The study of neurodevelopmental psychiatric disorders using magnetic resonance imaging

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Causes of psychiatric disorders

Neurodevelopmental psychiatric disorders, such as attention deficit hyperactivity disorder (ADHD), obsessive–compulsive disorder (OCD), early-onset schizophrenia (EOS) and major depression, are major causes of severe behavioural and cognitive impairment and social exclusion in childhood which persist into adult life and in some cases become aggravated in adulthood.

Early detection and intervention is crucial to ameliorate the behavioural symptoms, prevent academic malachievement and improve social integration. The development of targeted treatment such as pharmacological or behavioural intervention is, however, possible only if the behavioural and anatomical correlates of these disorders are fully understood.

The causal pathways of neurodevelopmental disorders

Complex biological and non-biological mechanisms are thought to underlie neurodevelopmental psychiatric disorders such as environmental adversities, genetic predisposition, the complex interaction between both, neurotransmitter imbalance, and structural and functional brain abnormalities. Evidence exists for close causal interconnections between these different biological and social systems. Specific genetic abnormalities, for example, have been shown to sometimes manifest only in their interaction with specific environmental adversities. Highly complex interactions between all these different potential causal pathways make the understanding of the aetiopathophysiology of psychiatric disorders extremely difficult.

The relationship between brain and behaviour

The relationship between abnormal behaviour and abnormal brain mechanisms is highly complex and bidirectional. While it has been traditionally assumed that the presence of abnormal brain structure and function could be the explanatory cause for abnormal behaviour, recent evidence on brain plasticity shows that abnormal behaviour can lead to lasting changes in brain structure and function. For example, environmental adversities like post-traumatic stress disorder in childhood have been shown to cause altered brain structure, brain function and neurotransmitter levels. Early intervention in pre-term born children, as another example, has been shown to lead to improved structure and function of frontal lobe areas. Transient juggling skills in adult life have been shown to lead to corresponding transient changes in brain structures responsible for the relevant hand movements. Abnormal behaviour can therefore cause abnormal brain function and brain structure, just as abnormal brain structure and function (for example, in children with birth complications or neurological conditions) can cause behavioural abnormalities and psychiatric disorders. The bidirectional nature of these interrelationships between brain and behaviour makes it extremely difficult to disentangle the causal pathways between brain abnormalities and neuropsychiatric conditions, especially in development, where the brain is even more plastic than in adult life. Findings of abnormal brain structure and function therefore cannot inform us about the causal pathways of mental disorders, but can give us information only on which brain regions are correlated with specific behavioural abnormalities. Knowledge of the precise behavioural and biological correlates of the disorder can, however, be used to develop targeted treatment in the form of either behavioural or pharmacological intervention.

Brain abnormalities in developmental psychiatric disorders

The use of magnetic resonance imaging (MRI) in developmental psychiatric disorders over the past decades has greatly advanced our understanding of the brain correlates of these disorders. Structural MRI shows the dysmorphology of brain regions, while functional MRI (fMRI) studies investigate the brain in action while patients perform computer tests that are designed to mimic the behavioural dysfunctions of the specific disorders. Very few fMRI studies exist in child psychiatric disorders, most being confined to ADHD, and no published studies exist as yet in children and adolescents with depression, early-onset schizophrenia and OCD. It has been suggested that neurodevelopmental psychiatric disorders are characterIzed by a dysfunction of fronto-striatal and fronto-cerebellar pathways of the brain, important for the fine modulation of behaviour.[1] Although there has been overlap between the different psychiatric disorders wIth regard to abnormalities in the brain areas that constitute these fronto-strio-thalamic and fronto-cerebellar pathways (e.g. in orbitofrontal and dorsolateral prefrontal cortex, anterior cingulate gyrus, caudate, thalamus, and cerebellum), differences in exact location, laterality and developmental course have, however, emerged for the specific childhood disorders.

Attention deficit hyperactivity disorder

ADHD develops in early childhood and is characterized by motor restlessness, impulsiveness and inattention, which manifest at a cognitive level as deficits in functions of inhibitory, attention and motivational control. Structural studies have found abnormalities predominantly in the right frontal cortex, in particular in right dorsolateral and inferior prefrontal cortices, brain regions that are thought to be crucial for mediating mechanisms of inhibitory control. Other brain areas, however, have also been implicated consistently across studies, such as the vermis of the cerebellum, the basal ganglia and the corpus callosum. A summary of all structural

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studies shows that the biggest effect sizes of about 10% reduction in size for ADHD compared to control groups are in right prefrontal cortex, caudate and the cerebellar vermis.[2] Functional imaging studies have confirmed abnormalities in predominantly right prefrontal brain regions and their striatal connections during tests of inhibitory and cognitive control (Figure 1).[3,4] Fronto-striatal and fronto-cerebellar mechanisms are crucial for the fine modulation of behaviour, which may explain the deficient control mechanisms of ADHD children at the motor, cognitive and social levels.[5]

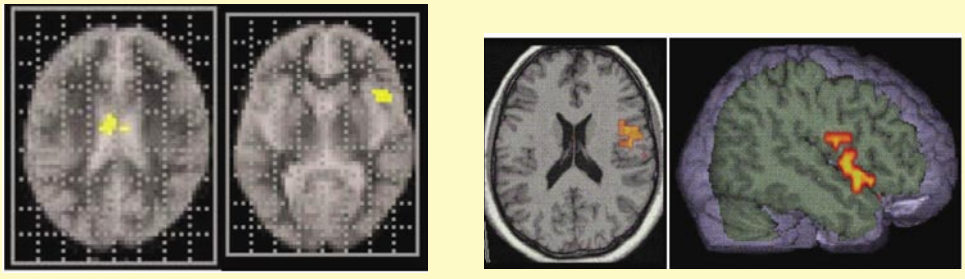
Paediatric obsessive–compulsive disorder

OCD typically develops early in childhood and is characterized by intrusive obsessions and compulsions, which the patient finds difficult to inhibit. It has therefore been argued that the core problem of OCD is a dysmodulation of fronto-striatal pathways that are important for inhibitory control. Neuropsychological studies have in fact confirmed deficits in OCD on a range of tasks of inhibitory control, including motor, cognitive and reflex inhibition. The brain abnormalities in OCD, compared to those observed in other disorders, seem to be relatively confined to the orbitofrontal cortex, anterior cingulate gyrus, caudate and thalamus.[6] Studies in paediatric OCD have shown volumetric, metabolic and biochemical abnormalities in the same brain regions. Our own pioneering fMRI study in children with OCD found reduced activation in orbitofrontal cortex, caudate and thalamus during motor and cognitive inhibitory functions.[7] In adults, the same regions of anatomical and biochemical abnormalities seem to be hyperactivated during rest and during symptom provocation. It has been speculated that the same fronto-strio-thalamic brain regions that are overactivated during stereotyped behavioural abnormalities related to compulsions and obsessions, are less recruitable for functions of inhibitory control that they normally mediate. A dysregulation of these orbitofrontal-strio-thalamic pathways would thus cause both the behavioural manifestations (obsessions and compulsions) and inhibitory problems in OCD.[8]

Adolescent depression

Compared to the other developmental psychiatric disorders, the onset for major depression is relatively late, with rare onset among young children but with a sharp rise in incidence during adolescence. As opposed to ADHD or OCD, where males are predominant, the female:male ratio is 2:1 in major depression in adolescence. There is evidence for a lateralization of negative emotions in left prefrontal brain regions, which is in line with evidence for left prefrontal cortex abnormalities in structural studies of children with depression.[9] The caudate has also been implicated in depressive children, pointing towards abnormalities in left hemispheric fronto-striatal pathways. In line with the clinical manifestations of a mood disturbance in the disorder, limbic brain regions that mediate emotional functions have been shown to be structurally and biochemically altered, such as the pituitary gland (which has been related to the increased cortisol secretions in depression), the amygdala (found to be involved in anxiety), and the anterior cingulate gyrus (that has been related to motivation).[10] Although negative mood appears to be the primary symptom of depression, neuropsychological studies have also associated depression with abnormalities in attention and motivation. Abnormalities in brain networks that are related to motivation and attention, such as the anterior cingulate gyrus, the caudate and the dorsolateral prefrontal cortex, may explain the observed link in major depression between a mood disturbance and motivational and attentional deficits during cognitive tasks. The laterality differences between predominantly left frontal abnormalities in major depression as opposed to predominantly right frontal abnormalities in externalizing disorders of behavioural inhibition (such as ADHD) are interesting to note. While right frontal brain areas have consistently been related to mechanisms of inhibitory control, there is evidence for a predominant role of the left prefrontal lobe for the initiation of action. The findings of a relationship between left dorsolateral prefrontal abnormalities in adults with depression and psychomotor slowness are in line with this dichotomy.

One of the most consistent findings in functional imaging studies of ADHD is reduced brain activation in the right inferior prefrontal cortex (and caudate) during performance of motor response inhibition tasks (stop task)



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(a) in children with ADHD when taken off medication.[3] (b) in medication-naïve children with ADHD.[4]

1