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Resting state functional connectivity in addiction: drug abuse and reward dysregulation

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RESTING STATE FUNCTIONAL CONNECTIVITY IN ADDICTION: DRUG ABUSE AND REWARD DYSREGULATION

by

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ABSTRACT

Introduction: With the advent of advanced neuroimaging, strides have been made towards better understanding the cognitive elements necessary for task processing. Resting state functional connectivity assessments using functional magnetic resonance imaging has allowed patient assessments of underlying neural networks in patient populations with variable constraints. Drug addiction, a chronically relapsing disorder, presents many variable constraints. Cellular and molecular changes in neural reward pathway of drug addicted patient populations have advanced, but circuit-level alterations with reward deficits are yet to be completely understood. Resting state functional connectivity investigations in patient populations that use illicit drugs are seen to have repercussions on neural networks.

Objective: Assess and compare reward-network resting state functional connectivity investigations in patient populations with illicit drug use.

Methods: A meta-analysis of several resting state functional connectivity studies. Patient populations for each study contained an experimental group of drug users with a group of non-drug using controls to assess changes in resting state functional connectivity of the reward network. Studies utilized *Diagnostic and Statistical Manuel of Mental disorders,* 4th edition, as the basis of diagnosing drug dependence and abuse. A 3 Tesla MRI scanner was utilized to assess the reward pathway of the drug abuse in all experiments with the

exception of one group using a 4 Tesla scanner. Band-pass temporal filtering from roughly 0.01 Hz to 0.1 Hz on residual signals was used to obtain low-frequency fluctuations needed for resting state connectivity analyses. Correlation maps were created by computing the correlation coefficients between the blood oxygen level dependent time course from the seed regions and from all other brain voxels. Regions of interest were chosen based on data from databases or previous studies.

Results: Four papers found widespread reductions in the connectivity of multiple reward pathway components. Results of these studies are consistent with perspectives suggesting that transition from drug use to addiction is driven by reduced functioning of reward systems and concurrently increased activation of anti-reward systems. Two studies suggested an increase in reward pathway of drug use, suggesting enhanced connectivity within reward and motivation circuits may be interpreted in the perspective of altered incentive salience for drugs and drug-associated stimuli.

Conclusion: At early stage of experimental data in this field, data interpretation necessitates caution. Small sample sizes, heterogeneous subject groups and variable experimental paradigms may have lead to opposing findings. With certainty, chronic drug use was found to alter reward pathway in patient populations.

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LIST OF ABBREVIATIONS

Amy.....Amygdala

Amyg.....Amygdala

BOLD..... Blood Oxygenation Level-Dependent

Caud..... Caudate

CCA ..... Chronic Cocaine Abusers

DA.....Dopamine

dACC .....Dorsal Anterior Cingulate Cortex

DMN ..... Default Mode Network

EEG.....Electroencephalography

Glu.....Glutamate

HC.....Healthy Controls

Hipp..... Hippocampus

Lat ..... Lateral

L VS .....Left Ventral Striatum

MCL..... Mesocorticolimbic

Med ..... Medial

MRI.....Magnetic Resonance Imaging

MTG.....Middle Temporal Gyrus

NAc.....Nucleus Accumbens

OEF.....Oxygen Extraction Fraction

OFC.....Orbitofrontal Cortex

PET .....Positron Emission Tomography

PFC .....Prefrontal Cortex

PRC.....Perirhinal Cortex

Put .....Putaman

PVG.....Periventricular Gray

ROI..... Regions of Interest

rsFC..... Resting-State Functional Connectivity

R VS.....Right Ventral Striatum

SN .....Substantia Nigra

TE.....Echo Time

TR ..... Repetition Time

vACC .....Ventral/Rostral Anterior Cingulate Cortex

VP ..... Ventral Pallidum

VTA .....Ventral Tegmental Area

INTRODUCTION

Despite having public health imperatives and intensive scientific investigation, drug addiction treatment outcomes have not significantly improved. More than 40 million people in the United States suffer from nicotine, alcohol, and drug addiction (Richter & Foster, 2013). Only about 10 percent of those people receive treatment (Richter & Foster, 2013). Far fewer receive effective, evidence-based treatment (Richter & Foster, 2013). Over the past several decades, noninvasive brain imaging has contributed important new insights into the neuroplastic adaptations that result from chronic drug intake (Sutherland, McHugh, Pariyadath, & Stein, 2012). Though these studies address changes in molecular and cellular functions (Morón & Green, 2010), systems-level assessments are needed to better capture the totality of the disease. This thesis summarizes recent advances in assessing network dynamics through resting-state functional connectivity (rsFC) imaging. This tool may inform specific neurobiological circuitry underlying reward dysregulation in drug-addicted patients with the aim of garnering new insights into more successful drug addiction treatments.

Functional connectivity is defined as the temporal dependency between spatially remote neurophysiologic events (van den Heuvel & Hulshoff Pol, 2010). The rsFC method addresses functional connectivity through the use of functional magnetic resonance imaging (fMRI) to measure spontaneous fluctuations in the blood oxygenation level-dependent (BOLD) signal without the subject performing a task (van den Heuvel &

Hulshoff Pol, 2010). Instead, fMRI looks at low-frequency oscillations between 0.01 hertz and 0.1 hertz (van den Heuvel & Hulshoff Pol, 2010). The basis of these low-frequency, resting-state fMRI oscillations is currently not fully understood. Resting-state fMRI studies are focused on measuring the correlation between spontaneous activation patterns of the brain (van den Heuvel & Hulshoff Pol, 2010). Studies have shown that results obtained in rsFC reflect the cognitive elements necessary for task processing in its entirety (Smith et al., 2009). Furthermore, networks identified using rsFC are consistent between individuals and across time, suggesting networks are conserved between populations (Chen et al., 2008). The advantages of rsFC over fMRI task-based experiments include a straightforward approach needing no complicated paradigms to achieve results. This is ideal when assessing patient populations with variable constraints such as drug addicts.

Drug addiction is a chronically relapsing disorder characterized by three behaviors: compulsion to seek and take the drug, loss of control in limiting intake, and emergence of a negative emotional state reflecting a motivational withdrawal syndrome when access to the drug is prevented (Koob & Volkow, 2010). The initial reinforcing effects of abused drugs are thought to be due to large and rapid dopamine increase in the mesocorticolimbic (MCL) system (Nestler, 2005). The MCL system, comprising the ventral tegmental area and three adjacent midline nuclei (caudal linear nucleus, interfascicular nucleus, and rostral linear nucleus of the raphe), is believed to play an important role in reward, motivation, learning, and movement (Yamaguchi et al., 2011).

As a result of these findings, studies have focused on neuroadaptations in midbrain dopaminergic areas and the structures to which they project. Understanding of cellular and molecular changes in the MCL has advanced (Morón & Green, 2010), but circuit-level alterations with reward deficits are yet to be completely understood. The following rsFC investigations give promise to understanding these complex underlying circuits by addressing the illicit use of cocaine, heroin, and prescription opioids and the repercussions they have on neural networks.

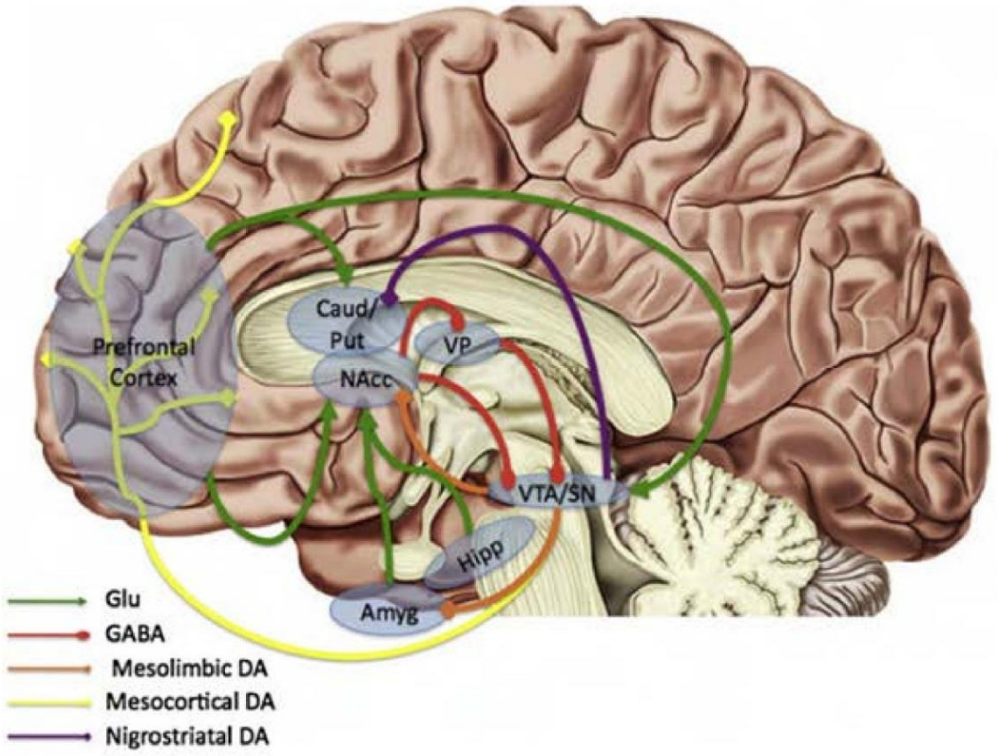

Figure 1. Mesolimbic and mesocortical dopamine pathways. The MCL system, comprising the ventral tegmental area and three adjacent midline nuclei (caudal linear nucleus, interfascicular nucleus, and rostral linear nucleus of the raphe) is believed to play an important role in reward, motivation, learning, and movement. The dopamine neurons of the ventral tegmental area project to the cortex (mesocortical pathway) and to the nucleus accumbens (mesolimbic pathway). The initial reinforcing effects of abused drugs are thought to be due to large and rapid dopamine increases in this system (Dichter,

Damiano, & Allen, 2012). (Amyg-Amygdala, NAcc-Nucleus Accumbens, Caud/Put-Caudate/Putaman, VTA/SN-Ventral Tegmental Area/Substantia Nigra, Hipp-Hippocampus, VP-Ventral pallidum, DA-Dopamine, Glu-Glutamate)

fMRI Dynamics and Neurophysiological Basis

One of the most exciting achievements in psychology, neuroscience, and modern medicine has been the ability to study the function and organization of the human brain noninvasively (Ulmer & Jansen, 2013). With current in vivo imaging, insights into intrinsic mechanisms of brain function and malfunction can be obtained, and the resulting data have illuminated essential clinical information that paves the way toward new forms of treatment.

The fMRI concept was an evolutionary step by utilizing preexisting MRI scanning technology. Most of MRI imaging focuses on signals generated from hydrogen atoms because of their inherent magnetic movements and natural abundance in biological systems (Pautler, 2004). To generate the MRI signal, a very strong external magnetic field is applied to orient the random spins of the hydrogen nucleus, a positively charged proton (Pautler, 2004). With the external magnetic field applied, a small portion of the spins will align at what is called the longitudinal plane, forming a net magnetization vector around the external magnetic field at the specified frequency. Nuclei of interest have a proportionality constant called the gyromagnetic ratio, which is directly proportional to the precessional frequency. Protons precess at frequencies that fall within the radio-frequency range, and a radio frequency is applied to the net magnetization

vector at a 90-degree angle known as the flip angle. The net magnetization vector absorbs the energy from the radio frequency, causing it to change direction and lie within the transverse plane for the duration of the radio-frequency pulse. This is known as the excitation stage. The pulse is then turned off causing the net magnetization vector to return to the longitudinal plane. The recovery back to the longitudinal plane is T1 recovery, and the decay of the transverse plane is known as T2 decay. The MRI signal is generated by the voltage induced in a receiver coil placed in the transverse plane that can detect the net magnetization vector movement (Figure 2) (Pautler, 2004). The echo time (TE) of a MRI is the time between the radio-frequency excitation pulse and the peak of the signal induced in the coil (center of the echo). The repetition time (TR) is the length of time between corresponding consecutive points on a repeating series of pulses and echoes (Figure 3) (Hendrick, 2005). The varying contrast seen in magnetic resonance images is due to different tissue types having an abundance of hydrogen atoms relaxing at different rates (i.e., differing values of T1 and T2 signals generated) (Pautler, 2004).

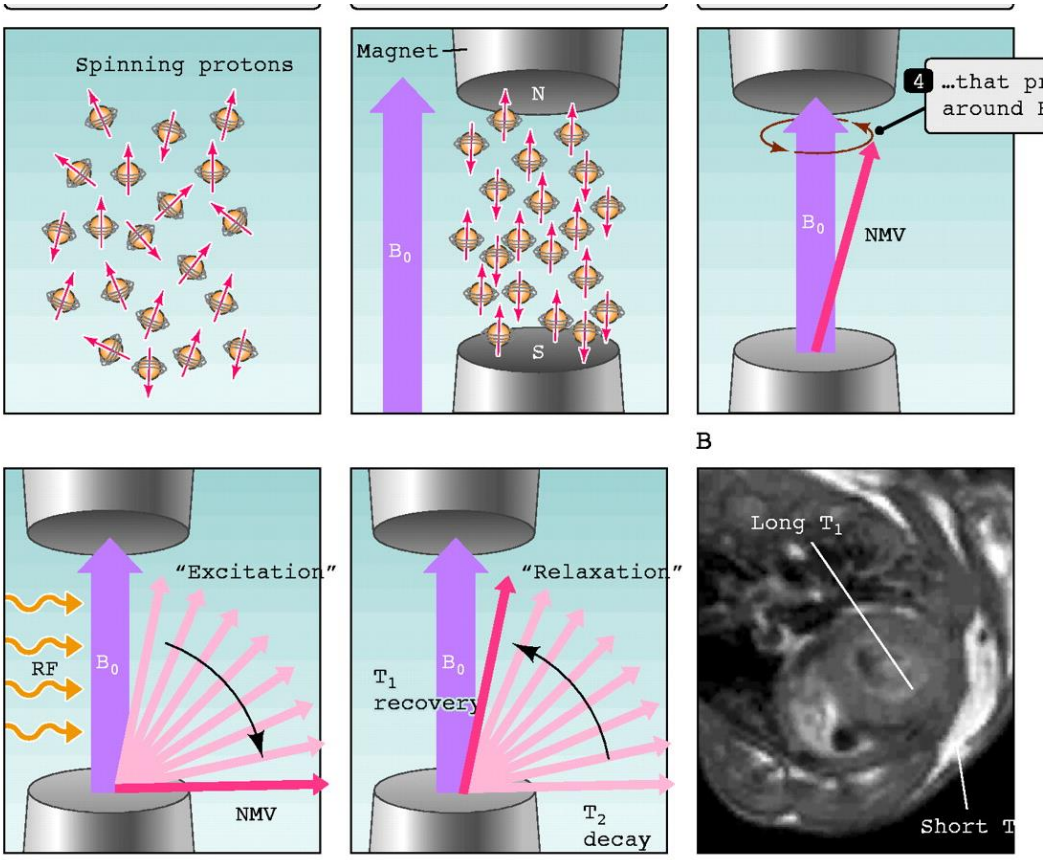

Figure 2. Basic description of MRI. Random-spin protons are aligned by an external magnetic field to form a net magnetization vector, which is the sum of all spins precessing around the magnetic field. Excitation causes the net magnetization vector to flip by application of a radio frequency. As the net magnetization vector realigns with the magnetic field after the radio frequency is turned off, a signal is generated that creates contrast as a result of the type of signal acquired (Pautler, 2004).

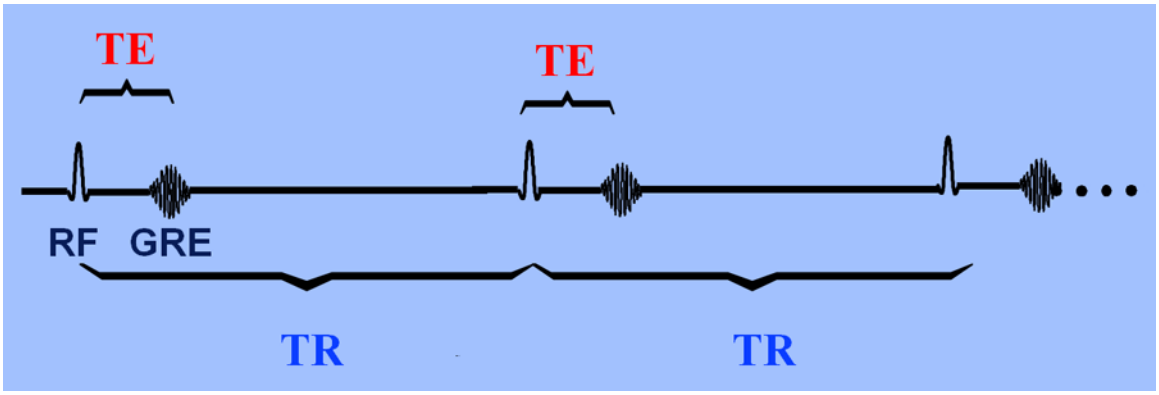

Figure 3. Schematic diagram of MRI signal. The echo time (TE) of a MRI is the time between the radio-frequency excitation pulse and the peak of the signal induced in the coil (center of the echo). The repetition time (TR) is the length of time between corresponding consecutive points on a repeating series of pulses and echoes (Hendrick, 2005).

While MRI focus remains on static anatomy of the brain and body, fMRI looks at changes in the neuronal activation and function of the brain. The journey to achieve this realization was an extensive one. Over 130 years ago, Angelo Mosso was the first to realize a relationship between the energy demand of the brain and the cerebral blood flow through his observations of increasing brain pulsations in patients with skull defects who performed a mental task (Sandrone et al., 2014). Building on Mosso's research through experiments on animal models, Roy and Sherrington (1890) found similar observations on the coupling of blood flow to neuronal activity. In 1936, Pauling and Coryell discovered the magnetic properties of blood.

Recognizing the findings of Pauling and Coryell, Ogawa (1990) hypothesized that the magnetic properties of deoxyhemoglobin and oxyhemoglobin could be used to augment

magnetic resonance imaging and create measurable changes in the MRI signal caused by blood flow to activated brain regions. Ogawa was the first to discover the blood oxygenation level-dependent (BOLD) contrast as the MRI contrast signal of oxyhemoglobin and deoxyhemoglobin. Ogawa was able to manipulate blood oxygen levels by changing the proportion of oxygen that was breathed in by anesthetized rodent animal models. Scanning the rodents in a 7-tesla MRI showed a map of blood flow in the brain, indicating that as the proportion of oxygen increased, the contrast of the image increased. These images were verified by reference images created from the separation of test tubes with the varying oxygenated blood. Ogawa was able to show that T2 decay produced the best quality images (Figure 4). The neurophysiologic basis of functional activity was proven through parallel monitoring of brain activity with electroencephalography (EEG) while the rodents were undergoing MRI scanning (Ogawa, Lee, Kay, & Tank, 1990).

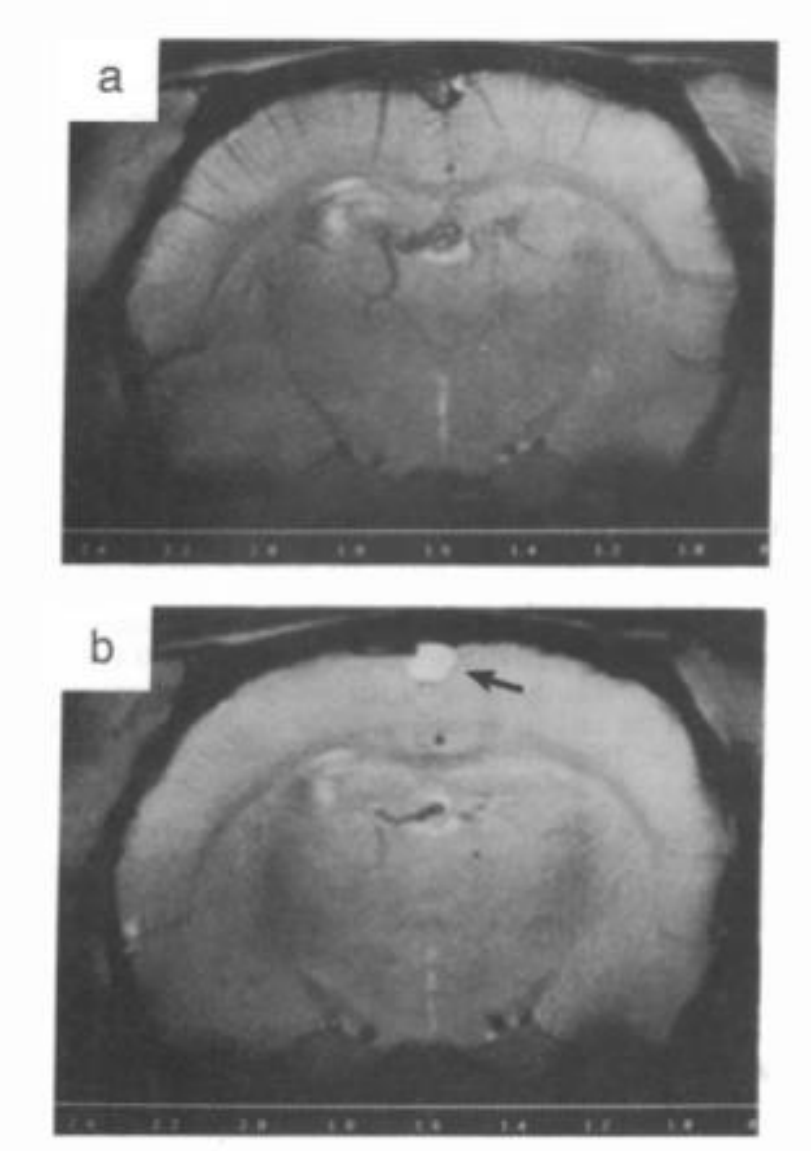

Figure 4. BOLD contrast and blood oxidation. Ogawa changed the amount of oxygen that rats were able to breathe in. Coronal slice brain images by fMRI indicated that **(a)** rats breathing in 100% oxygen had increased contrast as opposed to **(b)** rats breathing in 90% oxygen and 10% carbon dioxide (Ogawa, Lee, Kay, & Tank, 1990).

The underlying neurophysiology of fMRI has two aspects of great consideration: neuronal activity and intravascular events that lead to magnetic resonance images (Villringer, 2012). The homeostatic adjustment of blood flow to active neural tissue in delivery of nutrients is called the haemodynamic response (Ogawa & Sung, 2007). Glucose is the primary source of energy for the brain. Feedback regulation provided by the neural system alters the vascular system in order to increase blood flow to active neurons to replenish glucose stores. The firing neuron releases glutamate, which affects the neighboring support cells, or astrocytes. Astrocytes cause a change in the concentration of calcium ion, leading to a release of nitric oxide at the astrocyte-arteriole junction. Vasodilation due to nitric oxide causes arteriole expansion resulting in an increased flow of oxygenated blood rich in glucose to the active neural tissue. This tight coupling of synaptic activity to the BOLD signal allows fMRI to study functional responses of the brain in vivo (Ogawa & Sung, 2007).

Resting-State Functional Connectivity

The discovery of resting-state functional connectivity (rsFC) by Bharat Biswal (2012) was an accidental one. Biswal relates his personal history in *NeuroImage*. His recounting of his discovery is a familiar one often seen with new discoveries, involving both passion and skepticism. In 1992, Biswal began his graduate studies seeking to uncover the noise sources in the brain and what they contributed to. He started by creating a simple paradigm for subjects that consisted of the following: (1) rest scan, (2)

periodic bilateral finger tapping, (3) rest scan, (4) “random” finger tapping, and (5) rest scan. Initial results showed no differences in signal during the paradigm. In frustration, Biswal filtered out two noise signals from the data sets, respiration and heart rate. To his surprise, he found that the dominant noise sources on his scans were contributed by an unrecognized, low-frequency signal. From visual inspection, spatial patterns of temporal correlation were seen. To quantify the temporal correlation, Biswal utilized a voxel time-series from the sensorimotor cortex and compared it with every voxel in the brain. A voxel is a unit of graphic information which represents a 3-D cube of brain tissue of approximately a million brain cells (Figure 5) (Yuhas & Yuhas, 2012). By using this voxel comparison, Biswal (2012) found strong correlations between the left and right sensorimotor cortices. Driven by these findings, Biswal continued his research and discovered temporal correlation between functionally related brain regions while subjects were not cognitively engaged. This indicated that though the brain was not performing computations, it still had meaningful functional activity. Biswal’s findings, as with most scientific work, created more questions than answers, opening up a new avenue of research for the subsequent decades.

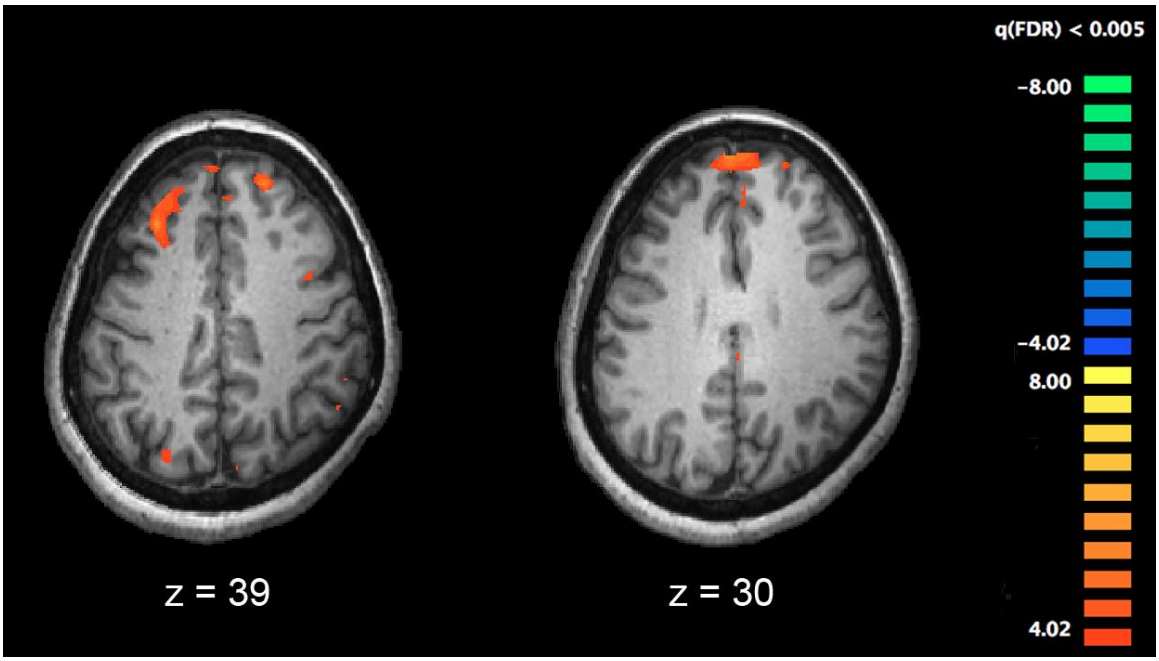

Figure 5. Brain activation patterns using fMRI voxels. In these brain images by fMRI (Kim, Matthews, & Park, 2010), orange visualizations are clusters of voxels representing brain activity related to a task. Contrast is created through changes in blood oxygen level, a proxy for mental activity. Multiple voxels in the magnitude of 10 s to 100 s create the depicted coloring (Yuhas & Yuhas, 2012).

To determine whether the findings were truly a resting-state functional connectivity and not artifact, Biswal (2012) conducted multiple studies with varying controls. Biswal changed every image and data processing parameter (e.g., TR, TE, thickness and number of slices, filter band width, and number of time points collected). The connectivity pattern remained consistent throughout the various conditions. Findings indicated that the BOLD mechanism seen in traditional task paradigms was also the mechanism responsible for the observed fMRI noise signal (Biswal, 2012).

Biswal's post-doctoral work was largely focused on resting-state functional connectivity in clinical populations (Biswal, 2012). The clinical population he addressed was a group of patients suffering from Tourette syndrome, with a hypothesis that motor tics were related to altered resting-state connectivity in the motor cortex. Biswal's study saw a significantly greater correlation in the sensorimotor cortex in Tourette's patients than controls. Both the correlation coefficient and the spatial extent of the sensorimotor cortex were greater in the Tourette's patients, indicating that the task-active system and resting system were interconnected. Since the inception of resting-state functional connectivity, numerous important insights into over 30 different kinds of disorders have been made (Biswal, 2012). To make collaborations and research more accessible, Biswal and Michael Milham created the Functional Connectome Project to aggregate resting-state functional MRI data sets from research centers worldwide for general distribution. Since the project's creation, data sets from more than 1400 subjects enrolled across 35 sites have been reposited, with 108,944 downloads by the general public at the time of this writing (https://www.nitrc.org/projects/fcon_1000/). Realizing the need for a journal that brings together research in all aspects of functional and structural connections of the human and animal brain, Biswal and Christopher Pawela launched *Brain Connectivity* in February 2011 (Figure 6) (Pawela & Biswal, 2011). Resting-state functional connectivity has become essential to the field of neuroscience and continues to allow researchers a better understanding of the inner workings of the brain.

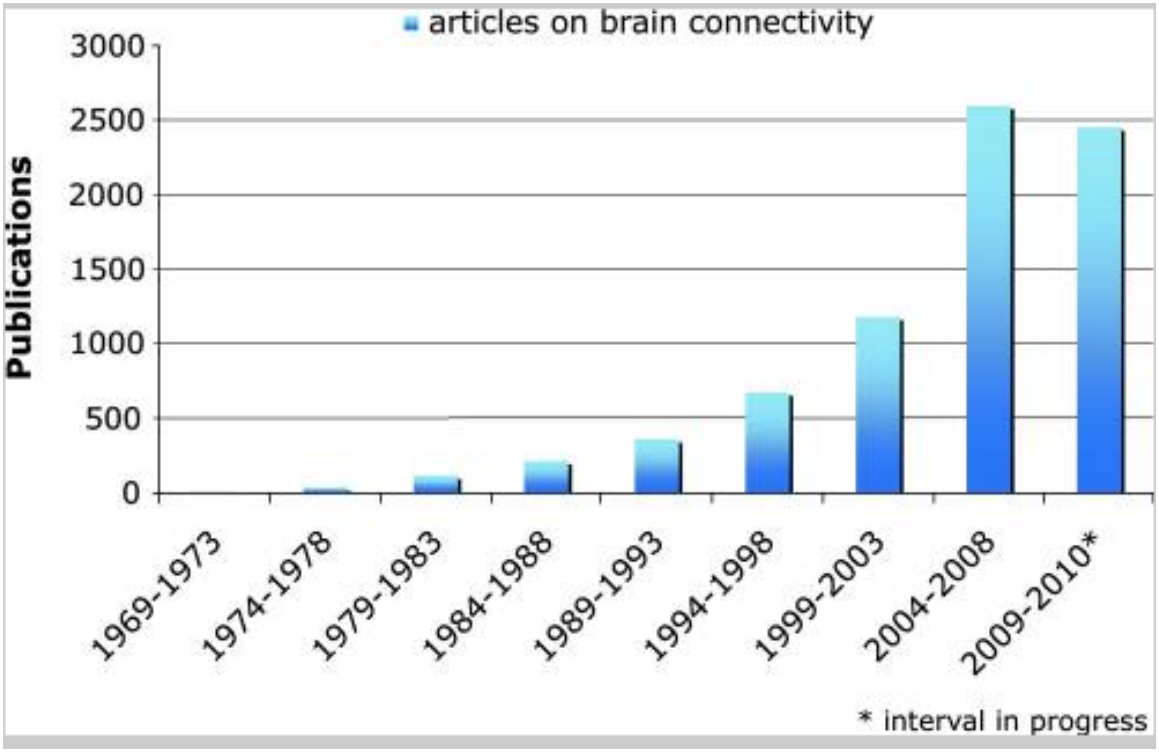

Figure 6. Growing trends in connectivity research. In 2011, Pawela and Biswal launched *Brain Connectivity*. Since Biswal's discovery of resting-state functional connectivity, research has exploded in this area, necessitating the need for a focused publication (Pawela & Biswal, 2011).

Default Mode Network

The intrinsic activity of the brain, referred to as its default mode network, is central to the study of resting-state functional connectivity. Shulman and colleagues made the first observation of an apparent default mode network of the brain in 1997. It was experimentally seen that subjects who focused lying with their eyes closed or on passive stimuli had pronounced activity in the cerebral cortex (Shulman et al., 1997). When these subjects were asked to perform a task, the activity was reduced but conserved in a highly specific constellation of areas, seemingly as if the network was turning on and off (Schulman et al., 1997). Building on the observations of Schulman and associates, Raichle (2001) set out to discover whether a baseline (or default) organized mode of brain function was present and suspended during more attention-demanding and goal-directed behaviors. Previous studies showed that regardless of the task subjects performed, there were consistent decreases in activity seen in conserved brain regions (Figure 7), indicating that the decreases were task independent (Raichle et al., 2001).

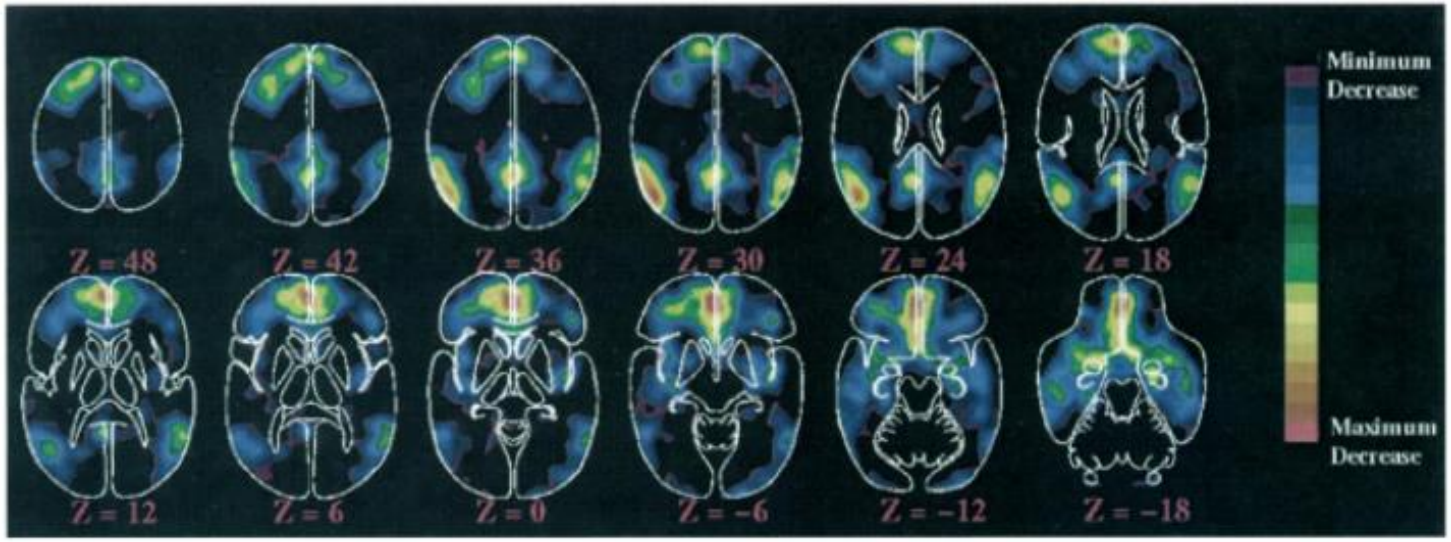

Figure 7. Regions of brain that decrease activity during attention-demanding cognitive tasks. Data represent a meta-analysis of 132 individuals over nine functional brain imaging studies. Imaging was collected by means of positron emission tomography (PET) (Raichle et al., 2001).

In order to account for the default mode observations, it was essential that a measurable baseline be chosen. To do so, the positron emission tomography (PET) oxygen extraction fraction was chosen (Figure 8). Oxygen extraction fraction (OEF) is a way to quantitatively measure the relationship of oxygen delivery to oxygen utilization in the human brain (Raichle et al., 2001). The OEF variable was chosen specifically because of the spatial uniformity seen in the resting state. When the OEF equilibrium was met, the baseline level of neuronal activity was achieved (Raichle et al., 2001). Coupling OEF measurements (obtained through PET) to regularly observed brain areas that had reductions in blood flow and BOLD signaling during goal-directed behaviors, Raichle hypothesized that the chosen regions should exhibit OEF values similar to the brain in the baseline state. Raichle concluded that the specific areas observed to decrease in activity during tasks were not activated in the resting state, but these areas were present and indicative of an unrecognized organization within the intrinsic activity of the brain (Raichle, 2015).

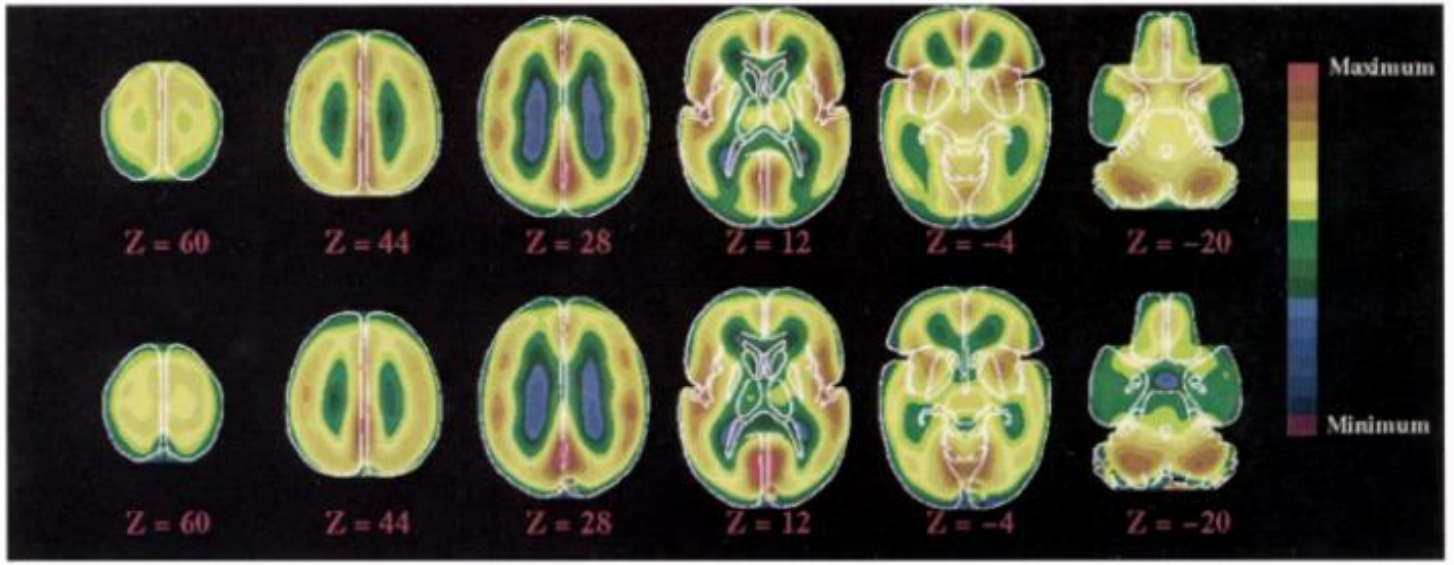

Figure 8. Quantitative maps of blood flow and oxygen consumption. Despite variations in blood flow (upper row) and oxygen consumption (lower row) of the brain, blood flow and oxygen consumption are extremely matched and reflected in the oxygen extraction fraction (OEF) (Raichle, 2001).

The function of the default mode network is still not fully understood. However, by application of what is known of the anatomical circuitry of the default mode network, functional insights have arisen. There are roughly three subdivisions of the default mode network. The first is the ventral medial prefrontal cortex, a critical element in a network of areas that receive and convey sensory information and relay information to the amygdala, the hypothalamus, and the periaqueductal gray matter of the midbrain (Raichle, 2015). This circuitry suggests that the default mode has a role to play within social behavior, mood control, and motivational drive (Raichle, 2015). The medial prefrontal cortex is the second major subdivision of the default mode network. The dorsal medial prefrontal cortex is associated with self-referential judgments (Gusnard & Raichle, 2001). The final major subdivision of the default mode network is believed to be the posterior cingulate cortex and the adjacent precuneus, including the lateral parietal cortex, which may play a part in the recollection of prior experiences (Vincent et al., 2006). The functions of the default mode network are constantly on and are enhanced or attenuated depending on the particular mental task (Raichle, 2015). The default mode network is conserved throughout all populations (Figure 9).

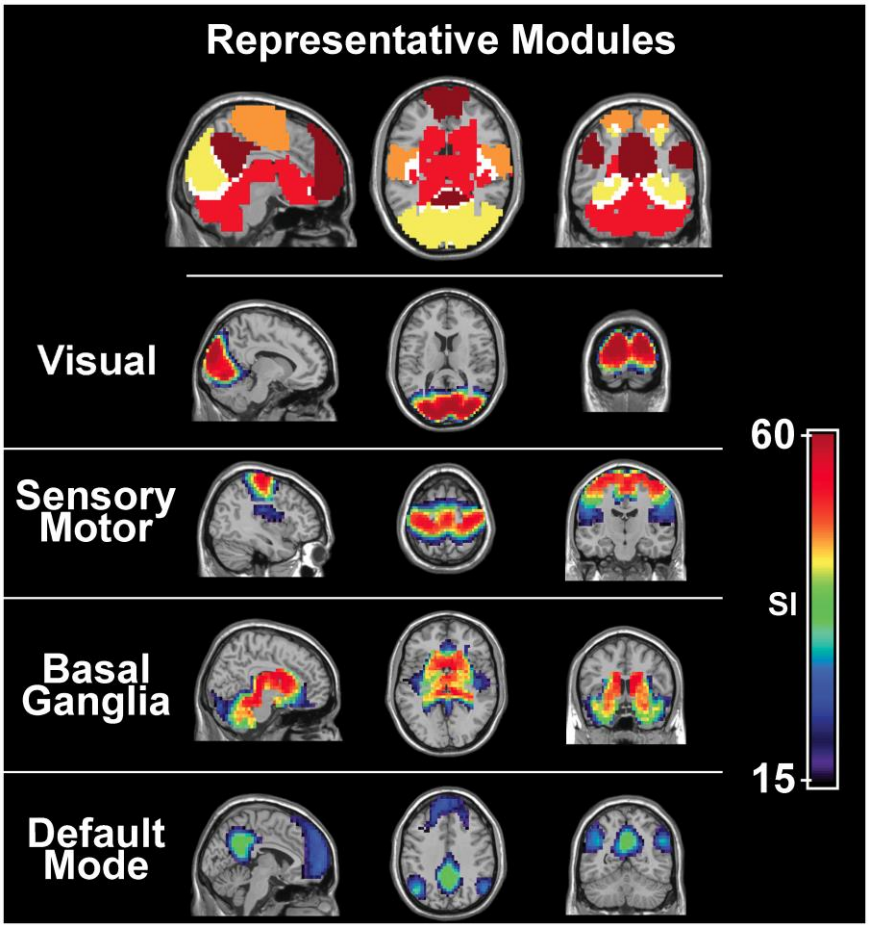

Figure 9. Functional modules consistent across subjects. An assessment of 194 subjects at voxel-level resolution showed that networks have been identified consistently across subjects. These networks are robust in nature and universally present (Moussa, Steen, Laurienti, & Hayasaka, 2012).

Since Raichle's seminal paper "A Default Mode of Brain Function" in 2001, nearly 3,000 papers have been published exploring this subject. The default mode network has been instrumental in the continued exploration of research encompassing neurophysiology and cell biology, self-referential processing and mind-wandering, functional connectivity processes, disease state-default mode network (DMN) relationships, and task-driven topics (Figure 10). Understanding the intrinsic workings of the brain has led to a better

understanding of complex disease states that defy simple explanations, such as Alzheimer's disease (Vlassenko et al., 2010), depression (Mayberg et al., 2005), and the scope of this thesis, drug addiction.

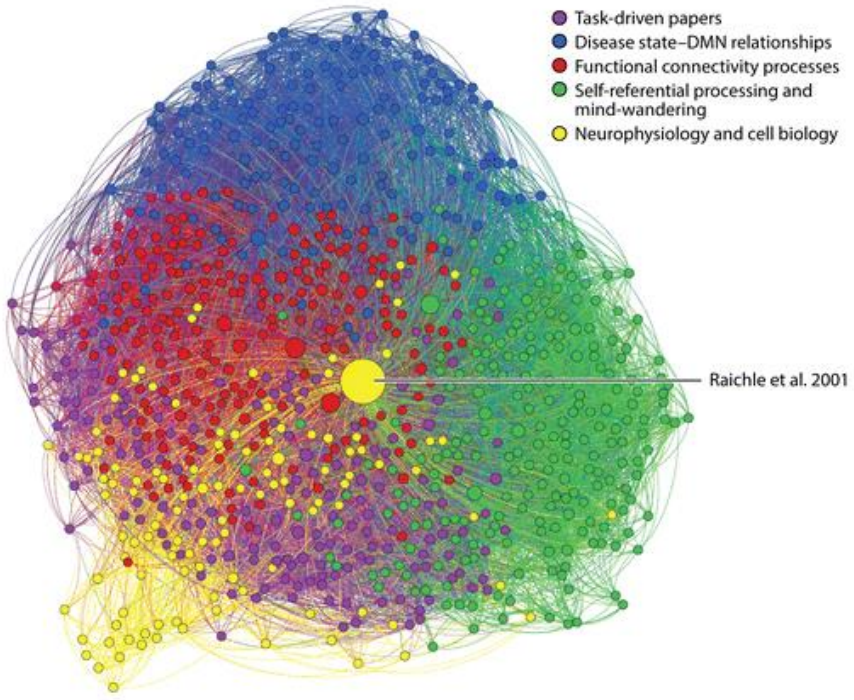

Figure 10. Impact of default mode network (DMN) study on current literature. Since the seminal paper "A Default Mode of Brain Function" by Raichle and colleagues (2001), nearly 3,000 papers have been published exploring this subject (Raichle, 2015).

Mesolimbic Reward Pathway and Addiction Models

The modern understanding of reward mechanisms began in 1954 by Olds and Milner. Their study gave rodents the choice to apply electrical stimulation to various brain regions (Olds & Milner, 1954). What they found was that stimulation of specific brain areas led to continuous self-stimulation (Olds & Milner, 1954). Heath (1963) conducted a similar study on humans and confirmed the results of Olds and Milner. The key component in reward assessment was identified to be the mesolimbic pathway (Adinoff, 2004). The mesolimbic pathway is composed of dopaminergic cell bodies of the ventral tegmental area of the midbrain that project and terminate at the nucleus accumbens in the ventral striatum (Gardner & Ashby, 2000). The dopaminergic neurons of the ventral tegmental area extend to the amygdala, the bed nucleus of stria terminalis, the lateral septal area, and the lateral hypothalamus as well. Together, these components of the mesolimbic pathway mediate reward (Gardner & Ashby, 2000).

Natural reward experiences (food, sex, etc.) and artificial reward experiences (cocaine, opiates, etc.) are accompanied by activation of the mesolimbic dopaminergic pathway (Adinoff, 2004). Activation of the pathway leads to an increase of extracellular concentrations of dopamine (Adinoff, 2004). Stimulants directly amplify the mesolimbic dopaminergic signal through various synaptic mechanisms such as the blocking of presynaptic dopamine transporters (Ritz, Lamb, Goldberg, & Kuhar, 1987) or the increasing of synaptic dopamine by upregulating synaptic vesicle release (Bunney & Aghajanian, 1978). Nonstimulant drugs indirectly interact with the mesolimbic pathway

through receptor-mediated responses by binding with G-protein-coupled receptors (Johnson & North, 1992) or ligand-gated ion channel receptors (Adinoff, 2004).

The mesolimbic pathway was observed to be anatomically distinct from the drug withdrawal response. Using rats, Bozarth and Wise (1984) explored the relation between withdrawal and reward by administering morphine into either the ventral tegmental area (VTA) or the periventricular gray (PVG) region for 72 hours. A distinct separation between withdrawal and reward was seen by administration of naloxone, an opioid antagonist. Rats that had morphine administered to the VTA had no signs of withdrawal upon administration of naloxone, but rats that had morphine administered to the PVG showed signs of withdrawal after naloxone administration. Although rats could not be trained to self-administer morphine into the PVG, they learned to do so with morphine injections into the VTA (Bozarth & Wise, 1984).

More recent evidence utilizing fMRI techniques showed an increase in brain activation in the mesolimbic pathway during cocaine administration to a patient cohort. Utilizing cocaine-addicted subjects, Breiter and colleagues (1997) administered cocaine while the subjects' brains were scanned. The subjects were then asked to distinguish the "rush" and the "craving" sensations after administration of cocaine. Images from the "rush" and the "craving" states showed differing activation levels in the VTA. The "rush" state had higher activation in the VTA not seen during the "craving" phase, further confirming the mesolimbic pathway and dopamine release to the reward experience (Breiter et al., 1997).

Historically, two hypotheses exist to explain the transition from reward to addiction: the dopamine depletion hypothesis and the sensitization hypothesis. The dopamine depletion hypothesis is the belief that drug-induced dopamine depletion reinforces the need for more drugs to replenish depleted dopamine stores (Bozarth & Wise, 1984). There is evidence to suggest upregulation in striatal receptors (Malison et al., 1998) and downregulation in dopamine receptors (Volkow et al., 1993). Treating cocaine addiction by activating dopaminergic receptors has not been successful to date (Malcolm et al., 2000), necessitating a need for further investigation in underlying circuitry to elucidate possible treatment paradigms. The sensitization hypothesis proposes that repeated administration of drugs leads to the dopaminergic system becoming sensitized to the drug and drug cues, necessitating an increase in use (Halikas, Kuhn, Crosby, Carlson, & Crea, 1991). Similar to the dopamine depletion hypothesis, the sensitization hypothesis has not yielded effective pharmacologic interventions.

As a result of the disappointing clinical response of the sensitization and dopamine depletion hypotheses, the recognition of four key insights shifted the role of dopamine in addiction. The first insight was that dopamine does not cause pleasure by itself. The second was that the increase of dopamine in the mesolimbic system was seen not only by administration of a reward but also in the anticipation of an incoming reward (Adinoff, 2004) as well as aversive states (Jentsch & Taylor, 1999). The third insight was from rat studies in which passive administration of cocaine led to higher extracellular increases in

accumbens dopamine compared with rats that self-administered (Hemby, Koves, Smith, & Dworkin, 1997). Finally, the fourth insight was that dopamine plays roles in acquiring behaviors and interpreting stimuli (Adinoff, 2004). Rather than the mesolimbic pathway being the "pleasure" pathway, data suggest that it is the "wanting" pathway, known as the incentive salience or the expectation of pleasure (Adinoff, 2004). It is now thought that the mesolimbic dopamine system controls the learning and interpretation of negative reinforcers and positive rewards, with dopamine appearing to signal goal-directed behaviors regardless of the type of reinforcement (Adinoff, 2004).

Brain Areas Involved in Addiction

Amygdala: Amygdalar activity is related to memory consolidation for emotionally arousing events. The amygdala is involved in assigning a reward value to stimuli and in the conditioning of fear to novel stimuli. For example, rodents favoring a specific cage that is identified with drug administration will lose this conditioned stimulus if the amygdala is ablated.

Anterior cingulate: Implicated in human disorders of emotion and attention, the anterior cingulate is involved in emotional self-control, focused problem-solving, error detection, performance monitoring, and adaptive response to changing conditions.[75] It plays a role in the detection of processing conflicts, particularly when low-frequency responses are executed,[76] but is influenced by both motivation and affective state.

Bed nucleus of the stria terminalis (BNST): Involved in autonomic and behavioral reactions to fearful stimuli, including the stress response, the BNST is considered part of the extended amygdala and shares with the nucleus accumbens a sensitivity to dopamine stimulation. In rats, the BNST is involved in the reinstatement of cocaine seeking after foot shock.[77]

Dorsolateral prefrontal cortex (DLPFC): Implicated in difficulties holding/maintaining several pieces of information "on line" or in short-term storage (i.e., "working memory"), the DLPFC is crucial for the control and regulation of cognitive activities, including the sequencing of events, planning, and the selection of goals.

Hippocampus: Critical for the acquisition of new factual information and the formation of new memories about personally experienced events (i.e., episodic memory), the hippocampus has been implicated in the loss of memory in Alzheimer's disease. Damage to the hippocampus results in anterograde amnesia and, to a lesser degree, in retrograde amnesia.

Insular Cortex: Important for the processing of pain, the insular cortex receives visceral, olfactory, gustatory, and other somatosensory inputs. It probably plays an important role in relating interoceptive signals to information from other modalities, and often shows activation in neuroimaging studies producing acute anxiety.

Orbitofrontal cortex (OFC): In addition to being implicated in disorders of impulsivity and decision making, the OFC is involved in situations that are unpredictable or uncertain, and modulates the reinforcement value of stimuli in the context of recent experience. It assesses and decodes the likely value or behavioral relevance of available choices of action and is therefore activated when there is insufficient information available to determine an appropriate course of action. Recent evidence suggests that the medial OFC (ventromedial cortex), with connections to the hippocampus and cingulate, is involved in assessing the familiarity or "rightness" of a situation and in integrating outcome expectancies. The lateral OFC, with connections to the amygdala and insula, is associated with the suppression of previously rewarded responses and is required to change behavior (i.e., to provide "stop" signals).[78]

Figure 11. Brain areas involved in addiction. The functions of brain areas are summarized in regard to addiction formation (Adinoff, 2004).

Specific Aims

The aim of this thesis is to assess recent rsFC investigations; specifically those that shed light on changes in functional connectivity in human brain as a result of illicit drug use. The goals are (1) to illuminate the precise nature of rsFC alterations in the reward-related neurocircuitry of drug addiction and (2) to garner new insights that may lead to more successful drug addiction treatments.

PARTICIPANTS

Six studies were examined for this review (Gu et al., 2010; Ma et al., 2010; Tomasi et al., 2010; Upadhyay et al., 2010; Wang et al., 2010; Wilcox et al., 2011). Each of the studies compared an experimental group of drug abusers with a group of non-drug-using controls to assess changes in rsFC of the reward network. All subjects in each of the studies were fully informed of the context of the research and provided written consents for their involvement. After thorough review, an inference was drawn upon studies of this nature; that is, no one study surpassed a sample size of 78 subjects (Gu et al., 2010). Possible difficulties obtaining larger sample sizes may be costs of MRI scanning time (about $500 per hour) or the feasibility of obtaining a large cohort of drug abusers sharing the same criteria (age, sex, intelligence, education, handedness, etc.). Experimental groups varied. Ma et al. (2010), addressing resting-state brain connectivity in chronic heroin abusers, used a heterogeneous experimental group of both methadone-maintained and abstinent users, whereas Wang et al. (2010), who also addressed functional connectivity of heroin abusers, utilized current heroin users with last heroin use being 3-7 hours before testing. All six studies used the *Diagnostics and Statistical Manual of Mental Disorders*, 4th edition, as the basis for diagnosing drug dependence and abuse. Finally, with the exception of one study (Wang et al., 2010), all subjects (control and experimental) were excluded based on any history of diagnosed neurological or psychiatric disorders. Wang et al. (2010) allowed patients with possible neurological or

psychiatric disorders to participate in their study as long as patients were free from illnesses that required hospitalization or regular monitoring (Wang et al., 2010.)

MATERIALS AND METHODOLOGY

A 3 Tesla MRI scanner was utilized to assess the reward pathway of drug abuse in all experiments (Gu et al., 2010; Ma et al., 2010; Upadhyay et al., 2010; Wang et al., 2010; Wilcox et al., 2011) with the exception of one group using a 4 Tesla scanner (Tomasi et al., 2010). Head coils were used to optimize readings in a majority of experiments (Upadhyay et al., 2010; Gu et al., 2010; Wang et al., 2010; Ma et al., 2010). Image acquisition varied from experiment to experiment. Single-shot gradient-echo planar imaging (Gu et al., 2010; Tomasi et al., 2010; Upadhyay et al., 2010), high-resolution T1-weighted spin-echo imaging (Ma et al., 2010), and T2*-weighted gradient-echo planar imaging (Wang et al., 2010) were all used. Image preprocessing was standard for all experiments. The first four points in the time series were discarded to avoid nonequilibrium effects in the fMRI signal. Raw data were corrected for temporal shifts between slices and for head motion and were spatially smoothed with a Gaussian kernel. Band-pass temporal filtering from roughly 0.01 Hz to 0.1 Hz on residual signals was used to obtain low-frequency fluctuations needed for resting-state connectivity analyses. Preprocessed time series were used in subsequent seed-based, regions-of-interest correlation analysis. Correlation maps were then created by computing the correlation coefficients between the BOLD time course from the seed region and the BOLD time course from all of the other brain voxels (Wang et al., 2010). Regions of interest (ROIs) were chosen based on data from the Talariach database (Gu et al., 2010; Ma et al., 2010) or from previous studies (Upadhyay et al., 2010; Wang et al., 2010; Wilcox et al., 2011).

RESULTS

Decreased rsFC of Reward Pathways

Four papers found widespread reductions in the connectivity of multiple MCL system components. Gu et al. (2010) described in their paper "Mesocorticolimbic Circuits Are Impaired in Chronic Cocaine Users as Demonstrated by Resting-State Functional Connectivity" the use of whole-brain resting-state fMRI connectivity analysis with "seed voxels." Seed voxels were placed within individual nodes of the MCL system to report changes in network-specific functional connectivity strength in cocaine users. When compared with matched healthy control participants, chronic cocaine users were found to have prominent decreases in rsFC strength from five of six MCL seed regions (Gu et al., 2010). The amygdala and rostral anterior cingulate cortex, as well as the hippocampus and anterior cingulate cortex, exhibited a reduction in functional connectivity(Gu et al., 2010). They also found that the ventral tegmental area showed reduced connectivity to much of the thalamus, including the medial dorsal thalamus seed regions (Figure 12). No differences were seen in connectivity regarding the nucleus accumbens. Furthermore, regression analysis in regions showing differences in group connectivity revealed that rsFC strength decreases as years of cocaine use increases (Figure 13). This study, the first to report circuit-level abnormalities in human cocaine users, demonstrated widespread reductions in connectivity of MCL system components that can be interpreted as possible difficulties in activating reward, learning, and emotional circuitry (Gu et al. 2010). In

addition, Tomasi et al. (2010) showed reduced functional connectivity in the dopaminergic midbrain in cocaine abusers in their paper "Disrupted Functional Connectivity With Dopaminergic Midbrain in Cocaine Users." Across subjects, a reduction in correlation with midbrain was seen in numerous portions of the brain (Tomasi et al., 2010).

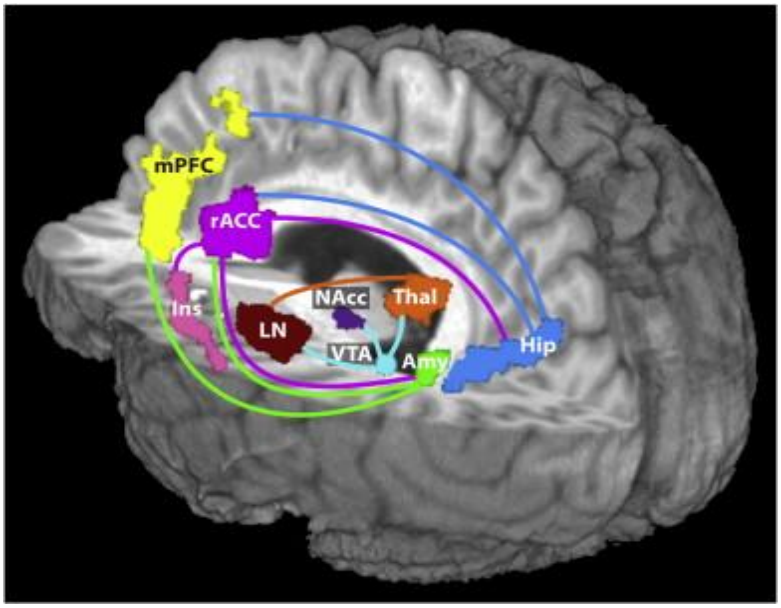

Figure 12. Functional connectivity in cocaine users. Schematic representation of regions showing decreased functional connectivity in cocaine users compared with matched healthy controls. Colored lines indicate reduced functional connectivity between seed regions. VTA: ventral tegmental area; NAcc: nucleus accumbens; Amy: amygdala; Hip: hippocampus; Thal: thalamus; rACC: rostral anterior cingulate cortex; mPFC: medial prefrontal cortex; Ins: insula; LN: lentiform nucleus (Gu et al., 2010).

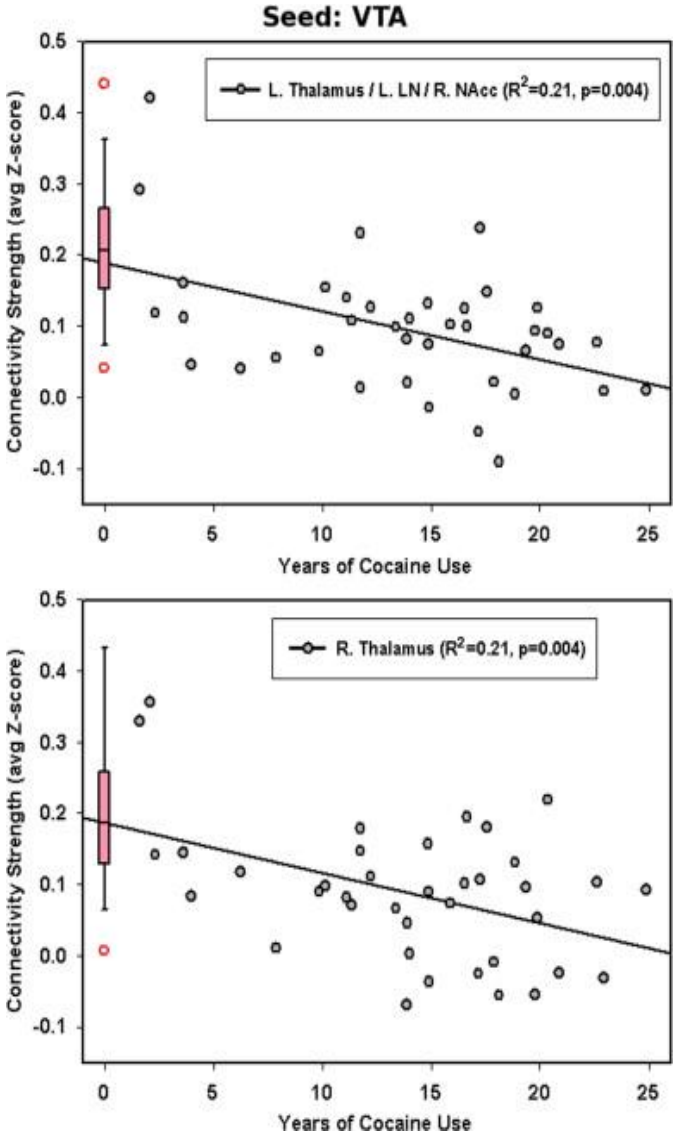

Figure 13. Regression analysis of rsFC strength. Multiple regression analysis showed a negative correlation between rsFC strength of seed regions of the ventral tegmental area (VTA) and years of cocaine use. A box plot on the left summarizes the connectivity strength from the healthy control group in the corresponding regions of interest. Open red symbols represent outliers in the healthy control group (Gu et al., 2010)**.**

Upadhyay et al. (2010) addressed alterations in brain structure and functional connectivity in prescription opioid-dependent patients. For this study, the authors hypothesized that the insula would show functional differences between the two groups. They derived this hypothesis based on a recently uncovered key role played by the insula in maintaining smoking addictions, perhaps by mediating conscious urges and emotional decision-making (Naqvi et al., 2007). Upadhyay et al. (2010) found significant decreases in rsFC in the insula and the various cortical and subcortical structures of the opioid-dependent subject group compared with the healthy control group (Figure 14A). More interestingly, the duration of opioid dependency and the functional connectivity strength of the anterior insula and the putamen were significantly anticorrelated when compared with healthy controls (Figure 14B). Upadhyay and coworkers also saw significant decreases in rsFC in three subdivisions of the amygdala (Figure 15A). In addition, there was an anticorrelation between functional connectivity with the laterobasal amygdala and duration of opioid dependency (Figure 15B). Finally, data suggested significant decreases in rsFC in the nuclear accumbens and multiple cortical and subcortical structures in the opioid-dependent subject group (Figure 16). The totality of these findings suggests that prescription opioid dependency is associated with structural and functional changes in brain regions implicated in the regulation of affect and impulse control as well as in reward and motivational functions (Upadhyay et al., 2010).

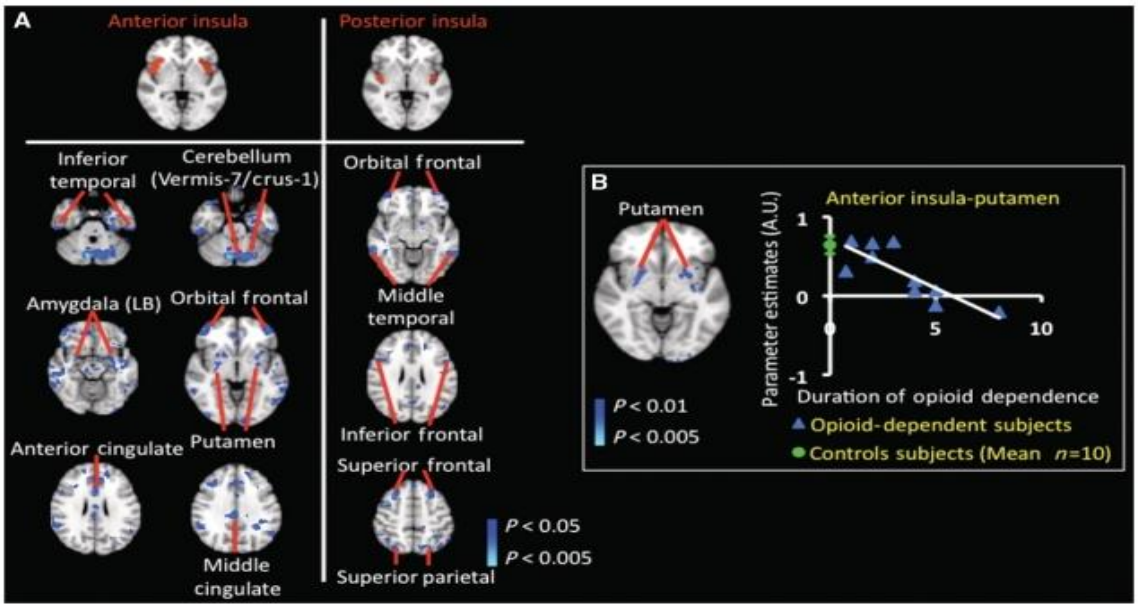

Figure 14A. Opioid subjects versus control subjects. Significant decreases in rsFC between the insula and various cortical and subcortical structures were seen in the opioid-dependent subject group compared with the healthy control group (Upadhyay et al., 2010).

Figure 14B. Effects of opioid dependence on rsFC strength. Duration of opioid dependence and rsFC strength were significantly anticorrelated. A longer duration of use resulted in a lower functional connectivity strength between the anterior insula and putamen (Upadhyay et al., 2010).

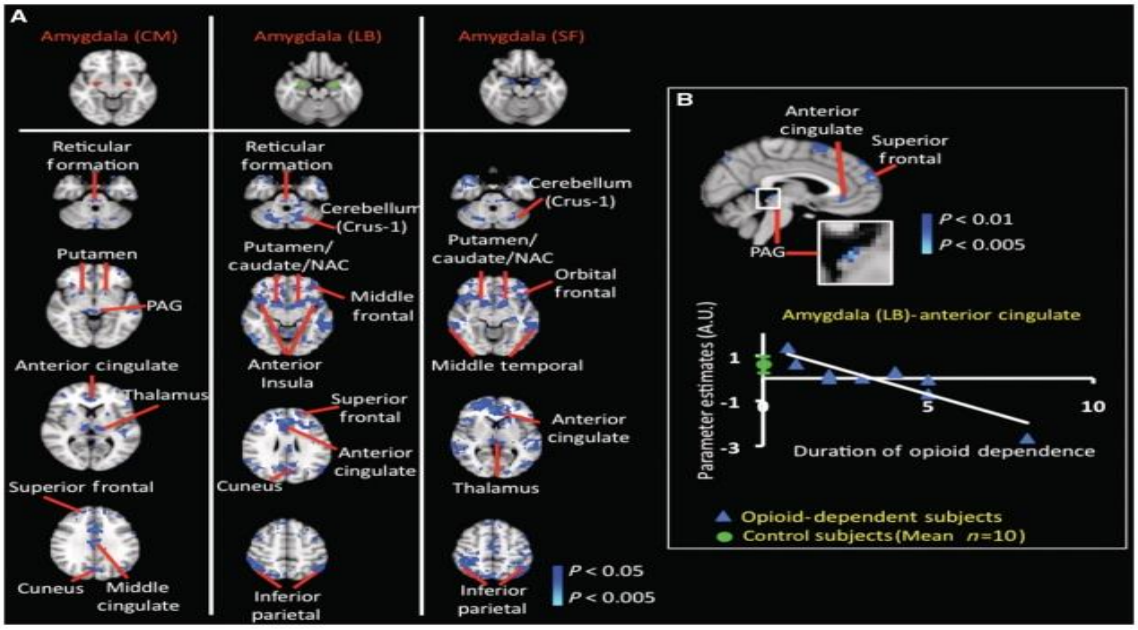

Figure 15A. Strength of rsFC in amygdala. Significant decreases in rsFC strength in all three subdivisions of the amygdala were seen in the opioid-dependent subject group compared with the healthy control group (Upadhyay et al., 2010).

Figure 15B. Effects of opioid dependence on rsFC strength. A significant anticorrelation was found between functional connectivity with the laterobasal amygdala and duration of opioid dependence (Upadhyay et al., 2010).

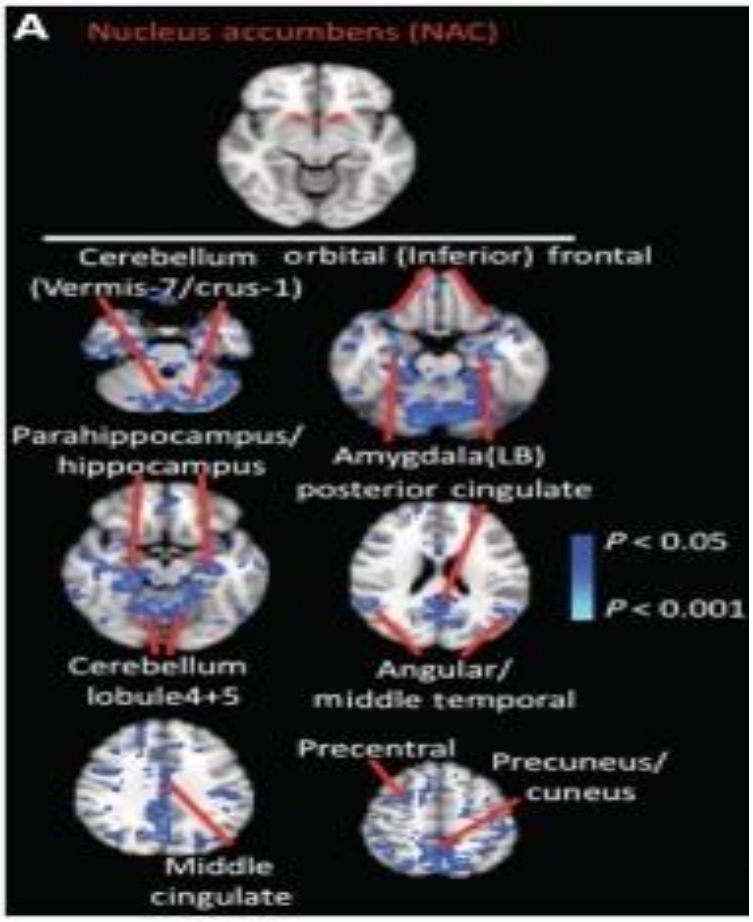

Figure 16. Strength of rsFC in nucleus accumbens. Significant decreases in rsFC strength of the nucleus accumbens and multiple cortical and subcortical structures were found in the opioid-dependent subject group (Upadhyay et al., 2010).

Finally, a paper by Wang et al. (2010) addressing functional connectivity of the ventral anterior cingulate cortex in heroin abusers also found a reduced functional connectivity in areas that reflect the reward system and an increased functional connectivity in areas that account for the abusers' intense craving for drug and for their relapse due to an increased desire (Figure 17) (Wang et al., 2010).

The results of these four studies support the importance of understanding plastic changes in brain function between drug addicts and healthy control individuals outside traditional reward-related circuits. These findings are consistent with perspectives suggesting that transition from drug use to addiction is driven by reduced functioning of reward systems and concurrently increased activation of anti-reward systems (Koob et al., 2005).

CMJ **Table 3.** Alteration of resting-state functional connectivity of vACC in heroin addicts compared with health controls

Contrast	Reigions	HS	BA	Cluster size (voxels)	Maximal T-peak	Primary peak location (Talairach coordinate)
Normal>Addiction	PCC/ pC	L	7/23/31	104	3.79	–10, –55, 49
		R	7/23/31	115	3.88	26, –58, 49
	ACC	L	24/32	266	11.73	–2, 38, –7
		R	24/32	225	35.55	4, 37, –5
	NAc	R	N/A	8	2.86	4, 15, –2
	PHG/Amygdala	R	27/34	16	3.18	18, –9, 16
	Thalamus	R	N/A	13	2.96	8, –27, 5
Addiction>Normal	Middle temporal gyrus	L	21	29	3.31	–44, 5, –25
		R	21	28	3.09	59, –4, –5
	Superior temporal gyrus	L	22/38	17	2.84	44, 7, –24
		R	22/38	10	2.86	55, 1, –10
	Ventral lateral prefrontal cortex	L	44/45	28	3.33	–53, 10, 14

Summary information for regions of activation shows the differences between heroin abusers and healthy subjects. The height and extend thresholds were set at P <0.002 and 3 voxels.

Figure 17. Alterations of rsFC in heroin addicts. The table summarizes information for regions of activation, showing contrast differences between heroin abusers and healthy subjects. HS: hemisphere; BA: brain area (Wang et al., 2010).

Increased rsFC of Reward Pathway

Two studies were reviewed that included data suggesting an increase in the reward pathway of chronic drug use. Ma et al. (2010), in their study "Addiction Related Alteration in Resting-State Brain Connectivity," addressed chronic heroin use on five regions of interest: bilateral nucleus accumbens, amygdala, dorsal anterior cingulate cortex, orbital frontal cortex including lateral areas, and medial orbital frontal cortex. They found that compared with controls, chronic heroin users showed increased functional connectivity between the nucleus accumbens and the ventral/rostral anterior cingulate cortex and between the nucleus accumbens and the orbital frontal cortex (Figure 18). They also found increased functional connectivity between the amygdala and the orbital frontal cortex. These results suggest enhanced connectivity within reward and motivation circuits that may be interpreted in the perspective of altered incentive salience for drugs and drug-associated stimuli (Ma et al., 2010).

Wilcox et al. (2011), in their paper "Enhanced Cue Reactivity and Fronto-Straital Functional Connectivity in Cocaine Use Disorders," evaluated the neural regions involved in subjective craving and how functional connectivity MRI may be altered in chronic cocaine users. Results showed increased connectivity between the left ventral striatum and the right orbitofrontal cortex for the cocaine group relative to the control group in the regions of interest (Figure 19A). The increased connectivity between reward and reward cue processing regions (ventral striatum, medial orbitofrontal cortex) with

regions which have a larger role in motivational decision-making and inhibitory control (rostroventral anterior cingulate cortex) may mediate the increased salience of drug cues with the greater potential for drug cues to trigger drug use. Increased anticorrelations for several bilateral posterior cortical regions, observed between cue processing regions and the posterior cingulate cortex, precuneus, and visual cortex in the experimental group compared with the healthy controls, may mediate the increased ability of cocaine cues to trigger cravings (Figure 19B) (Wilcox et al., 2011). Results suggesting enhanced connectivity within reward and motivation circuits may be interpreted in the perspective of altered incentive salience for drugs and drug-associated stimuli (Berridge et al., 1998.)

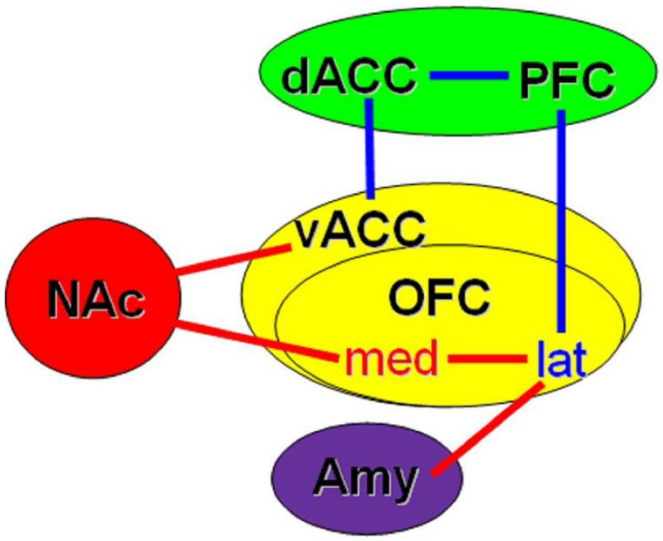

Figure 18. Schematic diagram showing differences in functional connectivity between experimental group and controls. Compared with controls, chronic heroin users showed increased functional connectivity between nucleus accumbens (NAc) and ventral/rostral anterior cingulate cortex (vACC), between NAc and medial (med) orbital frontal cortex (OFC), and between amygdala (Amy) and lateral (lat) OFC. However, compared with controls, chronic heroin users displayed reduced functional connectivity between prefrontal cortex (PFC) and dorsal ACC (dACC), between PFC and lateral (lat) OFC, and between dACC and vACC. The red lines depict enhanced connectivity in the experimental group; the blue lines show reduced connectivity in the experimental group. The background colors indicate different roles of the regions in drug addiction—red is reward, purple is memory and learning, green is cognitive control, and yellow is motivation, craving, and behavior guidance (Ma et al., 2010).

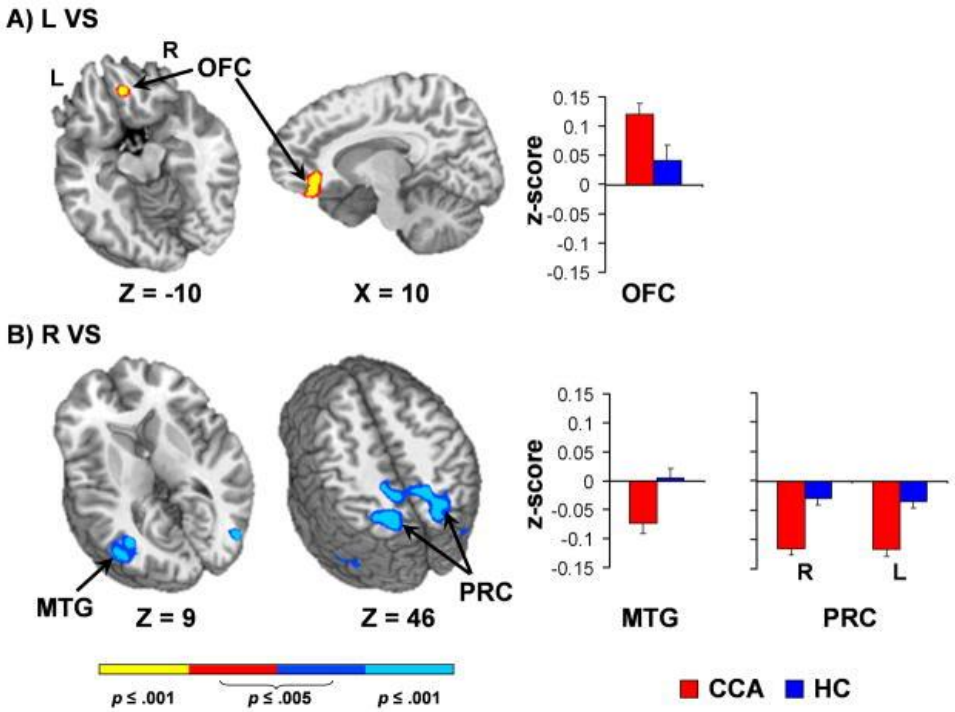

Figure 19A. Increased connectivity in cocaine users. Results showed increasing connectivity (positive correlations) between the left ventral striatum (L VS) and the right orbitofrontal cortex (OFC) in the group of chronic cocaine abusers (CCA) relative to the group of healthy controls (HC) in regions of interest (Wilcox et al., 2011).

Figure 19B. Anticorrelations in cocaine connectivity. Increased anticorrelations were seen for several bilateral posterior cortical regions (Wilcox et al., 2011).

DISCUSSION

Experiments addressing rsFC show changes in strength of circuitry and reward dysregulation when subjects have chronic drug use. At this early stage of experimental data in this field, data interpretation necessitates caution. Clearly, more work is needed in order to unravel the apparent complexities in addressing rsFC changes in reward-related circuitry. Problems inherent to this literature must be addressed. In particular, a choice of small sample sizes, though sometimes necessary, can result in wide confidence intervals or risks of errors in statistical hypothesis testing. The use of 20 subjects (Upadhyay et al., 2010), 27 subjects (Ma et al., 2010), and 30 subjects (Wilcox et al., 2011) is simply not large enough to achieve statistically relevant data.

This author further found numerous flaws in methodology when reviewing the literature. Ma et al. (2010) used a heterogeneous subject group of methadone-maintained individuals and abstinent heroin users when collecting data for their experimental group (Upadhyay et al., 2010). Duration since last drug use was also a factor. One particular study used faulty controls that may have abused illicit drugs (Gu et al., 2010). Others were found to have experimental groups with drug use 3-7 hours prior to scanning (Wang et al., 2010). Acute withdrawal (Gu et al., 2010; Ma et al., 2010; Tomasi et al., 2010; Wilcox et al., 2011) or acute drug effects (Ma et al., 2010; Upadyay et al., 2010) likely contribute to significant variance between and within rsFC studies. Finally, generalizing

across different abused drugs is complicated by the potential for drug-specific effects on underlying neural circuitry.

What can be said with certainty is that an altered reward pathway of chronic drug users was found within studies. Careful consideration of methodology must be taken into account for work to illuminate the precise nature of rsFC alterations in the reward-related neurocircuitry of drug addiction. With this in mind, future studies will garner new insights that may lead to more successful drug addiction treatments.

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