the callosum potentially provides a window to cortical changes in brain disorders, and such changes have been of clinical utility in the differentiation of dementia subtypes. The shape of other topographically organised and projecting structures, such as the basal ganglia, has similarly been shown to differentiate between subtypes of neurodegenerative disorders.

The first magnetic resonance imaging (MRI) study suggested alterations in corpus callosum size and shape. Since this initial study, the widespread availability of MRI scanning has resulted in a range of studies examining the callosum from a variety of morphological perspectives, revealing a number of ways in which the callosum in people with schizophrenia appears to differ from healthy controls, and across different stages of illness (Fig. 1). Two meta-analyses of these studies, almost 15 years apart, are consistent with the finding that the callosum is smaller in schizophrenia, although the latter meta-analysis suggests that this effect may be greatest in patients with first-episode schizophrenia. The difficulty in extracting the nature of the true signal regarding callosal morphology in schizophrenia across these studies is the significant variety of methodological approaches used (with manifold ways to account for head size, choose a consistent mid-sagittal image across participants and parcelate the callosum in anatomically meaningful ways), and the way that descriptors of the callosum are used (with manifold ways to account for head size, choose a consistent mid-sagittal image across participants and parcelate the callosum in anatomically meaningful ways), and the way that descriptors of the callosum are used in these studies: ‘shape’, ‘size’ and ‘reduction’ are terms that have different meanings according to the differences across methodological approaches and statistical models. This heterogeneity may thus dilute or alter the findings from meta-analyses that attempt to combine studies with varying methodology; thus large multistage cohorts who are examined across different phases of psychosis utilising the same sequence parameters and image analysis may be preferable.

Given that evidence suggests that brain changes may occur prior to illness onset, and may progress with transition to

†See pp. 55–60, this issue.
new interactions between different regions of the brain that are initiated in frontal cortical regions coincident with willed actions and fed posteriorly to sensory regions to suppress the sensory consequences of these actions, thereby allowing the brain to recognise these actions as ‘self’-generated. With subtle changes to white matter integrity, an introduced delay in this function disrupted. Consequent abnormalities in neural timing and synchrony between distal brain regions may thus produce characteristic symptoms of schizophrenia. One particular function is highly dependent on accurate timing in these distal brain regions: corollary discharges, which are neural signals that are initiated in frontal cortical regions coincident with willed actions and fed posteriorly to sensory regions to suppress the sensory consequences of these actions, thereby allowing the brain to recognise these actions as ‘self’-generated. With subtle changes to white matter integrity, an introduced delay in this function may result in ‘self’-generated phenomena being erroneously experienced as ‘other’: internal speech becomes

psychosis and/or established illness, a true understanding of shape changes as described by any particular method would be applied across different stages of illness: pre-psychotic, first-episode and established illness. Additionally, volumetric imaging – from which callosal shape can be derived – is limited in its capacity to inform on microstructural changes within brain regions. Recent white matter imaging techniques such as diffusion tensor imaging (DTI) suggest that some of the potential pitfalls of studying any structure in schizophrenia, where the choice of methodology may have an impact on the capacity to detect change. One key example is in accounting for head size; many callosal studies have covaried for intracranial volume to account for this, although using a linear transformation and scaling has been shown to be superior in detecting true between-group differences; transformation is part of the FreeSurfer pipeline used by Collinson and colleagues in their analysis. Furthermore, most studies of the callosus attempt to find local regional differences, thus moving from a pure area/volume measure to a de facto metric of shape. Choice of shape metric and method may similarly affect the capacity to detect results, with sophisticated, sensitive and anatomically informed shape analysis methods for the callosum now being described. A move to these more sophisticated methods, combined with the microstructural methods as utilised in the Collinson et al study, are – at least in part – the way to move the field forward.

Callosum and corollary discharges

How can an understanding of changes in the callosum inform us about the neurobiology of schizophrenia? As the brain’s largest white matter fibre bundle, if there are diffuse white matter changes in schizophrenia, callosal interhemispheric fibres – alongside long association tracts – are most likely to have both their structure and function disrupted. Consequent abnormalities in neural timing and synchrony between distal brain regions may thus produce the characteristic symptoms of schizophrenia. One particular function is highly dependent on accurate timing in these distal brain regions: corollary discharges, which are neural signals that are initiated in frontal cortical regions coincident with willed actions and fed posteriorly to sensory regions to suppress the sensory consequences of these actions, thereby allowing the brain to recognise these actions as ‘self’-generated. With subtle changes to white matter integrity, an introduced delay in this system may result in ‘self’-generated phenomena being erroneously experienced as ‘other’: internal speech becomes
external auditory hallucinations, internal images or thoughts are experienced as projected from an external source and somatic experiences as passivity phenomena.

Callosal microstructural abnormalities in schizophrenia are known to be accompanied by abnormal neural timing and correlate with the severity of these psychotic symptoms. Thus, alterations in the callosal macro- and microstructure may be an index in people with schizophrenia of the severity of neural timing abnormalities, and thus the likelihood of the pathognomonic reality distortions in these patients whereby the distinction between ‘self’ and ‘other’ breaks down during episodes of psychosis. The Collinson et al. findings do not completely align with this hypothesis however, as changes do not completely align with this hypothesis however, as changes

dissonance symptoms across illness stages. As the role of the callosum in established illness, as individuals are likely to experience these symptoms for some time.

Magnetic resonance imaging in psychiatric illness provides rich data-sets that allow for a wide range of investigative approaches. The callosus is an attractive candidate for neuroimaging analysis as it is readily segmentable, can be analysed in two as well as three dimensions, and has shape characteristics that can be measured manifolds. Additionally, its degree of connectedness with disparate brain regions means that it can be used as an index for both white and grey matter change in the brain. However, the increasing variegation in analytical approaches to callosal structure may magnify, rather than simplify, the heterogeneity of complex mental disorders such as schizophrenia. Making future callosal studies meaningful in the context of schizophrenia requires us to move into more whole-of-brain, whole-of-illness approaches, which tie both structure and function together. This may allow us to determine whether the callosus in schizophrenia is the ‘seat’ of the illness, or merely its reflector.

**Conclusion**

Magnetic resonance imaging in psychiatric illness provides rich data-sets that allow for a wide range of investigative approaches. The callosus is an attractive candidate for neuroimaging analysis as it is readily segmentable, can be analysed in two as well as three dimensions, and has shape characteristics that can be measured manifolds. Additionally, its degree of connectedness with disparate brain regions means that it can be used as an index for both white and grey matter change in the brain. However, the increasing variegation in analytical approaches to callosal structure may magnify, rather than simplify, the heterogeneity of complex mental disorders such as schizophrenia. Making future callosal studies meaningful in the context of schizophrenia requires us to move into more whole-of-brain, whole-of-illness approaches, which tie both structure and function together. This may allow us to determine whether the callosus in schizophrenia is the ‘seat’ of the illness, or merely its reflector.
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