

Nour MM & Howes OD (2015) Interpreting the neurodevelopmental hypothesis of schizophrenia in the context of normal brain development and ageing. *Proc Natl Acad Sci U S A*. 2015 May 26;112(21):E2745. doi: 10.1073/pnas.1502170112. Epub 2015 May 4.

## **Letter to the editor**

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Biological Sciences: Neuroscience

### **Title:**

Interpreting the neurodevelopmental hypothesis of schizophrenia in the context of normal brain development and ageing.

### **Authors:**

Matthew M Nour <sup>1</sup> & Oliver Howes <sup>1,2</sup>

### **Author Affiliations:**

<sup>1</sup> Institute of Psychiatry, Psychology & Neuroscience, King's College London, 16 De Crespigny Park, London SE5 8AF.

<sup>2</sup> Psychiatric Imaging, MRC Clinical Sciences Centre, Faculty of Medicine Imperial College London, Hammersmith Hospital Campus, Du Cane Road, London W12 0NN.

### **Corresponding Author:**

Dr Oliver Howes, Institute of Psychiatry, Psychology & Neuroscience, King's College London, 16 De Crespigny Park, London SE5 8AF. [oliver.howes@kcl.ac.uk](mailto:oliver.howes@kcl.ac.uk).

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Douaud and colleagues recently identified a transmodal network of brain areas (IC4) which show an 'inverted-U' relationship between age and gray matter volume (1). These findings lend support to the 'last in, first out' hypothesis, whereby phylogenetically recent cortical regions mature later, and degenerate earlier, than other brain regions. The IC4 network of brain regions overlaps with brain areas that are found to be abnormal in adolescent-onset schizophrenia ( $r=0.48$ ) and Alzheimer's disease ( $r=0.55$ ), which the authors present as archetypal disorders of neurodevelopment and neurodegeneration, respectively. This raises the intriguing hypothesis that the IC4 transmodal network may be vulnerable to a unitary whole-brain pathology that involves both early neurodevelopmental processes and later age-related degeneration.

The influential neurodevelopmental hypothesis of schizophrenia proposes that pathological neurodevelopmental processes, beginning as early as the first and second trimester, result in neuronal circuits that are primed to generate psychotic symptoms during adolescence or young adulthood, often in the context of heightened biological and psychological stress (2). Support for this model of schizophrenia is now widespread (2,3). Structural brain changes are present at symptom onset, and the disorder has been linked to a number of genetic and perinatal risk factors that may disrupt neurodevelopmental processes. Over the last 15 years, however, many studies have found that patients with schizophrenia also show accelerated age-related brain tissue loss after symptom onset, compared to healthy controls (4). There is evidence that these age-related trajectories differ between gray and white matter, suggesting a more nuanced interpretation of the findings reported by Douaud et al.

Specifically, patients with schizophrenia show *reduced* age-related relative gray matter *loss* compared to controls, despite having reduced absolute and relative whole-brain gray matter volume early in the disease course (5). These findings are consistent with an initial reduction in gray matter volume early in the illness (possibly secondary to a neurodevelopmental abnormality), followed by age-related accelerated white matter loss. Interestingly, white matter myelination in the frontal lobe also demonstrates an inverted-U shaped relationship with age (6), suggesting that the age-related vulnerability of phylogenetically recent brain regions extends beyond the gray matter.

In summary, the dichotomy between ‘neurodevelopmental’ and ‘neurodegenerative’ hypotheses in schizophrenia may be unhelpful (3). Like the authors of this present study, we agree that neurodevelopmental vulnerability to the identified transmodal network of gray matter may underlie some of the early structural abnormalities in patients with schizophrenia. We would like to highlight, however, that a ‘developmental’ abnormality may manifest itself in a progressive manner, unfolding differently throughout the course of the disease in both gray and white matter.

To address these questions fully will require large prospective structural imaging studies that utilize data-driven independent component analysis. Ideally, these studies should recruit patients from diagnosis, and scan them at regular intervals for a number of years. Correlation of the results with at-risk genotypes would also enrich our understanding of the neuroprogressive nature of schizophrenia (3) and other neurological and psychiatric disorders.

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Nil

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