

The neurobiology of addiction: the perspective from magnetic resonance imaging present and future

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ABSTRACT

Background and Aims Addiction is associated with severe economic and social consequences and personal tragedies, the scientific exploration of which draws upon investigations at the molecular, cellular and systems levels with a wide variety of technologies. Magnetic resonance imaging (MRI) has been key to mapping effects observed at the microscopic and mesoscopic scales. The range of measurements from this apparatus has opened new avenues linking neurobiology to behaviour. This review considers the role of MRI in addiction research, and what future technological improvements might offer. **Methods** A hermeneutic strategy supplemented by an expansive, systematic search of PubMed, Scopus and Web of Science databases, covering from database inception to October 2015, with a conjunction of search terms relevant to addiction and MRI. Formal meta-analyses were prioritized. **Results** Results from methods that probe brain structure and function suggest frontostriatal circuitry disturbances within specific cognitive domains, some of which predict drug relapse and treatment response. New methods of processing imaging data are opening opportunities for understanding the role of cerebral vasculature, a global view of brain communication and the complex topology of the cortical surface and drug action. Future technological advances include increases in MRI field strength, with concomitant improvements in image quality. **Conclusions** The magnetic resonance imaging literature provides a limited but convergent picture of the neurobiology of addiction as global changes to brain structure and functional disturbances to frontostriatal circuitry, accompanied by changes in anterior white matter.

Keywords Addiction, arterial spin labelling, blood oxygenation level dependent, brain structure and function, diffusion imaging, functional imaging, magnetisation transfer, magnetic resonance imaging, neuroimaging, voxel based morphometry.

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INTRODUCTION

Without doubt, the technology to image the structure and function of the brain non-invasively (referred to collectively as neuroimaging) has transformed our understanding of neurological and psychiatric disorders, arguably setting them on a convergent course. Addiction research has benefited greatly from the resurgence of experimental psychology and psychiatry that has been made possible by neuroimaging. Existing reviews of the extant literature have identified some of the major cortical and subcortical components of the complex neurobiological circuitry that forms the substrate for the compulsive seeking, excessive consumption and negative emotions accompanying withdrawal that characterize addictive behaviours. In

short, current cumulative knowledge implicates dopaminergic pathways with origins in the ventral tegmental area connected to the prefrontal cortex via the limbic system, in particular the nucleus accumbens, amygdala, ventral pallidum and hippocampus [1–5].

Measuring and understanding the consequences of the chronic consumption of alcohol by radiological examination has been of interest since at least the 1950s, with generalized atrophy of the brain depicted by pneumoencephalography [6,7]. Modern neuroimaging encompasses a large range of techniques based on a variety of physical phenomena. Although the contribution of radioisotope imaging has been highly significant in the discovery and mapping of the role of dopamine in addiction [8], magnetic resonance imaging (MRI) is the mainstay of

addiction imaging research due its safety, absence of radioactivity and flexibility in the information obtained. Advances in MRI technology continue, along with postprocessing algorithms that are creating new representations of MRI data, refreshing the vocabulary describing the brain in health and disorder.

Here, our current knowledge of the neurobiology of addiction is summarized with data from human studies using established methodologies for measuring the structure and function of the brain with MRI. The field is now sufficiently mature that distilling the germane features from the literature can be undertaken by meta-analysis, and where available these accounts will be drawn upon. With a contemporaneous account of the literature consolidated, recent efforts with new methods and technologies are examined for future opportunities that will increase the breadth of knowledge on the neurobiology of addiction.

METHODS

The objective of this review was a synthesis of the peer-reviewed literature of the current state of the art of neuroimaging, specifically MRI, in the context of addiction research with a view to projecting future developments in this area.

The primary approach was to assemble the relevant literature with a hermeneutic strategy [9]. Here, a small number of seminal papers [1–5] were identified for review followed by open-ended searches to locate relevant papers using the citation and author-tracking functionality of the PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>), Scopus (<http://www.scopus.com>) and Web of Science (<https://apps.whoofknowledge.com/>) on-line databases, and refining the narrative as the content of the evidence became apparent. Additional, expansive explorations were made using a conjunction of the search terms ‘addiction’ or ‘dependency’ and ‘MRI’ or ‘magnetic resonance imaging’ or ‘neuroimaging’, again followed by open-ended searches of citations and authors. Searching was terminated once a particular line of argument was substantiated. Any formal meta-analyses that were revealed by these strategies were prioritized in terms of their contribution to the narrative. Key, highly-cited papers on specific resources, methodologies and techniques acquired from previous qualitative reviews by the authors were also included.

Throughout the search processes no limit was placed on the earliest papers returned to permit a historical perspective. However, the most recent papers included were established by the time of the searches as of October 2015. Only papers with human participants were included. Studies with negative results were incorporated where the complementary, positive results were not supported by overwhelming evidence.

Current structural and functional MRI findings

Brain anatomy and structure

The most prevalent method for measuring brain structure, voxel-based morphometry (VBM) [10], draws upon the contrast between grey and white matter in high-resolution MRI to estimate tissue volumes, as well as ventricular volumes that are filled with cerebrospinal fluid (CSF). Following digital alignment of these tissue maps, statistical comparisons that search, for example, for significant case–control differences at every intra-cerebral location are possible in what is often termed a ‘whole-brain’ analysis.

Qualitatively, almost all drugs of abuse are associated with reductions in cortical volume, especially in the frontal lobes, reiterating the general observations made in the earliest studies. This is accompanied by increases in the volumes of subcortical structures associated with dependency on stimulants such as cocaine and methamphetamine [11]. A formal meta-analysis of the whole-brain VBM literature partly supports this view [12] with decreases in volumes in prefrontal cortex, but also in the insula, inferior frontal gyrus, pregenual anterior cingulate and anterior thalamus with, notably, the decline in grey matter in frontal regions related to duration of dependency. However, changes in the subcortices are not seen across the literature, which may be due to inconsistent results in the primary literature or a bias in the sensitivity of the VBM methodology in these regions of the brain [12].

Several studies to date show that different addiction groups have reduced grey matter volume compared to healthy controls in regions of the brain targeted by the specific drug of abuse, including alcohol [13], cocaine [14,15], amphetamine [16] and nicotine [17–19]. However, the approaches taken in these studies appear to neglect the contribution to structural deficits that arise from relapse, treatment outcome and abstinence; it is unclear how former addicts remain abstinent even with severe structural deficits in brain regions implicated in addiction [20]. Furthermore, there is evidence for shared structural deficits between addict and non-addict populations. Abnormalities in frontostriatal brain systems in both stimulant-dependent individuals and their biological siblings who have no history of chronic drug abuse [21] potentially devalue the clinical significance of these outcome measures for addiction.

White matter differences have been difficult to observe with whole-brain VBM in heavy cannabis users [22] and cocaine addiction addicts [23]. Detections of white matter changes have been associated with amphetamine use, with results equivocal concerning the direction and location of case–control differences [1]. This suggests that if addiction does lead to changes in white matter, they occur most probably at the microscopic scale without consistent observable changes in volume.

White matter microstructure

A complementary MRI technique probing brain structure is imaging the diffusion of water. Compared to grey matter, water diffusion has restricted motion in white matter due to the alignment of neuronal fibres. Using this observation, estimates of the trajectories of white matter tracts are possible with a technique known as diffusion tensor imaging (DTI).

DTI produces some of the most spectacular maps of the so-called human connectome, and has led to changes in our understanding of the way the brain is organized in the healthy population [24]. However, there remain some analytical issues that temper confidence in DTI, particularly with estimation of tracts that span large distances [25,26]. An overview of measurable DTI effects in chronic alcoholics draws a picture of reductions in white matter integrity in anterior parts of the brain, particularly the supratentorial and infratentorial white matter bundles, which may be ascribed to myelin degradation [27]. However, a more recent study of alcoholics appears to show an opposite pattern of abnormalities [28].

A simplified alternative to reconstructing white matter tracts with DTI is to measure the local direction of water diffusion and the speed of diffusion with the scalar values of fractional anisotropy (FA) and mean diffusivity (MD), respectively. While visualization of white matter connectivity is sacrificed, the established statistical apparatus for testing whole-brain effects can be deployed in the same way as VBM.

The corpus callosum has come under scrutiny for its role in alcohol addiction from early pathological reports of its reduced volume. A review of DTI data specifically within the corpus callosum [29] points towards decreased FA and increased MD in alcoholics, and a similar reduction in FA in cocaine addicts [23]. In both cases, the duration of addictive behaviours appears to amplify these effects, pointing towards a decrease in the density of fibre bundles. These results are in the absence of gross morphological brain changes, indicating that DTI may have enhanced sensitivity relative to VBM.

Reductions in FA in the corpus callosum, as well as the thalamic radiation and inferior longitudinal fasciculus, have also been observed in opiate addicts [30]. Again, effects associated with duration of drug use were significant, converging with evidence from an earlier study [31]. However, contrary to the regional data, FA in the corpus callosum did not differ between cocaine addicts and control participants when whole-brain testing for differences. Differences were found in FA in the inferior frontal lobe and increases in the anterior cingulate [23]. Other forms of addiction have also been studied with DTI, but without revealing any common underlying pathology. Case-control differences of individuals prone to obsessive gaming on the internet showed increases in FA in the thalamus and posterior regions of the cingulate cortex that do not overlap

with the more frontal differences observed with drug addictions [32].

Functional response to cognitive tasks

Functional MRI (fMRI) measures brain activity via the blood oxygenation level-dependent (BOLD) endogenous contrast [33], exploiting the distinct magnetic properties of oxygenated and deoxygenated blood for its detection by MRI. As neuronal activity requires oxygen, the BOLD signal is therefore related indirectly to local functional processing. Experiments with fMRI often induce specific cognitive processes with appropriate stimuli, highlighting the regions and circuits that are involved.

Common to much addictive behaviour is cue-reactivity, in which exposure to stimuli induces craving as a consequence of Pavlovian conditioning [34]. A descriptive overview of the literature suggests increased activation in addicted individuals, particularly in prefrontal and orbitofrontal regions [35]. However, a formal meta-analysis of fMRI data [36] reports that regions of increased cue-reactivity converged in nicotine, alcohol and cocaine addicts to the anterior cingulate cortex, amygdala and ventral striatum, which includes the nucleus accumbens. A concurrent meta-analytical investigation of fMRI and positron emission tomography (PET) studies broadly confirms this pattern [37]. Interestingly, several of these areas have also been observed by meta-analysis as being associated with food cues [38] and, to a lesser extent, in addictive behaviours towards internet gaming [39].

Inhibitory control is the suppression of pre-potent actions and resisting interference from extraneous stimuli to engage instead in goal-directed behaviours. In cocaine addicts, increased activity was observed in prefrontal and cingulate cortices, inferior frontal regions and cerebellum during response inhibition, irrespective of whether or not the action was inhibited successfully [40]. Conversely, in opiate addicts, activity in anterior cingulate cortex was attenuated during unsuccessful inhibition of response [41].

Functional MRI tasks invoking emotional responses activate the limbic system [42], which is increased in alcoholics when comparing negative to positive valenced images [43], primarily in insula, inferior frontal, medial temporal and parahippocampal regions. A similar task contrast in cocaine addicts also resulted in increased activation, but in parietal and medial prefrontal regions [44].

Current innovations

Imaging the structure and function of brain has identified key networks associated with addiction. Data processing algorithms are deriving new information from existing data and offering a broader view of the biology of addiction, mechanisms of drug action and potential applications of imaging to clinical management.

Brain perfusion

MRI techniques can supplant existing measurements using radioactive tracers, with concomitant improvements in participant safety. One such example is the measurement of blood perfusion with arterial spin labelling (ASL). Arterial blood is 'labelled' magnetically as it enters the brain. As the blood perfuses the tissues, the labelling alters the local tissue signal. Subtracting the labelled image from an unlabelled image produces a map of perfusion [45].

Drug dependence results frequently in cardiovascular problems that make up a significant proportion of drug-related morbidity [46] and effects cognitive performance through cerebral hypoperfusion [47]. Heart disease is well-known in chronic alcoholism [48], and the perfusion of frontal and parietal grey matter measured in case–control studies by ASL in alcoholics is significantly lower [49]. Similarly, in opiate users administration of heroin reduces perfusion in the insula, anterior cingulate and medial prefrontal cortices [50], and in a separate study more severe depressive symptoms are associated with reduced perfusion in prefrontal and middle frontal regions [51]. Internet gaming addiction demonstrates a more mixed picture, with both increases and decreases in perfusion widespread throughout the neocortex [52], suggesting a quite different disorder from that engendered by substance dependency.

The functionally connected brain

It has become known recently that brain networks not only appear in response to stimuli but are, in fact, configured and poised continually to receive input [53]. This remarkable transformation in the way the brain is conceived has had a profound effect on experimental design, with interest now on the so-called 'resting-state' or, more precisely, data acquisition in the absence of any specific external stimulus.

Functional connectivity between two or more brain regions refers frequently to the Pearson's correlation coefficient between corresponding BOLD time-series. A hypothesis-driven approach is to select a particular region, known as the 'seed', and then calculate the correlation between this region and every other location within a brain network, testing subsequently for statistical differences.

Prevailing ideas on the neurocircuitry of addiction have centred on dopaminergic pathways in the mesocorticolimbic pathway, with projections to the prefrontal cortex. This is an inviting target for seed-based connectivity analysis, and the literature has become rapidly populated with studies of this type (reviewed in [54]). In general, alterations to this circuit are found consistently across addictions to different drugs, although the direction of this effect is at times inconsistent, particularly between striatal regions and the prefrontal cortex.

If functional connections between all regions are calculated they can be represented as a network constructed from nodes (brain regions) linked by edges (significant functional connectivity). Topological properties of the network include measures of the global efficiency of communication, local concentration of connections, overall organizational structure, and so on [55]. Application of this approach to addiction research is under-represented to date, although preliminary data indicate some sensitivity.

In opiate users, networks had increased connectivity between neighbouring brain regions with an increased number of connections in regions overlapping with the mesocorticolimbic pathway; namely, components of the striatum and prefrontal cortex. Frontal and cingulate cortices, thalamus, cerebellum and areas of the temporal and parietal lobes also had increased connectivity implicating networks that mediate motivation, memory and learning [56]. By way of contrast, a similar analysis on internet addiction did not discover any overall change in topology. Nevertheless, localized increases in connectivity were routed through the parietal lobe, limbic system (middle and anterior cingulate cortex) and thalamus [57], suggesting some overlap in the substrate of addiction measured by the connectome.

Surface models of the cortex

A mesh representation of the grey matter mantle covering the cerebral hemispheres can be estimated from the inner (grey–white boundary) and outer (pial) surfaces. Measures of cortical thickness, volume and geometry can then be made that are complementary to volume estimates from VBM, which is a combination of thickness, surface area and gyrification [58].

Thinner cortices in cocaine addicts are seen in dorsal prefrontal and insula cortices, elements of the brain reward circuit that is also implicated by VBM, and are accompanied by an overall reduction in cortical volume [59]. However, amphetamine use is not related directly to a reduction in cortical thickness, but with comorbid alcohol consumption when there is thinning in frontal and pre-central regions [60]. Alcoholism in adults is itself linked to decreases in cortical thickness in frontal, pre- and postcentral, temporal and occipital cortical regions and correlated positively with severity of abuse [61]. Reduced cingulate cortex and inferior frontal gyrus thickness in adolescents appear to be predictive markers for transition to addictive behaviour, when subcortical and temporal regions are reduced further [62]. Interestingly, the lateral orbitofrontal cortex is also reduced in adolescents with internet addiction [63], indicating some similarities with a predisposition to alcohol abuse.

Pharmacological MRI

Pharmacological MRI (phMRI) is used to test how pharmacological agents modulate brain activation and/or cognitive performance during an fMRI study. Drugs are usually given in an acute challenge (i.e. as a single dose prior to the scanning session), although recently chronic drug treatment regimens have been used to mimic more closely the clinical outcome of drug administration [64]. Importantly, the use of phMRI may have some value with respect to neuroimaging biomarkers for addiction [65]. Here, such challenge studies may be able to demonstrate that patterns of activation in early drug abstinence are able to predict whether some addicts are likely to respond to a particular class of psychotropic, should it be developed as a medication for addiction and relapse prevention. The use of phMRI may allow neuroscience research in the addictions to make more informed inferences regarding the neurochemistry of underlying disturbances to particular cognitive processes in addiction [66–68].

Functional biomarkers for treatment monitoring

Addiction is associated commonly with increased brain activity to drug-related cues [69–75] and reduced activity to cues that predict non-drug rewards [76–81], together with reduced activity in response to the demands of executive control [41,82–86] and social cognition [87]. Examining neural responses within these domains is of particular interest with respect to the development of fMRI biomarkers that identify neural mechanisms for drug relapse during early abstinence, and for the treatment of addiction. There may be a common fMRI ‘signature’ across cognitive domains within loci that may be explored as potential targets for cognitive [88–90] and/or pharmacological [71,90–93] therapies in the addictions. This would be especially significant if distinct neural brain biomarkers could predict both successful and unsuccessful abstinence and treatment response.

Studies that have used fMRI to predict relapse and treatment response have been surprisingly scarce, but endorse imaging in addiction research. A seminal study of this type was conducted in methamphetamine addicts during a decision-making task. Activation patterns in the insular, posterior cingulate and temporal cortex obtained in early recovery predicted correctly 90% of participants who did not relapse and 94% of participants who did [94]. In a longitudinal study examining neural responses during reinforcement learning as a predictor of relapse in methamphetamine addiction, individuals who were abstinent and then relapsed 1 year later showed greater prefrontal activation during learning, but attenuated striatal, insular and frontal activation in response to feedback compared with those methamphetamine-dependent people who remained abstinent [95]. In a study exploiting

the processing of non-drug-related stimuli, higher activation in the striatum and insula in response to potentially risky rewards during in-patient treatment was found only in those patients who subsequently remained drug abstinent [96]. There are also several other studies which have demonstrated how BOLD activation patterns are able to predict relapse in addiction populations [97–100].

fMRI has also been used to predict treatment responses to medications in addiction. In alcoholic patients, the treatment response to naltrexone has been shown to be predicted by the level of pre-treatment cue-reactivity in the ventral striatum in response to alcohol-related cues [101]. Therefore, while somewhat scarce, there is good scientific evidence that endorses the use of fMRI for the identification of potential neural biomarkers for abstinence, relapse and treatment outcome in addiction. The search for such fMRI biomarkers is highly desirable as a prelude to the development of new interventions in addiction.

Future directions

There have been large improvements in MRI technology as a result of the evolution of precision engineering and electronics, with a trend towards increases in the static magnetic field of scanners to 7 T or greater, and the simultaneous acquisition of MRI data with physiological information available from radioligand imaging. Optimization of existing techniques will certainly yield the expected improvements in spatial resolution, signal-to-noise and increased sensitivity [102], as well as the development of new protocols to detect drug actions.

Quantitative structural relaxometry

In general, MRI scans depicting brain structure are not associated with SI units and are subject to variations in scanner hardware and software, environmental changes in the scanning room and so on, over and above the physiological variations that may be of interest. This is problematic for longitudinal MRI assessments and when combining data in multi-centre studies [103].

Designed for the measurement of absolute values of relaxation rates, MRI relaxometry makes several rapid acquisitions systematically varying key parameters. Variants of the technique have been shown to have excellent characteristics in comparisons across multiple scanning centres [104,105], with benefits to all areas of clinical neuroscience research. Of particular relevance to addiction, MRI relaxometry also makes possible quantitative measurement of myelin concentration through a process known as magnetization transfer. Protons in water molecules have their magnetic resonance properties altered by being bound to macromolecules such as myelin, assumed to be the predominant compound of this type in the brain, in a way that is related to its

concentration [106]. We have already seen from diffusion imaging that white matter degradation is significant in addiction, and that myelin loss may be part of the underlying process. Magnetization transfer, and MRI relaxometry in general, provide the means to follow the trajectory of brain changes reliably during drug-taking, remission and relapse as a potential predictor of their onset.

Susceptibility weighted venography

Magnetic susceptibility describes the behaviour of a material when placed in a magnetic field. A good example of this is shown in both deoxygenated and oxygenated haemoglobin, which have contrasting magnetic properties, and is the physical origin of the BOLD effect. It is also an effect that is exploited to obtain contrast between deoxygenated blood-filled vessels and the surrounding tissue, and thus visualize the venal system in fine detail [107].

Cardiovascular illness is a major comorbidity of addiction [46], and changes in cerebral blood flow are well known as a consequence of drug use [108], which may lead to an increased risk of intra-cerebral haemorrhage [109] detectable by susceptibility imaging. At increased MRI field strengths, susceptibility imaging is capable of detecting vessels < 1 mm in small structures relevant to addiction research, such as the thalamus [110] and midbrain [111], with possibilities for a more holistic understanding of the neurobiology of addiction.

Simultaneous MRI and PET

Most fMRI studies do not consider the problem of reverse inference; in other words, specific functional significance ascribed to fMRI activations on the basis of the known distribution of neurotransmitters and receptors. One common example of this concerns reports describing reductions in the BOLD signal in dopamine-rich areas of the brain (e.g. nucleus accumbens) in response to a non-drug reward (e.g. money) in an addiction population that is then attributed to deficits in this particular neurotransmitter. In fact, fMRI cannot make direct inferences about the neurochemistry underlying a particular functional process and how disturbances associated with addiction are alterations of this neurochemistry.

The advent of combined MRI and PET imaging systems can potentially overcome this problem. Although very much in its infancy, PET–MRI has the potential to demonstrate specifically that reductions in the BOLD signal in response to a non-drug reward are in brain regions that are the result of simultaneous and colocated reductions in dopamine release. Initial PET–MRI studies have already demonstrated that these complementary measures of brain function can provide new insights into the functional and structural organization of the brain [112]. This methodology is also likely to revolutionize drug development

strategies in addiction and potentially reduce the high costs incurred in drug discovery programmes.

CONCLUDING REMARKS

These are pioneering days for the investigation of addiction with neuroimaging. Individual reports across a wide range of measures of brain structure and function are often difficult to reconcile, or even contradictory. However, where the literature is reasonably well populated a more convergent picture is developing that encourages continued effort with the promise of a coherent narrative for this disorder. Imaging studies paint a picture of addiction as global changes to brain structure and functional disturbances to frontostriatal circuitry, accompanied by changes in anterior white matter. However, it is unlikely that neuroimaging alone will provide the evidence for a unifying theory of addiction. The wide variety of drugs or activities that are included within the description of addiction, and the physical and mental comorbidities that cause or are caused by addictive behaviours, contribute to the observed heterogeneity, emphasizing the importance of sample selection and participant stratification.

It might be argued that before rushing to meet the future, addiction research might be better served by consolidating what is already known and available. Meta-analyses have proved to be a vital tool in other areas of neuroimaging research, consolidating the evidence and streamlining the prevailing narrative [113]. Development of meta-analytical algorithms offer improved sensitivity, but obviously can only be as convincing as the quality and quantity of the primary literature permit. Increasing confidence in the literature on addiction could be facilitated by larger sample sizes in multi-centre studies, but also by open access to appropriate imaging data repositories, following the successes of initiatives for conditions such as autism [114] and Alzheimer's disease [115].

Clearly, MRI imaging is only one part of a wider effort to understand the aetiology and treatment of addiction. For brevity this review has not made reference to the literature using magnetic resonance spectroscopy [11] or, indeed, other imaging modalities. This is not to downplay their importance. What unites all these techniques, at least in the short to medium term, is that the greatest advances may not come from new measurements, but from applying innovations in data processing and computer modelling. Nevertheless, new techniques will lead to new opportunities. The monitoring and prediction of abstinence and relapse are key to supporting clinical decision-making, and the discovery of biomarkers that are sensitive to pharmacological or psychological therapies would be a significant step forward.

Declaration of interests

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