Available online at www.sciencedirect.com
ScienceDirect
European Psychiatry 23 (2008) 315–319
EUROPEAN PSYCHIATRY
http://france.elsevier.com/direct/EURPSY/

Original article

Psychiatric neuroimaging: Joining forces with epidemiology

David Glahn [a], Abraham Reichenberg [b,*], Sophia Frangou [c], Hans Ormel [d]

[a] Department of Psychiatry and Research Imaging Center, University of Texas Health Science Center at San Antonio, TX, USA
[b] Section of Cognitive Neuropsychiatry, Institute of Psychiatry, Kings College London, London, UK
[c] Section of Neurobiology of Psychosis, Institute of Psychiatry, Kings College London, London, UK
[d] Department of Psychiatry, University Medical Center Groningen, Groningen, The Netherlands

Received 24 August 2007; received in revised form 21 September 2007; accepted 30 September 2007
Available online 16 June 2008

Abstract

Severe mental illnesses such as schizophrenia and mood disorders have a major impact on public health. Disease prevalence and phenotypic expression are the products of environment and gene interactions. However, our incomplete understanding of their aetiology and pathophysiology thwarts primary prevention and early diagnosis and limits the effective application of currently available treatments as well as the development of novel therapeutic approaches. Neuroimaging can provide detailed in vivo information about the biological mechanisms underpinning the relationship between genetic variation and clinical phenotypes or response to treatment. However, the biological complexity of severe mental illness results from unknown or unpredictable interactions between multiple genetic and environmental factors, many of which have only been partially identified. We propose that the use of epidemiological principles to neuroimaging research is a necessary next step in psychiatric research. Because of the complexity of mental disorders and the multiple risk factors involved only the use of large epidemiologically defined samples will allow us to study the broader spectrum of psychopathology, including sub-threshold presentation and explore pathophysiological processes and the functional impact of genetic and non-genetic factors on the onset and persistence of psychopathology.

Keywords: Psychosis; Schizophrenia; Bipolar disorder; Risk factors

The major neuropsychiatric disorders – schizophrenia, mood and anxiety disorders – are among the top 30 causes of disability worldwide according to the Global Burden of Disease Study [24]. Neuroscientists and clinicians have still to meet the challenge of reducing this disability burden.

1. Unresolved issues in psychiatry

The main obstacle to date is our incomplete understanding of fundamental questions regarding the *nature* of mental illness and the *aetiological* and *pathophysiological* processes involved. With regards to the nature of mental illnesses we have still to reach a definitive consensus as to whether there are ''points of discontinuity'' separating the mental illness from normal variability, and whether mental illness represents distinct and identifiable nosological entities as opposed to dimensions of a similar underlying psychopathology.

Epidemiological and genetic studies have identified a large number of potential risk factors for psychopathological deviance ranging from purely biological such as genes (e.g. see Ref. [14]), to purely social such as urban environments (e.g. see Ref. [27]), and to complex interactions between biological and environmental factors (e.g. see Ref. [5]). However, we are still largely unable to define pathways by which such remote risk-conferring and potentially causative factors can exert their influence on behaviour and by inference on brain structure and function. Our restricted knowledge of the causative and pathophysiological mechanisms underpinning the expression of psychopathology means that primary prevention is currently not possible for psychiatric disorders. Secondary prevention is also limited as prognostic or treatment response markers that can be meaningfully incorporated into clinical care have not

* Corresponding author. Tel.: +44 20 7848 5241.
E-mail address: avi.reichenberg@iop.kcl.ac.uk (A. Reichenberg).

0924-9338/$ - see front matter © 2008 Published by Elsevier Masson SAS.
doi:10.1016/j.eurpsy.2007.09.014

been identified. Pharmacotherapy in psychiatry is not a disease but symptom-specific and based purely on empirical evidence using a ''trial and error'' approach. Psychotropics impact on multiple biological systems but we only have tentative hypotheses regarding the mechanism of action responsible for their therapeutic effects (e.g. see Ref. [31]). New drug development could benefit from improved understanding of therapeutic drug actions, as would clinical care, as it opens the possibility of individually tailored prescribing.

2. Brain imaging and psychiatry

Neuroimaging has been the single most important technological development in central nervous system (CNS) research and has led to unprecedented progress in our understanding of human brain structure and function in health and disease. Magnetic resonance imaging (MRI) has a pre-eminent position amongst all available imaging techniques because of the range of its potential applications, its exceptional safety profile and non-invasive nature. Indeed, brain imaging methods are revolutionizing human neuroscience, in general, and psychiatric research, in particular. The human brain imaging literature, including structural and functional studies, now exceeds 2000 peer-reviewed articles per year (Fig. 1) and continues to grow. For many years, brain imaging research focused heavily on young, healthy, and normal adult subjects. Over the past several years, however, normative studies of brain structure and function have been extended too much of the human lifespan, from childhood through extreme old age. Imaging has been successfully applied in adult populations in a wide range of psychiatric disorders, with particularly notable successes in mood disorders and substance abuse disorders. Most recently, imaging has demonstrated its value as an endophenotype, to study the brain effects of genetic variations, including disease-associated variations. These successes are now beginning to be translated into imaging-based investigations of psychiatric disorders.

The use of neuroimaging has led to significant breakthroughs in psychiatry particularly in the field of schizophrenia and mood disorders. Below we outline selected studies that highlight key developments but we acknowledge that many more colleagues have contributed state-of-the-art studies in each of the areas mentioned.

2.1. Imaging pathophysiological mechanisms

Amongst the earliest achievements in neuroimaging research was the identification of neural correlates of psychiatric symptoms (e.g. see Ref. [23]). The impact of these studies cannot be understated as they ushered in the current era of biological approach in understanding mental illness. Neuroimaging has perhaps contributed the most in the investigation functional neural activity associated with auditory hallucinations within an extensive network of cortical and sub-cortical areas including the inferior frontal cortex, the anterior cingulate gyrus, the right lateral temporal cortex, the left parahippocampal region and the thalamus, striatum and cerebellum [26,30].

2.2. Imaging the effect of risk factors

Most mental disorders seem to have multifactorial origins but at least for the major psychoses, genetic factors play the most significant aetiological role. Only a minority of neuropsychiatric disorders can be reliably attributed to single genes of major effect. Fragile X syndrome is one such disorder where neuroimaging has been instrumental in describing the associated variation in brain structure and function and its relationship to the behavioural and cognitive deviance seen in this syndrome [29]. In more complex disorders, neuroimaging has already begun to help us unravel potential mechanisms by which risk factors may act increase vulnerability. Studies are also beginning to assess the effects of environmental exposures on the human brain. Cannabis use during adolescence has been consistently associated with risk of developing schizophrenia in adult life [1]. Several studies have now shown specific effects of cannabis on brain function [16,17,6].

Most neuropsychiatric illnesses have more complex genetic origins, which include multiple risk genes, as well as environmental factors, necessary for the manifestation of the illness. Our ability to localize the genes predisposing illnesses such as schizophrenia, bipolar disorder, and major depression have been hampered in part by the heterogeneity of the behavioural presentation found in these illnesses. Since anatomic or functional imaging may be somewhat closer to the biological mechanisms disrupted in mental illness than observable behaviour, imaging may provide a vantage point to significantly reduce the symptom and course heterogeneity found in most illnesses. Similar ''final common pathway'' arguments have been successfully made in the context of how single genes impact behaviour [13]. Specifically, Hariri and colleagues [12] found that variation in the serotonin transporter gene influenced amygdala response to viewing fearful faces even though behavioural markers were insensitive to this genetic variation. Currently, there have been relatively few attempts to use imaging data which help to classify or categorize individuals with mental illness. In part, this is due to the cost of imaging methods. However, a more substantial obstacle is that psychiatric imaging studies rarely involve population sampling methods that would allow for the typification of the illness in general rather than understanding of a specific sample. This is an area where integration of imaging and epidemiological methods could significantly improve our understanding of mental illness, and subsequently the practice of psychiatry.

2.3. Imaging medication response

Arguably one of the most exciting contributions of neuroimaging to psychiatry was in the field of psychopharmacology where evidence for biological markers of treatment response is beginning to emerge. First Mayberg et al. [25] and subsequently Fu et al. [11] showed that changes in the activation within the anterior cingulate are an early marker of antidepressant response; additionally treatment-induced symptomatic improvement was also associated with reduced activation in