Journal Club

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Thalamic Shape: A Possible Endophenotype

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Review of Harms et al. (<http://www.jneurosci.org/cgi/content/full/27/50/13835>)

Schizophrenia is a debilitating mental disorder, yet the mechanism of illness remains unclear. The thalamus, a region of the brain involved in relaying motor and sensory information to the cortex, is thought to play a role in the pathophysiology of schizophrenia. Some, but not all, studies suggest structural abnormalities of the thalamus in schizophrenia, and volume changes have been related to type of antipsychotic used (Csernansky et al., 2004; Khorram et al., 2006). In addition, postmortem studies have observed losses in specific thalamic nuclei, including lower volumes and/or neuronal numbers in mediodorsal nucleus, anterior nucleus, and pulvinar (Young et al., 2000). These nuclei project to cortical areas traditionally identified as functioning abnormally in schizophrenia. More recent imaging techniques have provided an opportunity for a new type of structural study: shape analysis.

In a recent article in *The Journal of Neuroscience*, Harms et al. (2007) used a semiautomated technique to obtain thalamic volume and shape information from a sample of schizophrenia patients,

control subjects, and siblings of both groups. No thalamic volume differences were detected between the four groups, contrary to previously reported thalamic volume reductions in schizophrenia (Csernansky et al., 2004). To analyze shape, a statistical modeling approach was used to collapse 4790 data points into 15 principal component scores, summarizing a complex characteristic of brain structure (shape) in a minimal number of data values. Using this technique, they found that thalamic surface shape was different between schizophrenia and control subjects. These principal components were further reduced into a canonical score, summarizing thalamic shape in one value. Comparison of scores showed that the schizophrenia group differed significantly from their siblings, and the schizophrenia sibling group differed significantly from the controls but not from the control siblings [Harms et al. (2007), their Fig. 1 (<http://www.jneurosci.org/cgi/content/full/27/50/13835/F1>)]. Because these were abstract values whose magnitude and direction are not directly linked to thalamic regions, Harms et al. (2007) demonstrated biological relevance of these scores by showing a positive correlation between the scores and a composite image of thalamic shape [Harms et al. (2007), their Fig. 3 (<http://www.jneurosci.org/cgi/content/full/27/50/13835/F3>)]. Image analysis indicated that anterior and posterior thalamic regions showed depressions in the schizophrenia

group compared with controls [Harms et al. (2007), their Fig. 2 (<http://www.jneurosci.org/cgi/content/full/27/50/13835/F2>)]. These results suggest that inward deformation of select thalamic areas may underlie volume reductions reported previously. In addition, the results suggest that future studies of thalamic volume may have increased power if specific regions are investigated in isolation.

These findings are important to schizophrenia research because they provide a coherent link between postmortem and imaging findings and a starting point for future investigations. The thalamic shape abnormalities in the anterior and posterior regions reported by Harms et al. (2007) could reflect changes in connectivity between the thalamus and cortex, a part of the brain whose volume, gyrification, and function is abnormal in schizophrenia. Although structural images cannot differentiate thalamic nuclei, the concurrent use of other techniques, such as diffusion tensor imaging, could allow the noted deformations to be attributed to specific nuclei based on the area's cortical connectivity and could potentially corroborate postmortem measurements of individual nuclei. Pioneering work has already examined the tractography of the human thalamus in normal subjects (Behrens et al., 2003), and the automation of shape analysis presented by Harms et al. (2007) may allow shape information to be rapidly obtained from such data. Such analysis would also help in discerning

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whether deformations of the thalamic surface are caused by reductions in the outer thalamic nuclei or by other, less-visible areas of the thalamus.

In addition to contributing a new perspective on structural imaging in schizophrenia, Harms et al. (2007) suggest that thalamic shape may be an appropriate endophenotype. The hunt for endophenotypes has recently intensified in psychiatric research, in hopes of simplifying the search for the genetic component of schizophrenia. An endophenotype refers to a measurable phenotype that lies intermediate to its underlying genotype and a disease. Therefore, in the case of complex disorders like schizophrenia, the genetic underpinning of an endophenotype is easier to identify because it is directly related to a measurable trait (Gottesman and Gould, 2003).

For thalamic shape to be a useful and valid endophenotype candidate, several criteria must be satisfied. The endophenotype must (1) be associated with illness in the population; (2) be independent of disease state; (3) be heritable; (4) cosegregate with illness in affected families; and (5) be present in nonaffected family members at a higher rate than in the general population (Gottesman and Gould, 2003). The study by Harms et al. (2007) addresses the last three criteria to some extent, but leaves the rest unresolved.

Much of the support for a thalamic shape endophenotype in the study by Harms et al. (2007) rests on the canonical weight scores, which showed an ordering of values with lowest scores seen in the schizophrenia group, higher in schizo-

phrenia siblings, and highest in controls. However, the nonschizophrenia subjects are young (aged 14–30), and therefore may still be at risk of developing schizophrenia or other psychotic disorders. If individuals in the schizophrenia sibling group go on to develop the disorder, they do not illustrate an intermediate endophenotype, and would suggest thalamic deformation as a biological marker. Furthermore, given that thalamic size can decrease after switching to an atypical antipsychotic (Khorram et al., 2006), it is possible that thalamic shape is state dependent, precluding its use as an endophenotype. Indeed, the large reductions in anterior and posterior thalamic areas found by Harms et al. (2007) may simply reflect the large number of patients taking atypical medications. The search for neuroanatomical endophenotypes in schizophrenia would benefit from investigation of thalamic shape and volume variation in the general population by providing information about the biological variation of these measures. Because the control groups used by Harms et al. (2007) were matched to subject groups and recruited using advertisements rather than random sampling methods, it cannot be claimed that controls' thalamic measures reflect those of the general population. On the other hand, support for the heritability of thalamic volume and its use as an endophenotype has recently been demonstrated in mice. The identification of genetic loci associated with thalamic size (Dong et al., 2007), which may be altered in schizophrenia (Csernansky et al., 2004), lends support for thalamic volume

as an endophenotype. Likewise, identification of such loci for thalamic shape would be helpful in clarifying the usefulness of shape analysis in identifying schizophrenia susceptibility genes.

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