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## **ETHICAL IMPLICATIONS OF BRAIN IMAGING IN PSYCHOSIS AND PSYCHOPATHY**

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### **Abstract**

In recent decades, advances in structural and functional brain imaging have identified brain abnormalities associated with psychiatric disorders. This surge in knowledge about the biological underpinnings of psychiatric constructs including psychosis and psychopathy is potentially useful for improving treatment and diagnosis, but also necessitates the consideration of its ethical implications. More recent studies highlight the power of brain imaging as a potential early diagnostic aid for schizophrenia, raising issues about the desirability of this information for individuals, services and society. More fundamentally, the increasing emphasis on the biological component of psychiatric disorders may change the way patients view themselves and their potential for recovery, and alter stigmatisation by others. The association of particular imaging findings with psychopathy and antisocial personality disorder gives rise to even more complex ethical implications involving accountability and diminished responsibility. Mitigating evidence based on brain scans is being used in court cases already, despite several methodological and fundamental problems. These include the translation from scientific group-bases analysis to individuals, the misleading and “seductive allure” of brain images to the layperson, and the difficulty of providing definitive evidence for brain-behaviour causality. In sum, progress in brain imaging alters our notion of psychiatric disorders and opens new possibilities for applications, whether or not ethically or scientifically justified. In order to avoid hampering a potentially positive impact of this progress on patients and wider society, it is important that the ethical implications are considered in time, by all parties involved.

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## 1. Introduction

During the nineteenth and early twentieth centuries, the absence of evidence of biological causes of psychiatric disorders meant they were distinguished from neurological diseases with known organic causes. Technical innovations in recent decades, including magnetic resonance imaging (MRI), have transformed views of psychiatric disorders in many cases from disorders of the mind to disorders of the brain. Nowadays, schizophrenia and even the less severe but more common personality and mood disorders are also understood to have organic associates. The continued refinement of acquisition and analysis techniques in brain imaging has the potential not only to increase our understanding of psychiatric disorders and improve treatment, but also to generate applications as diagnostic aids and in prognostication.<sup>1</sup> In addition, the conceptual shift of psychiatry towards biology could impact upon society in various ways, for example by bringing about changes within the operation of the legal system, or by affecting stigma. In this article we will review briefly what brain imaging has contributed to our current knowledge of psychosis and disorders associated with antisocial behaviour, and discuss some of the ethical implications.

## 2. Psychosis

Psychosis literally means an abnormal condition of the mind. In clinical practice however it is used to refer to more severe forms of psychiatric disorder, such as schizophrenia, which are characterised by hallucinations and delusions. Hallucinations, such as “hearing voices”, are defined as perceptions in the absence of an external stimulus. Patients suffering from psychosis are, at least at times, convinced that these perceptions arise from the external rather than the internal world. Delusions are powerful and persistent beliefs that are out of keeping with reality given the patient’s educational, cultural and social background; and they are arrived at in an abnormal fashion<sup>2</sup>. Delusions are often bizarre and most typically involve delusions of persecution and control.

Psychotic symptoms are most characteristic of schizophrenia, but also occur in mood disorders and dementia. Schizophrenia and bipolar disorder (“manic depression”) are surprisingly common, with a prevalence of 0.5% - 1% each, and tend to present first in adolescence or in the early twenties. In schizophrenia, the distressing psychotic symptoms are often accompanied by negative features (a cognitive deficit) such as lack of motivation. Together the symptoms usually lead to a lifelong course of disrupted everyday functioning and although antipsychotic drugs can alleviate positive symptoms in a many patients, they are less effective against negative symptoms.

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<sup>1</sup> SM Lawrie, B Olabi and AM McIntosh, “Do We Know Anything about the Pathophysiology of Schizophrenia of Clinical Utility?” (In Press) *World Psychiatry*.

<sup>2</sup> A Sims, *Symptoms in the mind: An introduction to Descriptive Psychopathology* (Edinburgh: Saunders, 2003).

Both Kraepelin and Bleuler, who were the first to describe schizophrenia (or “dementia praecox”) believed that psychosis had an organic cause. Because early post-mortem studies failed to find consistent organic pathology, however, schizophrenia and similar psychotic disorders were initially labelled as examples of “functional psychosis” as opposed to “organic psychoses” which included dementia and delirium. In the mid-1970s, when analysis of computed tomography (CT) scans showed striking ventricular enlargements in schizophrenic patients,<sup>3</sup> the neuropathology of psychosis was revived as a major focus of research. Evidence of brain abnormalities in psychosis has since accumulated, and became more detailed with the development of higher resolution magnetic resonance imaging (MRI), the measurement of brain function using positron emission tomography (PET) and functional MRI. By now, hundreds of structural and functional MRI studies have demonstrated that psychosis is associated with reductions in gray and white matter, as well as abnormal brain function, most consistently in the (medial) temporal and prefrontal lobes.<sup>4</sup> By enabling detailed, automated studies of the brain *in vivo*, advanced techniques for acquisition and analysis of brain imaging have been central to improvement in our knowledge of psychosis.

This increase in knowledge about the underlying mechanisms of development of psychotic disorders may benefit patients by identifying new targets for medication, making drugs more effective and/or reducing side effects. Although this strategy has so far not proven to be very successful, more progress is expected as imaging research continues to integrate with molecular genetics to bridge the gap between genetic and molecular mechanisms and symptom development. Another promising role for imaging is in the identification of biomarkers for responsiveness to specific treatment, which will facilitate individualised choice of treatment and ongoing guidance. Finally, better knowledge of the core neural mechanisms will also facilitate development of treatments other than medication. It will improve and inspire advances in various forms of therapy, and assist implementation of innovative treatments such as deep-brain stimulation.<sup>5</sup>

So far, no abnormality has been found that is apparent in every patient with schizophrenia but not in healthy individuals. Despite this, when analysed in a multivariate manner, some imaging markers can discriminate between patients with schizophrenia and healthy controls with an accuracy of 80 to 90%.<sup>6</sup> An obvious advantage of studying brain structure *in vivo* is the possibility of longitudinal investigations that will measure changes over time. We know from epidemiological

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<sup>3</sup> EC Johnstone et al, “Cerebral Ventricular Size and Cognitive Impairment in Chronic Schizophrenia” (1976) 2 *Lancet* 924-926.

<sup>4</sup> See for example: D Arnone et al, “Magnetic Resonance Imaging Studies in Bipolar Disorder and Schizophrenia: Meta-Analysis” (2009) 195 *British Journal of Psychiatry* 194-201; ME Shenton et al, “A Review of MRI Findings in Schizophrenia” (2001) 15 *Schizophrenia Research* 1-52; and SM Lawrie et al, “A Systematic and Quantitative Review of Volumetric Magnetic Resonance Imaging Studies” (1998) 172 *British Journal of Psychiatry* 110-120.

<sup>5</sup> P Krack et al, “Deep Brain Stimulation: from Neurology to Psychiatry?” (2010) 33 *Trends in Neurosciences*. 474-484.

<sup>6</sup> C Davatzikos et al, “Whole-Brain Morphometric Study of Schizophrenia Revealing a Spatially Complex Set of Focal Abnormalities” (2005) 62 *Archives of General Psychiatry* 1218-1227.

studies that psychosis is highly heritable, with increasing risk for individuals with affected family members and a steeper risk-increase for identical twins.<sup>7</sup> By following up young people at high genetic risk of schizophrenia, we have shown that at least some of the characteristic gray matter reductions in schizophrenia are already present before the onset of symptoms. Moreover, some of the baseline and repeated assessments could predict schizophrenia in individual participants with a power of up to 80% and exclude it with 93-98% power based on clinical, cognitive, genetic or imaging measures.<sup>8</sup> Although these predictive values are striking, it should be stressed that this research is still in an early stage and that neuroimaging markers are not used in the diagnosis or prediction of psychiatric disorders at present. Whilst indicative of future applications in this area, the above studies require replication in independent samples. A common limitation of studies aiming to classify participants according to diagnosis is that the testing of the model's accuracy is often performed on the same sample that was used to develop the model (technically leads to "overfitting"). In practical terms this means it is unclear how well the model could classify a new individual. Secondly, longitudinal imaging studies that include premorbid patient data are extremely rare and if they exist the patient group tends to be small.

Nevertheless, it is clear that there is a surge of neuroimaging studies attempting to classify and predict psychiatric disorders (also see<sup>9</sup>) with reasonable success, raising the possibility of clinical applications in the near future. It is thus necessary to explore the desirability of such applications, as well as their ethical justifiability. One dilemma is that in practice, some individuals would inevitably be given a false positive or false negative diagnosis or prediction. It is highly debatable whether the possibility of such misclassification would justify the benefits it could have for those who are classified correctly. This, of course, depends on what can or would be done to prevent the development of the psychosis in those who are predicted to develop it. From what we know at the moment, such preventive treatment could vary from the suggestion of lifestyle adaptations, through, for example, education on the adverse effects of cannabis use in those who are already at high risk,<sup>10</sup> to more extreme measures such as the prescription of antipsychotic medication. Similar dilemmas already occur in regard to the prediction of Alzheimer's disease; as there is however no effective prevention of Alzheimer's disease at present. It is a matter of debate as to how valuable this knowledge is for the individual at risk. In the case of schizophrenia, there is so far no universally effective antipsychotic for patients, let alone for prospective patients. In addition, the widespread action of antipsychotic drugs on the

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<sup>7</sup> I Gottesman. *Schizophrenia Genesis: The Origin of Madness* (New York: Freeman, 1991).

<sup>8</sup> EC Johnstone et al, "Predicting Schizophrenia: Findings from the Edinburgh High-Risk Study" (2005) 186 *British Journal of Psychiatry* 18-25; DE Job et al, "Grey Matter Changes Can Improve the Prediction of Schizophrenia in Subjects at High Risk" (2006) 4 *BMC Medicine* 29; and HC Whalley et al, "Functional Imaging as a Predictor of Schizophrenia" (2006) 60 *Biological Psychiatry* 454-462.

<sup>9</sup> C Ecker et al, "Describing the brain in autism in five dimensions—magnetic resonance imaging-assisted diagnosis of autism spectrum disorder using a multiparameter classification approach" (2010) 30 *Journal of Neuroscience* 10612-23.

<sup>10</sup> DM Semple, AM McIntosh and AM Lawrie, "Cannabis as a Risk Factor for Psychosis: Systematic Review" (2005) 19 *Journal of Psychopharmacology* 187-194.

brain means most have some side effects, including sedation, muscle spasms and weight gain, with the possibility of complete intolerance and additional problems with prolonged use.

It is beyond the scope of contemporary science to inform these ethical judgments. What is necessary are systematic studies of different populations and their perceived preferences based on different risk estimates. Should the imaging technology become widely available, it would ideally be up to every individual to decide whether they want to know an estimate of their risk and whether to choose preventive treatment. The critical requirement is that they should be well-informed.

Functional MRI ‘lie detection’ and genetic screening for many physical and mental conditions are already being offered as commercial services by private companies in the US and elsewhere. An indirect concern about individual assessment of risk of developing psychosis is that it could be used in areas outside the control of academic or medical institutions. Even if public services, because of unresolved ethical dilemmas or for financial reasons, would not make individual risk assessment available, private companies might choose to do so. In academic and medical settings, identifiable human information of any source is subject to legislation, and anonymity of the data is protected by ethical considerations. With the rise of techniques in genomics, appropriate national and international legislation has been put in place to protect genetic data from use for unintended purposes. No such specific legislation has yet been established in relation to neuroimaging data. The concern of a majority of public health workers and patients that brain scan data will have a negative impact on their private US health insurance<sup>11</sup> may therefore be a realistic one.

Further, by emphasising the biological “brain component” associated with psychosis, advances in brain imaging also impact on society on a more fundamental level. On the one hand it has been suggested that emphasis on a biological cause could lead to feelings of helplessness, while on the other hand knowledge of the biological basis of the condition could help remove social stigma and self-blame from patients and their relatives. Ultimately, it may depend on the individual. A recent study provides evidence of potentially positive effects of brain imaging on patients with major depression.<sup>12</sup> Of seventy-two patients questioned, 76% thought that having a brain scan as diagnostic aid would help them accept their condition more easily, while only 14% thought it would cause them to worry about it more. A majority of both mental health workers and patients agreed that the use of imaging in clinical psychiatry would help others to accept the patient’s condition, and 71% of those who blamed themselves for their depression thought brain imaging would reduce this negative feeling. In addition, patients and mental health workers believed that the use of brain imaging would encourage treatment adherence, for both cognitive therapy and medication. It should be borne in mind that this survey was somewhat hypothetical in that it started from the assumption that imaging is a reliable diagnostic tool, able to identify psychiatric disorders in each individual; nevertheless the conclusion remains

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<sup>11</sup> J Illes et al, “In the Mind’s Eye: Provider and Patient Attitudes on Functional Brain Imaging” (2008) 43 *Journal of Psychiatric Research* 107-114.

<sup>12</sup> J Illes et al, “In the Mind’s Eye: Provider and Patient Attitudes on Functional Brain Imaging” (2008) 43 *Journal of Psychiatric Research* 107-114.

that many patients and mental health workers have a positive attitude towards brain imaging.

### 3. Psychopathy

Psychopathy is characterised by an abnormal lack of empathy combined with immoral conduct, masked by an ability to appear outwardly “normal”. These individuals are at high risk of violence and of substance misuse. As patients, they can be particularly difficult to work with. Although the term psychopathy is still used, the diagnosis of psychopathic traits is difficult and time consuming, requiring subjective judgments about affective and interpersonal personality difficulties. In current psychiatric classification systems psychopathy falls under the broader category of antisocial personality disorder. This is defined in more behavioural terms including a propensity to crime and lying, a failure to work or honour financial obligations, and impulsivity and aggression.

Advances in brain imaging raise similar ethical concerns in relation to antisocial personality disorder as they do in psychosis, although basic research in this area is less popular and has received less funding, and therefore less is known so far. Since psychopathy is more prevalent among offenders than in the general population,<sup>13</sup> ethical implications of research in this group are made more complex by the addition of the legal and philosophical issues of accountability and diminished responsibility.

The frequency of a history of traumatic brain injury in prison populations is estimated to be as high as 87%, with as many as 29% having a history of moderate to severe brain injury (defined as more than 30 minutes unconscious and/or memory loss for a prolonged time outside of the time surrounding the trauma).<sup>14</sup> Such traumatic brain injury and any resulting brain damage could in certain cases be considered to mitigate responsibility for criminal behaviour; this could also be argued for neuropathology not caused by trauma. MRI studies increasingly show structural and functional brain differences between antisocial, violent and psychopathic groups of people and “normal” participants. These include associations between antisocial behaviour and deficits in prefrontal lobe function and structure and executive functioning.<sup>15</sup> In our own studies of convicted offenders, we showed social cognition deficits both behaviourally and on functional MRI.<sup>16</sup> PET and functional MRI research in healthy controls with no history of offending demonstrated a strong correlation between impulsive-antisocial traits as measured by the Psychopathic Personality Inventory and mesolimbic dopamine release, as well as greater activation in the mesolimbic reward

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<sup>13</sup> See for example: J Coid et al, “Psychopathy among Prisoners in England and Wales” (2009) 32 *International Journal of Law and Psychiatry* 134-141.

<sup>14</sup> B Slaughter, JR Fann and D Ehde “Traumatic Brain Injury in a County Jail Population: Prevalence, Neuropsychological Functioning and Psychiatric Disorders” (2003) 17 *Brain Injury* 731-741.

<sup>15</sup> MC Brower and BH Price, “Neuropsychiatry of Frontal Lobe Dysfunction in Violent and Criminal Behaviour: a Critical Review” (2001) *Journal of Neurology, Neurosurgery and Psychiatry* 720-726; also Y Yang and A Raine, “Prefrontal Structural and Functional Brain Imaging Findings in Antisocial, Violent, and Psychopathic Individuals: a Meta-Analysis” (2009) 174 *Psychiatry Research* 81-88.

<sup>16</sup> L Robinson et al, “A Preliminary fMRI Study of Social Cognition in Recently-Liberated Prisoners” (2010) Submitted.

system during the anticipation of a monetary reward.<sup>17</sup> The authors concluded that hypersensitivity of the mesolimbic reward system underlies impulsive-antisocial personality traits.

Drawing a parallel with psychosis, these findings and others raise the intriguing but disquieting possibility that psychopathy and antisocial personality disorder could be conceived of as neuro-developmental disorders. This provides a further possible rationale for treatment for those affected. Whether therapy - psychotherapy or cognitive behavioural therapy aimed at increasing social cognition skills or empathy – could be effective is still controversial. At present, no effective evidence-based treatment for antisocial personality or psychopathy exists. However, the lack of availability of successful treatments could be due to the limited knowledge we have about the aetiology and a shortage of clinical trials with adequate follow-up periods.<sup>18</sup>

One additional ethical implication of brain imaging findings related to psychopathy is the use of brain images as mitigating evidence in criminal court cases. Not only structural, but also functional MRI and PET data are being used for this purpose already.<sup>19</sup> Although evidence on the basis of biology may have the advantage of excluding malingering, there are both methodological and conceptual reasons why brain imaging evidence should be treated with caution. Firstly, it should always be borne in mind that the brain differences and associations are usually found at a whole group level, are by no means absolute, and cannot currently be used to classify an individual as a psychopath. Frontal lobe dysfunction undoubtedly can contribute to violent behaviour, especially when impulsive, but it is by no means *sufficient* to completely explain such behaviour. Also, the putative prefrontal and mesolimbic disruptions appear to be more associated with aggressive personality traits than with violent *behaviour* per se. In other words, there are people, with a similar degree of frontal lobe dysfunction as offenders, who do not offend. Secondly, a causal relation is difficult to establish unequivocally in science, let alone in a real life situation in one individual. Often the brain scans are obtained after the crime has been committed, leaving the possibility that the findings arose after, or as a (direct or indirect) result of the criminal act. On a scientific level, precisely which brain regions are a direct 'cause' of aggressive behaviour and which are merely indirectly involved is ambiguous. On a fundamentally philosophical level, to what extent a brain variable should be considered as causal to personality, or merely as a correlate or substrate, remains debatable. In sum, despite scientific limitations and philosophical complications, brain imaging data are being used as legal evidence. From the perspective of clinical neuroscience, it should be borne in mind that MRI images do not speak for themselves and require interpretation from an expert. Experiments have demonstrated that neuroscientific information and brain images, even when

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<sup>17</sup> JW Buckholtz et al, "Mesolimbic Dopamine Reward System Hypersensitivity in Individuals with Psychopathic Traits" (2010) 13 *Nature Neuroscience* 419-421.

<sup>18</sup> C Rodrigo, S Rajapakse and G Jayananda, "The 'Antisocial' Person: an Insight into Biology, Classification and Current Evidence on Treatment" (2010) 9 *Annals of General Psychiatry* 31; also RT Salekin, "Psychopathy and Therapeutic Pessimism. Clinical lore or clinical reality?" (2002) 22 *Clinical Psychology Review* 79-112.

<sup>19</sup> V Hughes "Science in Court: Head Case" (2010) 464 *Nature*, 340-342.



completely redundant, can potentially “seduce” the layperson into believing false arguments.<sup>20</sup>

#### **4. Summary and Conclusion**

Structural and functional brain imaging are powerful techniques, increasingly able to classify and even predict schizophrenia. This prompts ethical questions about the desirability of that information, and different scenarios of risk assessment and potential treatment require evaluation in different populations. Patients themselves may have a positive attitude towards brain imaging, which they can feel might reduce social stigma and feelings of self-blame. Psychopathy and antisocial behaviour are also associated with structural and functional abnormalities in the brain, but these studies have received less funding and are less well-replicated. At the moment, it is unlikely that such abnormalities can ever entirely explain criminal behaviour, let alone signify treatability with any predictive value. For this and other reasons, the use of brain scans as mitigating evidence in court needs to be treated with extreme caution.

In conclusion, brain imaging alters our notion of psychiatric disorders and opens possibilities for applications, whether or not justified on the basis of the underlying science. Scientists need to be aware of the implications of their research for the broader society in order to be able to properly communicate the true meaning, current limitations and future potential of their findings. For the use of brain imaging scans in most situations outside of academia or medicine it should be acknowledged that expert advice is absolutely necessary. It is important that the ethical implications of new scientific developments in psychiatry are given immediate consideration so as not to hamper or delay what could prove to be very positive benefits for patients and society as a whole.

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<sup>20</sup> DP McCabe and AD Castel, “Seeing is Believing: the Effect of Brain Images on Judgments of Scientific Reasoning” (2008) 107 *Cognition* 343-352; also DS Weisberg, “The Seductive Allure of Neuroscience Explanations” (2008) 20 *Journal of Cognitive Neuroscience* 470-477.