

## Origins of cognitive dysfunction in schizophrenia: clues from age at onset

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The age at which someone with schizophrenia first becomes psychotic is a variable trait related to prognosis. An earlier onset of psychosis is associated with a more severe course, irrespective of duration of illness (Suvisaari *et al*, 1998). An understanding of the factors that contribute to age at onset, and how they interact, might therefore provide important information about the pathological mechanisms operating in this disorder. For example, the finding that there is a significant genetic contribution to age at onset suggests that this might be a sensitive phenotype for the detection of susceptibility genes or genes that modify the presentation of the illness (Cardno *et al*, 2001). This evidence comes from twin studies, which find that age at illness onset correlates much more highly in affected monozygotic twin pairs than in dizygotic twin pairs (e.g. Kendler *et al*, 1987), and from family studies, the majority of which find that a younger age at onset is associated with a higher familial risk of schizophrenia (Kendler & MacLean, 1990). Unfortunately, the search for genes linked to early onset has been relatively disappointing (e.g. Cardno *et al*, 2001). However, Anttila *et al* (2003) have now found a highly significant association between the presence of a *NOTCH4* gene promoter polymorphism (T25C) and a younger age at onset in male Finnish patients who became psychotic a mean of 4.5 years earlier than patients without this allele. The *NOTCH4* gene has previously been implicated as a direct susceptibility gene for schizophrenia (Wei & Hemmings, 2000) but most studies have failed to replicate this finding (e.g. McGinnis *et al*, 2001; Sklar *et al*, 2001; Fan *et al*, 2002). Evidence supporting *NOTCH4* as a gene contributing to early onset comes from a study by Takahashi *et al* (2003) who found an association between the presence of a specific polymorphism and age less than 19 years at illness onset. NOTCH is a membrane-bound receptor which influences neural

development in a number of ways (see Wassink *et al*, 2003). This finding implies that the allelic combination of genes that influence brain development may also modify the presentation of schizophrenia in individuals who are already vulnerable.

Obstetric complications too have been associated with younger age at onset (Verdoux *et al*, 1997), indicating that environmental factors are also active in this regard. The availability of obstetric records of patients and family members identified from large case registers has enabled the mechanism by which obstetric complications contribute to risk of schizophrenia to be specified. In studies of three different populations, foetal hypoxia was associated with an increased rate of schizophrenia (Cannon *et al*, 2000; Rosso *et al*, 2000; Dalman *et al*, 2001; Thomas *et al*, 2001). In two of these studies (Cannon *et al*, 2000; Rosso *et al*, 2000) foetal hypoxia was specifically related to early onset. Other findings from the latter two studies suggest that foetal hypoxia alone is insufficient to cause schizophrenia but interacts with, or adds to, a pre-existing genetic vulnerability. An explanatory model, proposed by the authors of these two studies, suggests that foetal hypoxia causes neurotoxic damage to the developing temporal lobe, and that this brings forward the age at onset because it reduces the amount of synaptic pruning required to cross the 'psychosis threshold' in adolescence.

### EPISODIC MEMORY IMPAIRMENT AND AGE AT ONSET

In the September 2004 issue of the *Journal*, Tuulio-Henriksson and colleagues provided behavioural evidence relevant to the findings of both genetic and environmental influences on age at onset of schizophrenia (Tuulio-Henriksson *et al*, 2004). In the context of an epidemiological study of Finnish families having at least one child with schizophrenia, these workers assessed 239 patients with tests of IQ, memory and

executive function. Age at onset was significantly and specifically associated with performance of the California Verbal Learning Test (CVLT), in that poorer word list learning and delayed recognition memory were both associated with a younger age at onset. The patients in the study had been ill for a mean of 12 years, but when the researchers controlled statistically for the possible contributions of age at assessment, duration of illness and severity of illness, the age at onset effect remained the same. Thus, impaired memory may be a risk factor for – rather than a consequence of – an earlier onset. This finding supports that of Jeste *et al* (1998), who found a significant correlation between age at onset and learning, measured by a composite memory score derived from a number of tests including the CVLT, in 82 people with schizophrenia.

A previous finding from the study of Finnish families was that age at onset decreased as family risk of schizophrenia increased (Suvisaari *et al*, 1998). However, Tuulio-Henriksson *et al* (2004) found no association between CVLT performance and familial loading for schizophrenia. This implies that genetic vulnerability to schizophrenia and memory impairment were operating as independent risk factors for a young age at onset in this population. It also suggests that memory impairment might be more related to environmental than genetic triggers. A clue to the origin of the memory impairment in schizophrenia comes from the observation that foetal hypoxia is an environmental risk factor for an early onset of schizophrenia, as described above. Learning and episodic memory, as assessed by the CVLT, are thought to reflect the integrity of the hippocampus and amygdala, and these medial temporal lobe structures are well known to be particularly vulnerable to neurotoxic damage caused by a number of noxious insults including not only hypoxia but also viral infection, prolonged febrile seizures and even prolonged psychological stress. Thus, exposure to any of these hazards might produce further damage to an already vulnerable limbic system and, by doing so, bring forward the onset of psychosis. In this regard, it is tempting to speculate that drug misuse, a prominent environmental hazard which also seems to bring forward the age at onset of schizophrenia (e.g. Addington & Addington, 1998), may be operating by this mechanism. Exactly how severity of memory impairment is related to earlier

onset of psychosis is a matter of speculation, but a plausible explanation is that it is indicative of the degree of damage to limbic structures implicated in the generation of psychotic symptoms, rather than an intervening variable with causal significance.

## EXECUTIVE DYSFUNCTION AND RISK OF SCHIZOPHRENIA

Tuulio-Henriksson and colleagues found that worse visuospatial working memory was related to increased genetic susceptibility to schizophrenia (Tuulio-Henriksson *et al*, 2004). This finding is consistent with that of Glahn *et al* (2003), who found evidence from a twin study that visuospatial working memory is an endophenotype of schizophrenia. This suggests that impaired executive processes, reflecting the integrity of the prefrontal cortex, might be more related to the function of susceptibility or modifying genes than impaired memory processes. This finding may also be relevant to the observation that a *NOTCH4* polymorphism is associated with earlier onset, as described above. Wassink *et al* (2003), like most other researchers, failed to find any link between *NOTCH4* polymorphisms and the schizophrenia trait. However, they did find an intriguing correlation between the presence of one particular (CTG)<sub>n</sub> allele, and increased frontal grey matter on magnetic resonance imaging and superior performance on the executive Wisconsin Card Sort Task (WCST). This is direct evidence for a genetic influence on a cognitive function thought to be a core feature of schizophrenia. Curiously, the reverse finding was true in controls: the presence of this allele was correlated with decreased amounts of frontal grey matter and worse WCST performance. Thus, the expression of this particular polymorphism may be modified by other genetic factors present in schizophrenia (Wassink *et al*, 2003).

The finding that expressions of the same gene appear to have an impact on executive function and age at onset of schizophrenia implies that some modifying genes might exert their action on the prefrontal cortex. Executive dysfunction was not associated with age at onset in the study by Tuulio-Henriksson *et al* (2004). However, the tasks used to assess executive function in that study were arguably less probing of cognition than the CVLT, which was used to assess memory. These tasks assessed the ability to reverse presented

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sequences of digits or elements in a spatial array (reverse digit and spatial span); many would consider that more appropriate tests are ones that tax the ability to manipulate and update changing information in working memory necessary for ongoing task performance. It is possible that performance on such tasks might also have been related to age at onset. For example, Jeste *et al* (1998) found a positive correlation between executive measures of abstraction and flexibility derived from tests such as the WCST, a demanding task considered to rely heavily on working memory processes. Furthermore, there are hints from the Tuulio-Henriksson study itself that some executive functions might be implicated in risk of early onset. For example, the word list in the CVLT consists of groups of words belonging to specific categories. The strategic use of semantic clusters to aid encoding and retrieval is considered a prefrontal function. Tuulio-Henriksson *et al* (2004) found that the degree to which the patients used this strategy was inversely related to a younger age at onset.

## THE SEARCH FOR SUITABLE ENDOPHENOTYPES

We are now entering a phase of schizophrenia research in which a major focus will be the search for more sophisticated endophenotypes to aid the identification of susceptibility and modifying genes. Possibly, these will be based on combinations of imaging and cognitive features. These features are prey to the environmental influences that contribute to the schizophrenia phenotype. The power of studies such as that by Tuulio-Henriksson and colleagues in this regard is that they allow environmental and genetic influences to be teased apart in an unbiased way. The addition of cognitive assessments to this type of epidemiological study, although time-consuming, labour-intensive and expensive, should be encouraged.

## DECLARATION OF INTEREST

None.

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