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Human Functional Neuroimaging Connectivity Research in Dependence

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SYNOPSIS

Functional and effective connectivity are relatively new techniques in the analysis of functional neuroimaging studies in humans. They have previously been used in studies of 'normal' psychological and neurological processes such as vision before gradually transferring into use in pathological disease states such as schizophrenia. These techniques are now beginning to extend into the field of substance misuse and dependence. So far, most functional neuroimaging studies in this field have shown consistent patterns of activation in several brain regions, and theories are emerging based upon these and animal models. Studies of brain connectivity can now begin to help further unravel the tangle of disparate brain regions and their connections that underpin the psychopharmacological processes of dependence.

KEY WORDS

dependence, alcohol, opioids, stimulants, functional neuroimaging, connectivity

INTRODUCTION

Addiction, or substance misuse, is a large social problem worldwide. To date the majority of treatments are empirically derived from experience and evidence from the clinic. Gradually, neuroscience is beginning to shed light on the underlying mechanisms of dependence which should pave the way for potential new treatments. The techniques of functional neuroimaging give the ability to visualise neuronal function in the living human drug user and therefore open a window to the understanding of addiction processes unavailable from any other technique.

Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) together have produced a considerable body of research to aid the understanding of the fundamental mechanisms of addiction and dependence. The majority of neuroimaging studies in dependence, to date, have focused on regions of brain activation in response to specific drug related stimuli or on changes in neurotransmitter function.

In the studies reviewed in this paper, two main techniques have been used to image brain activation. fMRI uses the differing magnetic properties of oxy- and deoxyhaemaglobin to produce images of the blood oxygen level dependent (BOLD) response. It has good spatial and temporal resolution, but the noisy and confined scanner environment is not always conducive to the psychological state under investigation. PET, with radiolabelled water ($H_2{}^{15}O$) or ^{18}F-flurodeoxyglucose (^{18}FDG), can be used to image blood flow or glucose metabolism, respectively. Connectivity analysis requires a time-series of brain activation images which means that only fMRI and $H_2{}^{15}O$-PET are amenable to these techniques.

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WHAT IS CONNECTIVITY - EFFECTIVE AND FUNCTIONAL

Traditionally, studies of neural activation using functional neuroimaging have used analysis techniques designed to demonstrate whether or not a region is activated by a specific task or stimulus. Connectivity concerns linkage between such brain regions. There have been two particular types of connectivity that have been described: functional and effective. Functional connectivity is the simpler form, based on temporal correlation between levels of activity in the brain regions. The premise is that brain regions involved in the same function will tend to be activated at the same time and deactivated at the same time. Therefore, activation levels in such areas should be temporally correlated. Obviously, searching for such correlations requires a time-series of brain images such as is acquired in typical fMRI or water-PET studies.

Effective connectivity is more complex. It requires a pre-defined, usually anatomically derived, model of interconnections between the brain regions to be specified. These connections are then examined using mathematical techniques, such as dynamic causal modelling or structural equation modelling, to assign strengths and directions of modulation to the connections (see /2,7,8,11,22/ for examples). Both techniques of measuring connectivity can be further expanded to examine changes in the level of connectivity resulting from external manipulations, for example drug administration or psychological task/9/.

ACTIVATION PATTERNS IN DEPENDENCE

Many studies have used the available neuromaging methods to examine patterns of activation in response to drugs of abuse, or related stimuli (see /4/ for review). There is a consistent cluster of regions that have been found to be activated by drug-related stimuli in both heroin and cocaine users. Studies have found the anterior cingulate, dorsal prefrontal and orbito-frontal cortices, plus the hippocampus and amygdala, to be implicated in cue-induced responses to drug-related stimuli.

There is considerable overlap with regions shown to be affected by acute doses of drug /1,3,5,10,16,18,25,30/. For example, acute doses of an abused opioid (hydromorphone) and cocaine have produced relative increases in brain activation in the anterior cingulate, thalamus and amygdala /1,25/. Methylphenidate, as a substitute for cocaine, has been shown to induce activation in the basal ganglia and orbito-frontal cortex /29/. This activation was also shown to correlate with drug-induced craving for cocaine.

Injected cocaine, rather than a substitute, was shown in one study to induce activity, as measured with fMRI, in three distinct temporal patterns /1/. Subjects reported an initial 'rush' in response to the cocaine that correlated with the time course of activation in the basal forebrain, ventral tegmental area (VTA), insula cortex, thalamus, prefrontal cortex and caudate bilaterally, plus the right cingulate cortex. The VTA is one of the two sites of dopamine neuron cell bodies and the origin of the ascending meso-cortico-limbic dopamine pathway, which animal research has long implicated in substance misuse. A later network also appeared, related to the subjective experience of 'craving', involving the nucleus accumbens (NAcc), amygdala and right parahippocampal gyrus. Interestingly, these are regions frequently found activated with cue-exposure paradigms.

In a PET study using injected heroin to study regional cerebral blood flow (rCBF) changes in response to heroin and heroin-related cues, heroin caused increases in rCBF in the brain stem in a region congruent with, but more extensive than, the VTA /26,27/. However, in contrast to the majority of studies reported above, this study did not report any activations in the anterior cingulate, orbito-frontal or dorsolateral prefrontal cortex in response to a drug-related video. Craving for heroin and the immediate response to heroin-related stimuli were also shown to have associations with brain activation in disparate regions /5/. In this study, subjectively described craving correlated with activation in the left orbito-frontal cortex, whereas the initial response to a stimulus, involving imagined drug exposure, activated the left anterior cingulate region independent of the experience of craving.

FUNCTIONAL CONNECTIVITY STUDIES IN DEPENDENCE

To date, very few connectivity analyses have been carried out on functional neuroimaging studies of substance misuse. The first was carried out by Sell *et al.* /26/, who found activation in the midbrain in response to both a drug-related video and an injection of heroin. They also carried out an analysis of functional connectivity looking for regions showing a psychophysiological interaction. This describes the situation in which the correlation between two regions is modulated by a psychological condition, or where neural activation in response to a psychological stimulus is modulated by the level of activation in another brain region. They report three areas where activity correlated with the level of midbrain activation only during the drug-related video; specifically, these regions were the anterior cingulate, left dorsolateral prefrontal cortices and the left extended amygdala. All of these are regions that other studies have implicated in drug cue-responsivity. Heroin also appeared to alter the relationship between the level of rCBF in the anterior cingulate and basal forebrain regions. The authors suggest that this could be interpreted as heroin altering the manner in which these brain areas respond to the presentation of drug-related stimuli via its effects on midbrain activation.

Work in our own unit has examined the neural circuits associated with responses to auditory stimuli related to heroin craving. Using a technique of psychophysiological interaction similar to that described earlier /26/, we examined the patterns of functional connectivity associated with anterior cingulate activation in response to the stimulus and the orbito-frontal activation of craving /6/. This analysis showed that the activation in the left anterior cingulate cortex that occurred in response to drug-related auditory stimuli was associated with inactivation of the visual cortex and activation of auditory areas. It also showed that the correlation between the activity in the anterior cingulate and sensory cortex relating to intra-abdominal sensation was modulated by the subjective experience of craving (see Fig. 1). A second network of correla-

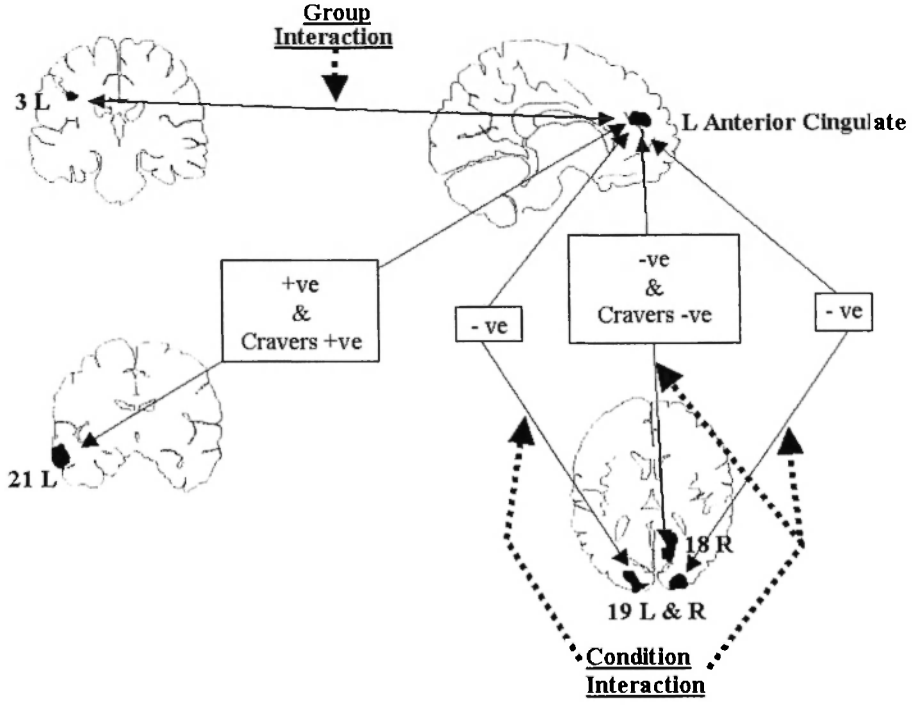

Fig. 1: Brain regions (Brodmann areas) associated with activation in the left anterior cingulate region following exposure to heroin related cues. Solid lines with labels indicate a direct relationship between brain regions with the label specifying the analyses when this relationship was demonstrated. Dotted lines denote a modulation of the relationship by scan condition or subject group. Reproduced from /6/ with permission from Elsevier.

ted activity showed functional connectivity between the left and right orbito-frontal cortex, the left posterior insula and left parietal lobe. Again, this network that positively correlated with subjective craving also showed a negative association with visual areas (see Fig. 2). There was also evidence that the nature of the stimulus - drug-related or neutral - altered the association between the left orbito-frontal region and the left hippocampus and an area of the brain stem centred around the red nucleus. The association between the orbito-frontal cortex and the hippocampus could have been predicted, as the stimuli used in this study were based on autobiographical memories. The red nucleus is implicated in the integration of motor responses. It is therefore possible that this finding represents some enhancement of preparation for action in response to heightened craving. However, the limited spatial resolution of PET means it is not possible to be certain that this finding is located in the red nucleus.

Although not explicitly a study examining substance misuse, another group has shown that methylphenidate tends to decrease both functional and effective connectivity in a cortico-striatal-thalamic circuit activated by a spatial memory task /12,13/. This suggests that, unsurprisingly, there are direct effects of stimulants in acute doses on connectivity outside the context of dependence.

Cocaine also decreases local functional connectivity within brain regions (e.g. motor cortex, visual cortex) /19/. This study focused on correlations of activity between voxels within the same localised region over the course of 'spontaneous' fluctuations in activity in a 'resting' state. This analysis was conducted following injections of saline and cocaine. The regions examined were specifically chosen to be areas where there

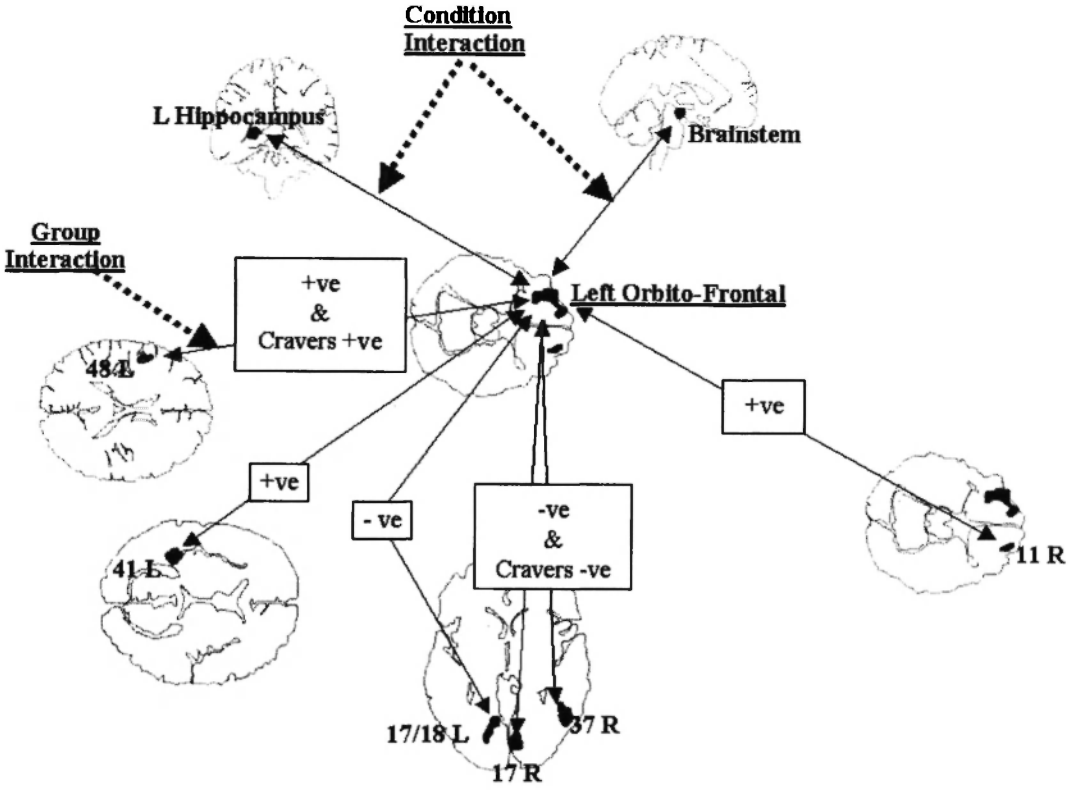

Fig. 2: Brain regions (Brodmann areas) associated with the left orbito-frontal cortical region activation correlated to subjective heroin craving. Solid lines with labels indicate a direct relationship between brain regions with the label specifying the analyses when this relationship was demonstrated. Dotted lines denote a modulation of the relationship by scan condition or subject group. Reproduced from /6/ with permission from Elsevier.

was minimal dopamine innervation. The authors suggest that these measured decreases in local functional connectivity may be due to dopamine effects on microvasculature or decreases in neuronal firing. Dopamine has known effects on vascular walls in the brain /17/; however, it is also known that cocaine decreases regional cerebral glucose metabolism /21/, which supports the cause being a simple decrease in 'spontaneous' fluctuations resulting in less measurable connectivity.

Some studies have examined the structural element of connectivity due to fears of the neurotoxicity of some abused drugs. Cocaine has been demonstrated to produce white matter lesions, suggesting that this is one possible mechanism of altered connectivity which is particularly associated with stimulant misuse /20/. Diffusion tensor imaging (DTI) is a relatively new technique which can be used for examining white matter and its integrity. The tubular nature of myelinated axons creates a non-spherical effect on the magnetic field measured by MRI. Therefore it is possible to measure the relative net direction of white matter tracts at any given point. Specific disruption has been noted in the orbito-frontal cortex of cocaine users /20/. This region has been implicated in the compulsive nature of drug craving and drug seeking behaviours /28/. The possibility of functional impairment of the orbito-frontal cortex has been supported by data showing impairment in human drug users in decision making functions related to the orbito-frontal cortex at a level between that of normal controls and patients with brain injuries in the orbito-frontal cortex /24/.

DO THESE FINDINGS FIT THE MODELS?

The hedonic homeostatic dysregulation model of dependence /14,15/ proposes that alterations in the reward and affective systems of the basal forebrain along with the hypothalamic-pituitary-adrenal stress response system underlie a process of spiralling distress driving withdrawal and relapse. They implicate the extended amygdala and meso-corticolimbic dopamine system as brain regions in which changes would be expected. Very few of the neuroimaging studies of substance misuse have been able to show activation in such areas. Some studies have shown activation of the amygdala and hippocampus in support of this theory /1,6,25/ and others have shown activation of the brainstem in regions that are known to have connections to the regions of the extended amygdala /6,26/.

The incentive-sensitisation theory /23/ predicts that neural systems implicated in drug dependence should show enhanced activation in response to drug and drug-related stimuli that persists for long after the cessation of drug use, potentially years after; they should be consistent across drugs of abuse and should not mediate the pleasurable effects of drug taking. The body of literature published to date supports the main assertion that drug-related stimuli induce enhanced activation within a common neural system that may even increase with extended abstinence /5/. However, neuroimaging has not yet been able to show that the incentive pathways are different from the pathways that mediate the pleasurable aspects of drug responses.

The lack of evidence for these models from the neuroimaging data is likely to have many causes. One obvious immediate limitation of current methods of functional neuroimaging in humans is the limited spatial and temporal resolution of the techniques in comparison to those possible in animal models. Even the best PET scanners can only achieve a spatial resolution of 2 mm voxels and a temporal resolution of the order of tens of seconds. Under optimal conditions, fMRI is able to improve on these figures to 0.5 mm and hundreds of milliseconds; nevertheless, this is still insufficient to differentiate core and shell of the nucleus accumbens, for example.

Substantial progress has been made in our understanding of changes in neurotransmitter function in substance misuse as a result of PET, particularly in understanding the potential role of dopamine in stimulant misuse (see /28/ for review). In comparison there is a relative paucity of activation studies that seek to elucidate functional neural networks underlying the psychological processes of dependence. In part this may be due to the understandable tendency for such experimental techniques to first be applied to the study of 'normal' neurological processes (e.g. vision /9/) and only later extended into the study of patho-

logical states. When these techniques are applied to pathological states it is much more common for them to be applied to such conditions as schizophrenia and bipolar disorder, with substance misuse lagging some way behind. This lack of studies is likely to be a major contributor to the lack of data supporting the theoretical models.

CONCLUSION

This review has outlined the use of functional neuroimaging in humans to begin to investigate the neural circuits of dependence. There are certainly insufficient data yet accumulated to differentiate between the predictions of any of the models of dependence yet described. However, the methodology for image analysis continues to move forward with techniques such as functional and effective connectivity analysis. Unfortunately, there are as yet no fMRI studies in substance misuse that have been used to examine the patterns of effective connectivity and only a few examining functional connectivity. Given the enormous potential of such techniques, it is to be hoped that, as computing power increases and imaging procedures improve, this deficit will be short-lived.

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