

Substance Dependence as a Neurological Disorder

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1. Introduction

Traditionally, explanations of drug addiction adhered to a moralistic perspective. This perception, still held by many individuals and policy makers, suggests addiction is a problem to be addressed through the criminal justice system (Brown, 2011; Leshner, 1997). However, this approach has yielded little success in addressing the problem (Lee et al., 2010) and may serve to stigmatize addicts and act as a barrier to initiating treatment (Brown, 2011). Moreover, early theories of addiction grounded in learning theory have proven insufficient in explaining several key aspects of addictive behaviour (Robinson & Berridge, 1993). More recently, addiction has been viewed as disease which is characterized as a chronic relapsing disorder in which behavior is marked by a compulsion to seek and take drugs, a loss of control in limiting intake, and the emergence of a negative emotional state upon withdrawal (Koob & Le Moal, 1997). With recent advances in neuroscience and more widespread adoption of the disease model of addiction, current theories have shifted their emphasis to explaining addiction as a brain disease, subserved by varying degrees of cellular, molecular and neurocircuitry dysfunction (Koob & Le Moal, 1997; Volkow et al., 2011).

The defining features of what constitutes a “disease” varies (White et al., 2002). Most current theories focus squarely on the issue of voluntary control (Hyman, 2007; Lyvers, 2000). More specifically, they view addiction as a disease involving the erosion of voluntary control (Hyman, 2007; London et al., 2000; Lubman et al., 2004). It is noteworthy that addicts themselves most often attribute relapse to impulsive action with no known cause (Miller & Gold, 1994). While a comprehensive review of the neural underpinnings of addiction and how it informs the disease model is beyond the scope of this chapter, this review will emphasize how changes in neurological function related to the loss of voluntary control serve as a thread that runs through the addiction literature. The neural circuitry most often linked to the voluntary control of behaviour are the various regions of the prefrontal cortex and their interconnections with limbic and striatal regions (Feil et al., 2010; Goldstein & Volkow, 2002; Lubman et al., 2004; Volkow & Fowler, 2000). The role of dysfunction within this circuitry is bolstered by the observation that addicts show, hypofunction in various regions of the prefrontal cortex (Li et al., 2009; Volkow et al., 1991), perform poorly on measures related to behavioural control (Fishbein et al., 2007; Ornstein et al., 2000; Rubio et al., 2008), and often perform similarly on neuropsychological tests as those who have suffered damage to the prefrontal cortex (Rogers et al., 1999).

The prefrontal cortex represents a complex and heterogeneous structure with multiple subregions interacting with various subcortical circuits (Feil et al., 2010; Tekin & Cummings, 2002). The functions of the prefrontal cortex have been broadly characterized as executive functions. The construct of voluntary control of behavior overlaps considerably with that of executive function, the latter of which is more commonly used in the literature and will be used for the remainder of this chapter. Executive function includes a set of higher order regulatory and supervisory functions including: planning, cognitive flexibility, abstract thinking, rule acquisition, initiating appropriate actions and inhibiting inappropriate actions, and selecting relevant sensory information (Stuss, 2007). The initial part of this chapter describes the various subdivisions of the prefrontal cortex and links between these areas and executive function domains.

While the dependence profile of the classes of addictive drugs varies somewhat (Fernandez-Serrano et al., 2011), research in recent decades suggests that the neurochemical adaptations and neural circuitry underlying the addictive process is remarkably similar across abused substances (Feil et al., 2010; Robinson & Berridge, 2003; Volkow et al., 2011). This chapter will review research implicating the prefrontal cortex and executive abilities for each major class of addictive drugs (Psychostimulants, Opioids, Alcohol, and Nicotine). Many drug addicts use and/or are dependent on multiple substances (Degenhardt & Hall, 2003) and therefore research investigating executive dysfunction among polysubstance users will be addressed in an additional subsection.

Currently much of the focus in addiction research is to understand how various neural states are related to different aspects of addiction (Crews & Bottiger, 2009; Goldstein & Volkow, 2002; Volkow et al., 2011). Within each drug class discussed in this chapter three major areas will be addressed 1) the degree to which executive abilities are able to predict vulnerability to develop compulsive drug use; 2) impairment of executive abilities and cortical neurocircuitry among drug addicts related to the maintenance of addictive behaviour and continued risk of relapse; 3) the relationship between neurological functioning and recovery from addiction and how treatment interacts with this process.

Substance dependent individuals represent a highly heterogeneous group, and the variables related to the development of this disorder are many (e.g., temperament, social and environmental factors, genetics, etc.) (Conner et al., 2010). Drug addicts show impaired executive function and decreased activity in the prefrontal cortex (Dom et al., 2005; Feil et al., 2010). Several prospective studies suggest lower scores on measures of executive abilities among adolescents is predictive of future vulnerability to drug dependence suggesting executive dysfunction is among the variables conferring vulnerability for drug addiction (Mezzich et al., 2007; Najam et al., 1997). Moreover, the delayed maturation of the prefrontal cortex may be related to vulnerability of developing drug problems during adolescence (Bickel et al., 2007).

In addition to predating the development of addiction other studies, suggest chronic drug exposure may impair executive abilities and associated cortical function. The severity of drug use has been linked to the degree of executive impairment (Bolla et al., 1999; Verdejo-Garcia et al., 2006). Today, several theories of addiction are based on specific executive dysfunctions including: inhibitory response control and impulsivity (Crews & Boettiger, 2009; Feil et al., 2010; Jentsch & Taylor, 1999; Lubman et al., 2004; McNamee et al., 2008;

Volkow et al., 2003), decision making (Dom et al., 2005; London et al., 2000; Schoenbaum et al., 2006), affect dysregulation (Cheetham et al., 2011; Tekin & Cummings, 2002) cognitive performance (Pfefferbaum et al., 1997), and temporal discounting (Mackillop et al., 2011). A variety of hypotheses exist to explain how individuals with compromised executive abilities might be more predisposed to cyclical patterns of drug dependence. For example, impaired outcome expectancies may decrease the ability to make adaptive decisions and recognize the negative consequences of decisions (Schoenbaum et al., 2006). Attenuated inhibitory control may impair functional goal directed behaviours and promote participation in poorly conceived, prematurely expressed risky behaviour (Crews & Boettiger, 2009). Moreover, executive impairments in temporal discounting may render addicted individuals less likely to choose the delayed rewards of sobriety by minimizing the perceived benefits of future rewards (Bickel et al., 2007). Alternately, failure of inhibitory control mechanisms may result in maladaptive and uncontrolled drug use even when faced with disastrous consequences (Lubman et al., 2004).

Given that impairment of executive abilities and their neural substrates appear central to the development and maintenance of addictive behaviour, presumably, the recovery process should involve improvement of executive functions. This literature is in its infancy and this chapter will review research examining the relationship between improvement in executive function and recovery from substance dependence. It has been suggested that treatments that focus on improving executive abilities (such as cognitive behavioural therapy and motivational interviewing) may be effective in promoting recovery (Bickel et al., 2007; Lubman et al., 2004) and that recognition of this relationship may generate novel treatment approaches centered on augmenting activation of the prefrontal cortex and executive abilities, such as biofeedback, electrical or magnetic stimulation, and cognitive enhancing drugs (Bickel et al., 2007, Crews & Boettiger, 2009; Ersche & Sahakian, 2007). Longitudinal studies investigating treatment efficacy and related neural and behavioural changes are methodologically challenging and difficult to interpret, but may promote advances regarding the timing of treatment and matching clients to effective interventions (Bickel et al., 2007).

2. The prefrontal cortex and executive function

The frontal lobes represent arguably the most advanced structure of evolution and reach their zenith in humans, comprising almost one third of the total cortex. The prefrontal cortex, the most anterior portion of the frontal lobes, is a heterogeneous area that has been further subdivided based on their neuroanatomical connectivity and functionality, the latter of which is often revealed through deficits on neuropsychological tests or impairments resulting from lesions to the frontal regions. Multiple classification schemes based on neuropsychological and anatomical features have also been articulated (Stuss, 2007; Tekin & Cummings, 2002). One useful nomenclature for the regions of the frontal lobes has been described by Tekin & Cummings (2002) characterizes five frontal subcortical circuits. The circuits originate in the supplementary motor area, frontal eye field, dorsolateral prefrontal region, lateral orbitofrontal region, and anterior cingulate region. In some cases lesions within this circuitry have been linked to behavioral deregulation. Dorsolateral prefrontal circuit lesions are associated with executive dysfunction, orbitofrontal circuit lesions have been linked to disinhibition of behavior and anterior cingulate circuit lesions are associated with apathy (Tekin & Cummings, 2002).

Stuss (2007) has proposed dividing the prefrontal cortex into lateral and ventromedial regions. According to this nomenclature, these regions subserve four somewhat overlapping functions. The first, *executive cognitive*, involves the control and direction of more basic automatic functions. The functions of this unit include the ability to plan behavior, monitor the outcome of behaviors, and switch behaviors when necessary. Impairments in these behaviors are typically seen following lesions to the lateral prefrontal cortex. The second functional unit, *behavioral-emotional self-regulatory*, which is subserved largely by the ventromedial prefrontal cortex, are behaviors invoked when an adaptive response is required in a novel situation but when habitual ways of responding are not appropriate or environmental cues and cognitive processing of the situation are inadequate in arriving at the most adaptive response. This region processes emotional information as they are related to rewards, which aids in higher level decision making. *Energization regulating*, the third function, involves the ability to generate and maintain both cognitive and behavioral actions. Deficits in this ability result in the syndromes of abulia and apathy in which the individual is unable to sustain behaviors. Moreover, this function is seen as providing energy for the other frontal functions to operate. Lastly, *metacognitive* processes involve self-awareness, aspects of personality, and social cognition.

The use of neuropsychological tests to measure frontal lobe functions is notoriously difficult due, in part, to the fact that these abilities are typically invoked in novel problem-solving situations (Kramer & Quitania, 2007). Moreover, most neuropsychological tasks are multifaceted in terms of the component skills necessary to successfully complete the task. As a result, lesions of a diffuse nature can result in impairments on “frontal lobe” tasks. Additionally, given the abundant connections of prefrontal cortex to various neural circuits a lesion to any non-frontal area can also result in deficits on executive measures (Tekin & Cummings, 2002). There are many tasks utilized in research on the prefrontal cortex and many of these clinical measures began their life in laboratory settings only to find their way into clinical situations. While most of these measures likely tap more than one aspect of executive functioning, it is believed that certain measures may be more selective for specific executive domains. Fernandez-Serrano et al., (2011) provides a summary of the various measures used to assess each executive domain.

3. Alcohol

3.1 Executive dysfunction and vulnerability to alcohol dependence

Genetics have clearly emerged as a risk factor for developing alcoholism and some research suggests genetic polymorphism related to impulsivity may play a role in this vulnerability, yet research in this area remains equivocal (Verdejo-Garcia et al., 2008). Moreover, the genetic vulnerability for alcoholism does not appear to be alcohol-specific, but represents a general vulnerability toward sociopathy, impulsivity, and substance abuse and dependence, complicating causal attributions (Kendler et al., 2003). It remains difficult to delineate whether impairment in executive abilities among alcoholics results from a genetic vulnerability, alcohol use itself, or a combination of these factors. Some studies report the offspring of alcoholics who do not themselves abuse alcohol at the time of testing show evidence of executive dysfunction, suggesting vulnerability may pre-date use induced impairment (Lovallo et al., 2006; Sher et al., 1991). Other research suggests that a family history of alcoholism and adolescent substance use represent unique risk factors for poor neuropsychological functioning during adolescence (Tapert & Brown, 2000).

Longitudinal studies are emphasized in the section below because they consider the variability in maturation of executive abilities across time. The relationship between cortical development during adolescence and alcohol dependence have been reviewed extensively elsewhere (Brown et al., 2008, Crews et al., 2007) and underscore the importance of neural development of executive functions and alcohol exposure during adolescence as a risk factor for alcoholism. Corral et al. (2003) compared neuropsychological test results between young children with a high-density of alcoholism within their families to those with no family history. Testing was conducted when participants averaged 11 years of age and then again 3.5 years later. Performance across time on a digit span procedure was shown to increase in those with a high-density of familial alcoholism until it was comparable to those in the control group. Performance on the Wisconsin Card Sorting Test among high-density children did not show the same degree of improvement over time compared to controls.

Other studies have examined executive abilities, family history, and antisocial behaviour as predictive factors in the development of alcohol dependence. Nigg et al., (2004) employed the longitudinal approach to examine the executive functioning of boys who varied in familial risk for alcoholism and antisocial behaviour. Participants were followed between 3 and 14 years of age. Executive dysfunction (response inhibition, response speed, and symbol-digit modalities) was greatest among those with a family history of alcoholism who did not possess antisocial comorbidity. However, the relationship between executive dysfunction, antisocial behaviour, and substance abuse remains to be clarified. Nigg et al., (2006) study of individuals tested repeatedly across early and late adolescence (15-17 years of age) found that poor response inhibition predicted combined alcohol related problems, number of illicit drugs used, and comorbid alcohol and drug use. In contrast to their previous results, these findings were independent of both familial alcohol history and antisocial personality disorder, leading them to stress that alterations in response inhibition across time may be an important variable in the development of drug and alcohol related problems.

Brain imaging studies have also implicated executive dysfunction in the development of alcoholism. Functional Magnetic Resonance Imaging applied during performance of a visual oddball task to reveal bilateral attenuated activity among male sons of male alcoholics in the inferior parietal lobule and inferior frontal gyrus, suggesting dysfunction within the frontoparietal circuitry is linked to working memory (Rangaswamy et al., 2004). Deckel et al., (1995) examined young adult males and found that neuropsychological measures of executive function predicted the age of first drink, and scores on the Michigan Alcoholism Screening Test. Moreover, the age subjects reported their first drink and frequency of drinking to "get high" were associated with left-frontal slow alpha electroencephalograph activity. Similarly, Chanraud et al., (2007) reported the age of first drinking was linked with decreased gray matter volume in frontal cortex, cerebellum, and pons using Magnetic Resonance Imaging suggesting that these regions may be more vulnerable to the neurotoxic effects of alcohol during adolescence.

Two recent imaging studies further suggest that disruption of various regions of the prefrontal cortex and related executive abilities is antecedent to significant drug and alcohol exposure. Hill et al., (2009) used Magnetic Resonance Imaging to investigate orbitofrontal cortex anatomy among a sample of high-risk offspring from multiplex alcohol dependent

families (defined by the presence of a pair of adult alcoholic brothers) compared to controls lacking a family history of alcohol dependence. High-risk participants with decreased right/left orbitofrontal volumes and attenuated white matter ratios, which were associated with elevated scores on the Multidimensional Personality Questionnaire control scales, suggesting reduced white matter in the orbitofrontal cortex is related to increased impulsivity. In addition, Andrews et al., (2011) examined neural activation via Functional Magnetic Resonance Imaging during a monetary reward task sensitive to multiple components of addictive behaviour in individuals without past or present alcohol or substance abuse histories, but who differed in family history of alcoholism. Overall, the results suggest impulsivity and differential reward sensitivity are associated with a positive family history of alcoholism.

3.2 Impairment of executive function in alcohol dependence

Anatomical deficits and functional impairment in various regions of the prefrontal cortex and across multiple executive domains has been well documented in alcohol dependent individuals and has been extensively reviewed elsewhere (Lyvers, 2000; Sullivan & Pfefferbaum, 2005; Verdejo-Garcia et al., 2008). This section will highlight research that integrates neuroimaging and neuropsychological testing in the study of executive function and alcoholism. Chanraud et al., (2007) using Magnetic Resonance Imaging and voxel-based Morphometry found bilateral attenuation of gray matter was most pronounced within the dorsolateral prefrontal cortex among alcohol dependent individuals. Gray matter deficits correlated with decreased executive performance on the Trail Making Test-B, letter number sequencing subtest, and Wisconsin Card Sorting Test performance, but not scores on the Stroop Interference Test. Similarly, Akine et al., (2007) reported young alcohol dependent individuals showed reduced activation in the right dorsolateral prefrontal cortex, anterior cingulate, left pulvinar of the thalamus, and right striatum using Functional Magnetic Resonance Imaging during a modified False Recognition Task designed to engage frontal lobe activity, though performance on this task did not differ from controls. These results are consistent with several other reports linking reduced activity within the prefrontal cortex and performance on specific executive measures (Dao Castella et al., 1998; Noel et al., 2001).

3.3 Executive function, treatment, recovery and alcohol dependence

Several studies have investigated the role of executive function during short-term abstinence from alcohol. Noel et al., (2002) reported subjects who relapsed two months after completing an inpatient treatment program showed lower bilateral activity in the medial frontal gyrus and poorer performance on frontal lobe tasks compared to abstainers. Similarly, Bowden-Jones et al., (2005) observed recently detoxified alcoholics who were more impulsive according to the Barratt Impulsiveness Scale, sampled significantly more cards from bad decks on a gambling task, and consistently risked more points across all odds on a decision making task were more likely to relapse within 3 months compared to abstainers. These findings are bolstered by recent research using a combined cross sectional and longitudinal approach examining abstainers, resumers, (based on 12 month abstinence), and controls using an arterial spin labelling perfusion Magnetic Resonance Imaging. After 7 days of abstinence, resumers showed reduced frontal and parietal gray matter perfusion compared to controls and abstainers. When assessed at 35 days, resumers had significantly lower frontal perfusion than the other groups (Durazzo et

al., 2010). Overall, research suggests greater executive function and related activity in the prefrontal cortex may be central to maintaining short-term abstinence from alcohol.

Research examining the effects of chronic alcohol use on executive abilities and cortical function remains equivocal. Some studies suggest these deficits are deeply ingrained, long-lasting, and predispose individuals to continued problems (Mann et al., 1995; Fein et al., 1990). Other studies suggest there is significant potential for recovery of executive abilities during prolonged abstinence from alcohol dependence. Fein et al., (2006) reported a sample middle-aged, long-term alcoholics averaging 6.7 years of abstinence performed similarly to a sample of non-alcohol users on eight domains of neuropsychological abilities including frontal lobe tasks. In another longitudinal study, alcoholic men who had achieved abstinence for a month were repeatedly assessed using a battery of tests of executive function, motor function, and Magnetic Resonance Imaging. Abstainers showed increased improvement than relapsers on measures of delayed recall of drawings, visuospatial function, attention, gait, and balance. Shrinkage in 3rd ventricle was significantly correlated with improvement in nonverbal short-term memory in all participants (Sullivan et al., 2000).

A limitation of the literature described above is that these studies fail to identify and/or provide significant depth regarding the treatments that study participants received in order to achieve abstinence and therefore, little is known regarding whether specific therapeutic approaches may be more amenable than others to promoting executive abilities and abstinence. The results of research examining the effectiveness of treatment for alcohol addiction as a function of the degree of cognitive impairment are also mixed (Leber et al., 1985; Teichner et al. 2002). However, recent research suggests activating cortical circuitry related to executive functions or strengthening executive abilities themselves may be advantageous in treatment. Boggio et al., (2008) reported transcranial direct current stimulation of the dorsolateral prefrontal cortex was able to reduce cue-induced craving for alcohol compared to sham stimulation in a sample of recently abstinent alcoholics. Problem drinkers who received working memory training over 25 days were found to both improve working memory and reduce alcohol consumption for more than a month post-training (Houben et al., 2011).

4. Psychostimulants

4.1 Executive dysfunction and vulnerability to psychostimulant dependence

Numerous genetic targets have been implicated in the vulnerability to develop psychostimulant addiction (Kreek et al., 2005). Among these targets, recent research suggests that gene/environment interactions may influence gray matter volumes within the prefrontal cortex. Alia-Klein et al., (2011) compared cocaine dependent men to controls using Magnetic Resonance Imaging and genotyping for Monoamine Oxidase A (MAOA) polymorphism. Cocaine addicted individuals possessed attenuation of gray matter volume in the orbitofrontal, dorsolateral, temporal cortex, and hippocampus. Reductions in the orbitofrontal cortex were solely related to genotyping and lifetime cocaine use. Decreases in the prefrontal cortex and hippocampus were associated with lifetime alcohol use beyond genotyping. Similarly, methamphetamine addicts may show a genetic vulnerability related to executive impairment, as prevalence of the dopamine receptor type 2 (DRD2)- Taq A1 allele and the number of perseverative errors on the Wisconsin Card Sorting Test was found to be increased in methamphetamine addicts compared to controls (Han et al., 2008).

High impulsivity has also been suggested as a predisposing factor for psychostimulant use. Elevated scores on self-report measures of impulsivity have been reported in young stimulant users (Leland & Paulus, 2005) and reports of impulsivity among cocaine dependent subjects were related to age of initial cocaine use (Moeller et al., 2002.) Psychological variables may also interact with impulsivity and other executive functions to increase vulnerability to psychostimulant dependence. It has been recently reported that childhood trauma was linked to executive dysfunction on the Wisconsin Card Sort test and impulsivity using the Barratt Impulsivity Scale in a sample seeking treatment for crack cocaine use (Narvaez et al., 2011).

Other research supports the role of cocaine exposure itself in executive impairment and cortical dysfunction. For example, Ersche et al., (2011), has shown anatomical changes in the orbitofrontal cortex, insular and striatal regions are related to the duration of cocaine dependence, inattention, and compulsivity of cocaine consumption. Makris et al., (2008) has reported thinner gray matter in the prefrontal cortex was linked to reduced judgement and decision making in a cocaine dependent sample, though some thickness differences were associated with cocaine use independent of nicotine and alcohol consumption leading these authors to suggest brain structure abnormalities in addicts trace their origin to drug use as well as toward a predisposition to drug addiction.

4.2 Impairment of executive function in psychostimulant dependence

Deficits across multiple domains of executive dysfunction have been reported among psychostimulant dependent populations (Camchong et al., 2011; Ersche et al., 2011; Henry et al., 2010; King et al., 2010; Kubler et al. 2005; Leland & Paulus, 2005; Verdejo-Garcia et al., 2008). Recent research suggests executive deficits in psychostimulant addicts revealed through the use of neuropsychological measures translate into deficits in everyday functional impairment, as methamphetamine dependent subjects reported greater impairment in measures of daily functioning and performed poorly on a measure of performance-based skills compared to controls (Henry et al., 2010).

These executive impairments among psychostimulant addicts are likely the result of anatomical and functional deficits within regions of the prefrontal cortex. Magnetic Resonance Imaging has revealed cocaine and methamphetamine dependent individuals possess reduced grey matter densities across multiple regions of the frontal cortex including the ventromedial orbitofrontal cortex, lateral orbitofrontal cortex, and cingulate cortex (Ersche, et al., 2011; Franklin et al., 2002). Functional imaging has also revealed reduced activity within the orbitofrontal regions of the prefrontal cortex among psychostimulant dependent populations (Volkow et al., 2001).

Studies assessing executive function concomitantly with functional imaging methods have revealed varying degrees of cortical and subcortical activation are linked to executive changes. Goldstein et al., (2002) reported metabolism in the orbitofrontal gyrus is correlated with aspects of behavioural control via a self-report measure in abstinent methamphetamine addicts. Kubler et al., (2005) demonstrated significant deficits on working memory and visuospatial performance in a cocaine dependent sample compared to controls. However, on a verbal task in which cocaine users and controls performed similarly, reduced activation within the prefrontal, cingulate cortices and striatal regions was observed among cocaine

dependent subjects. Recently, Camchong et al., (2011) showed cocaine addicts possess increased functional connectivity within the perigenual anterior cingulate network in the left medial frontal gyrus and middle temporal gyrus compared to control subjects. Abnormalities in functional connectivity were positively associated with task performance in delayed discounting and reversal learning in cocaine dependent subjects.

4.3 Executive function, treatment, recovery and psychostimulant dependence

Significant variability exists within the literature regarding the persistence of executive deficits (Chang et al., 2002; Hoffman et al., 2006) and structural and functional differences (Chang et al., 2002; Kim et al., 2005) during abstinence from psychostimulant dependence. While this literature generally supports the persistence of executive deficits within these samples, some research suggests gross deficits in executive function may be less durable (Fernandez-Serrano et al., 2011).

The majority of the research cited above involves cross sectional comparisons between abstinent psychostimulant addicts and non-using control subjects. Longitudinal studies of executive abilities are generally lacking and show disparate results. Di Sclafani et al., (2002) reported greater executive impairment in a sample of crack-cocaine dependent subjects compared to controls at 5-6 weeks of abstinence. After 6 months of abstinence these deficits were still present. In contrast, adolescents with a diagnosis of methamphetamine abuse or dependence who showed poor neuropsychological performance compared to controls demonstrated improvements on the PEG Board Test and forward digit span task that were related to the length of abstinence (King et al., 2010).

Few studies have examined executive abilities as a function of abstinence greater than a year. Selby & Azrin, (1998) found no significant improvement in neuropsychological function following 36 months of cocaine abstinence among incarcerated adult male felons with a history of cocaine dependence, however this was not surprising as these participants' neuropsychological performance was similar to matched control subjects. However, limited research suggests some improvement in executive abilities with prolonged abstinence. Toomey et al., (2003) examined neuropsychological function between 50 pairs of twins in which only one twin had a history of heavy stimulant abuse ending at least a year prior to assessment. Twins with a history of psychostimulant abuse performed poorly compared to those without a history of abuse on measures of attention and motor function, but better on a measure of visual vigilance. In addition, Salo et al., (2009) has demonstrated recently abstinent methamphetamine addicts show augmented stroop reaction time interference compared to control participants and compared to methamphetamine addicts who initiated abstinence more than a year prior to being assessed. Stroop reaction time interference was also positively correlated with the length of participants' abstinence suggesting that protracted psychostimulant abstinence may yield improvement in executive function.

Studies examining executive abilities among abstinent stimulant users often fail to report details of treatment that participants received in order achieve abstinence and therefore, little is known regarding the interaction between treatment modality, executive function and recovery from psychostimulant addiction. However, research employing Transcranial Magnetic Stimulation has linked decreased cocaine craving to activation of the dorsolateral prefrontal cortex (Camprodon et al., 2007).

5. Opiates

5.1 Executive dysfunction and vulnerability to opiate dependence

Several studies linking executive abilities and vulnerability to substance dependence have included opiate users (Najam et al., 1997; Tarter et al., 2003; Mezzich et al., 2007), however there are few studies specifically examining neurological functioning as a predictor of opiate dependence. Bauer et al., (1999) found that a family history of paternal opiate dependence was not related to P300 event related potentials during performance of the Stroop Task.

5.2 Impairment of executive function in opiate dependence

There is a relative lack of empirical studies examining deficits in executive function specific to opiate addicts (Feil et al., 2010, Gruber et al., 2007). However, a growing body of evidence has demonstrated impaired performance among opiate dependent subjects on executive measures including; the Stroop Task, Ruff Figural Fluency Test, Go/No go task, measures of impulsivity, gambling tasks, delay discounting tasks, attention, and working memory (Brand et al., 2008; Fishbein et al., 2007; Forman et al. 2004; Lee & Pau, 2002; Kirby & Petry, 2004; Mintzer & Stitzer, 2002; Ornstein et al., 2000; Rapeli et al., 2006; Pirastu et al., 2006). However, reports of executive deficits among opiate addicts are not universal (Ersche & Shikian, 2007; Pau et al., 2002), may be less significant than observed in psychostimulant addicts (Ersche & Shikian, 2007), and research suggests that some of deficits may be highly transient and reflect changes related to recent abstinence (Rapeli et al., 2006).

Studies have investigated structural deficits associated with chronic opiate use. Pezawas et al., (1998) using Computerized Tomography found that compared to controls opiate dependent individuals showed significant cortical volume loss and that this loss in the frontal cortex was associated with a shorter period of abstinence before relapse. Lyoo et al., (2006) using Magnetic Resonance Imaging and voxel-based morphometry found reduced gray matter density in the bilateral prefrontal cortex and several other regions in opiate dependent subjects compared to controls. Using similar imaging methods, Liu et al., (2009) reported gray matter reductions in the right prefrontal cortex, left supplementary motor cortex, and bilateral cingulate cortex among opiate addicts.

Functional imaging research also implicates hypofrontality and executive impairment as a consequence of chronic opiate use. Forman et al., (2004) using event-related Functional Magnetic Resonance Imaging in individuals performing the Go/No go task found that relative to controls, opiate dependent subjects had reduced anterior cingulate error signal activation and poorer task performance. Using Functional Magnetic Resonance Imaging while heroin dependent subjects and controls performed the Arrow Task (which assesses cognitive regulation and impulsivity) it was found that heroin addicts had greater impulsivity and performed more errors. Neural activation of heroin dependent subjects was attenuated in the anterior cingulate cortex and augmented in the left dorsolateral prefrontal cortex, bilateral inferior parietal, and left medial temporal regions relative to controls (Lee et al., 2005). Another study combining Positron Emission Tomography with performance on the Cambridge Risk Task revealed heroin dependent subjects had significant under-activation in the lateral orbitofrontal region compared to controls and that abnormal task related activation was correlated with duration of intravenous heroin use. Being conservative following loss of points on the task was negatively associated with activation of the pregenual anterior cingulate and insula cortex in controls, but not opiate users (Ersche et al., 2006).

5.3 Executive function, treatment, recovery and opiate dependence

Abstinence from opiate dependence has been linked to persisting executive and cortical deficits. Fu et al., (2008) used functional Magnetic Resonance Imaging to examine the neural mechanisms of response inhibition while abstinent heroin addicts performed the Go/no go Task. Neural response inhibition in the anterior cingulate cortex, medial prefrontal, and inferior frontal lobe activity was linked to response inhibition and competition on the behavioural measure. Moreover, heroin dependent subjects showed impaired response inhibition that persisted several months into abstinence. These results are further supported by studies reporting heroin addicts who had been abstinent for between 3 and 18 months performed more poorly than controls on the Porteus Maze Test of impulse control (Lee & Pau., 2002) and significant deficits in episodic memory and impulsivity following three months of abstinence (Prosser et al., 2006). Other studies support executive impairment lasting as long as a year into abstinence in verbal fluency (Davis et al., 2001) and impulsivity but not attention, mental flexibility and abstract reasoning (Pau et al., 2002).

Research has also investigated the extent to which executive function changes in response to treatment and is predictive of clinical outcome. Passetti et al., (2008) found that performance on two measures of decision making (Cambridge Gambling Task and Iowa Gambling Task), but not on measures of planning, motor inhibition, reflection impulsivity or delay discounting were predictive of abstinence from illicit drug use at 3 months in opiate dependent subjects following 6 weeks of community drug treatment. Similarly, Gruber et al., (2006) examined subjects upon entering methadone maintenance therapy and again following two months of treatment. Improvements in verbal learning and memory, visuospatial memory, psychomotor performance, and decreased frequency of drug use were observed compared to baseline.

In an unpublished study from our lab changes in executive function on a battery of neuropsychological tests administered an average of 47 days post-admission and then again 90 days later among 16 heroin dependent individuals undergoing Methadone Maintenance Therapy were investigated. At the time of initial testing, participants showed significant deficits in the: Stroop Color Word Test, Porteus Mazes Test, and a trend toward poorer performance on the Wisconsin Card Sorting Test compared to the normative population. Methadone maintained clients showed significant improvement in Figural Fluency Test and the Stroop Interference Score between the two test times. Six family members of the Methadone maintained participants completed the Frontal Systems Behavioral Scale and reported significantly greater levels of disinhibition and a trend towards increased apathy among study participants. Family members also reported a trend towards improvement in apathy and executive function across the three months of Methadone Maintenance Therapy. In addition, Stroop Interference Scores at both time points were predictive of opiate abstinence. Stroop Interference Scores after 4 months of treatment were also predictive of cocaine and opiate abstinence. Participants who were opiate negative after 4 months showed improved performance on the Stroop Interference Test while those testing positive for opiates did not show improvement across time. While caution is warranted when interpreting these results due to the small sample size, these results are consistent with a growing literature that suggests recovery from opiate addiction is accompanied by improved executive abilities and may be predictive of clinical outcomes. (Meil et al., 2008).

6. Nicotine

6.1 Executive dysfunction and vulnerability in nicotine dependence

There is a lack of research directly examining executive dysfunction as a predictive factor in the development of nicotine dependence. However, childhood attention problems were shown to be a significant predictor of adult smoking (Kahalley et al., 2010). In addition, impairment in working memory has been shown to be related to an earlier age of onset of smoking. Further, male smokers initiated smoking at an earlier age and were more impaired during tests of attention than female smokers and non-smokers, leading these authors to suggest that neurotoxic effects of nicotine are more severe when use occurs earlier (Jacobsen et al., 2005). Research has also begun to link impulsivity to the development of nicotine dependence in adolescent smokers (Chase & Hogarth, 2011).

6.2 Impairment of executive function in nicotine dependence

Until recently, executive dysfunction associated with nicotine dependence has received relatively little attention. Impairment in nicotine dependent populations has been documented in specific aspects of executive function such as working memory, cognitive flexibility, emotion regulation, and inhibitory control (Billieux et al., 2010; Jacobsen et al., 2005; Kahalley et al., 2010; Razani et al., 2004). In addition, Spinella (2003) found self-reported scores on the apathy, disinhibition, and executive dysfunction subscales of the Frontal Systems Behavioral Scale were related to nicotine dependence.

Limited imaging studies have also examined deficits in prefrontal cortical function in nicotine dependent individuals. Cigarette smokers showed smaller gray matter volumes and lower gray matter densities than nonsmokers in the prefrontal cortex, along with smaller volumes in the left dorsal anterior cingulate cortex and lower gray matter densities in the right cerebellum (Brody et al., 2004). Gallin et al., (2006) reported decreases in grey matter volume and lower grey matter density were observed in smokers in the frontal regions which were inversely associated with the magnitude of lifetime exposure to tobacco smoke. Research also finds increased activation of frontal regions associated with inhibitory control (such as the left orbitofrontal cortex and dorsolateral prefrontal cortex) in response to smoking related cues, suggesting the importance of these regions in resisting the urge to smoke (Brody et al., 2002).

6.3 Executive function, treatment, recovery in nicotine dependence

Studies also found evidence of persistent deficits amongst former smokers over varying periods of abstinence. Neuhaus et al., (2006) revealed persistent fronto-striatal dysfunction in former smokers despite a mean of 11 years of abstinence from cigarette smoking. In addition to other functional differences, they reported decreased cortical activation in orbitofrontal and left dorsolateral prefrontal regions amongst previous smokers when completing an auditory oddball task. These results are grossly consistent with Dawkins et al., (2009) who found no evidence of improvement on a measure of attentional bias in a small group of successful quitters over a period of three months. The successful quitters also showed no improvement on two different indices of response inhibition.

Limited research has also investigated executive function and treatment outcomes for nicotine dependence. Brega et al., (2008) reported participants' scores on the Behavioral Dyscontrol Scale was a significant predictor of whether they had achieved abstinence. Moreover, research employing brain stimulation of the dorsolateral prefrontal cortex in nicotine dependent subjects suggests this procedure may be effective in combatting nicotine dependence and further implicates executive abilities in the recovery process (Eichhammer et al., 2003).

7. Polysubstance dependence

7.1 Executive dysfunction and vulnerability in polysubstance dependence

The genetic predisposition for drug addiction may involve impulsivity (Kreek et al., 2005). Self-reported impulsivity has been recently shown to be a predictor of current and future substance use in a 3 year longitudinal study of adolescents (Krank et al., 2011). Broader aspects of executive function have also been linked to the familial factors in the development of drug addiction. Najam et al., (1997) administered children with a high and low risk for drug abuse, based on a history of paternal diagnosis, a battery of neuropsychological tests at 10-12 years of age and a drug use measure two years later. Poorer executive function performance on the Stroop task, Memory Scan, Motor restraint, and the Wechsler Intelligence Scale for Children III, was significantly associated with subsequent substance abuse. Executive cognitive functioning discriminated between children who were at high and low risk of abuse based on familial history.

A series of longitudinal studies by Tarter and colleagues have suggested that Neurobehavioral disinhibition, a construct combining affective, behavioural, and cognitive indicators of self-regulation, is a significant predictor of substance dependence between childhood and young adulthood (Kirisci et al., 2006; Mezzich et al., 2007; Tarter et al., 2003). For example, Mezzich et al., (2007) reported that neurobehavioral disinhibition in boys, measured at age 10-12 and again at age 16 significantly predicted substance use disorders by age 19. Included in their measure of neurobehavioral disinhibition are several common test of executive function including Stroop test, Porteus Maze Test, Vigilance Test, Forbidden Toys Test, Block Design Test, and Motor Restraint Test. The executive functioning component of this composite accounted for 30% of the variance at each time point, implicating it as a major component of this trait, though it should be noted that many consider other aspects of neurobehavioral disinhibition (e.g., aspects of self-regulation) as falling under the executive function umbrella. In addition, Functional Magnetic Resonance Imaging has revealed that scores on the neurobehavioral disinhibition trait are negatively correlated with frontal cortical activation (McNamee et al., 2008). It has also been suggested that drug use itself may be related to the development of executive impairment among drug addicts as Verdejo-Garcia et al., (2006) reported that the severity of use was predictive of executive deficits in a sample of poly-substance abusers. Specifically, the severity of cannabis use predicted apathy and executive dysfunction and the severity of cocaine use was predictive of greater behavioural disinhibition.

7.2 Impairment of executive function in polysubstance dependence

A recent review comparing the specific and generalized effects of abused substances on neuropsychological performance by Fernandez-Serrano et al., (2011) concluded that drugs of

abuse are commonly associated with significant impairment in multiple neuropsychological domains including episodic memory, emotional processing, including updating and decision making. However, some drugs were linked to greater impairment of certain neuropsychological abilities such as enhanced effects of alcohol and psychostimulants on impulsivity and cognitive flexibility compared to other drugs. Individual studies in which polysubstance dependent subjects are compared to controls support the idea that polysubstance dependence produces significant executive impairment (Cunha et al., 2010). Studies directly comparing neuropsychological profiles between individuals dependent on different drugs suggest widespread executive deficits, but that distinct patterns of deficits may be observed between drugs (Ershe & Sahakian, 2007; Ornstein et al., 2000). Neural imaging studies also support the idea that polysubstance use yields deficits in prefrontal cortical gray matter volume (Liu et al., 1998).

7.3 Executive function, treatment, recovery and in polysubstance dependence

Research regarding the longevity of executive deficits among polysubstance user suggests impairment may persist at least up to a year (Grant et al., 1978). Fernandez-Serrano et al., (2010) recently reported that polysubstance dependent individuals enrolled in therapeutic communities averaging 24 weeks of abstinence showed substantial deficits on multiple measures of executive function including measures of working memory, fluency, shifting, planning, multi-tasking, and interference. A second study by this author also found widespread executive impairment in a population of abstinent polysubstance abusers following an average of 32 weeks of abstinence (Fernandez-Serrano et al., 2010). A recent long-term longitudinal study by Hanson et al., (2011) examined adolescents with and without alcohol and substance dependence, who were tested repeatedly for neuropsychological performance for 10 years. Ninety-four percent of substance dependent participants met criteria for alcohol dependence and dependence on at least one other drug. At baseline and subsequently, controls performed better on neuropsychological measures than substance dependent participants. Heavy use patterns over time were associated with impaired neuropsychological functioning on measures of verbal learning and memory, visuospatial memory and verbal/attention/working memory. In addition, participants who discontinued alcohol and drug use during this period showed improvement in cognitive function.

Studies investigating the effectiveness of treatment among abstinent polysubstance dependent subjects suggest the degree of neuropsychological deficits may be important in determining clinical outcomes. Fals-Stewart and Schafer, (1992) reported that in substance abusers admitted to a therapeutic community, performance on the Digit Symbol and Block Design Subtests of the Wechsler Adult Intelligence Scale were predictive of time in treatment. In another study, the decision to stop drug use following a prevention intervention during adolescence was predicted by the severity of childhood neurobehavioral disinhibition (Kirisci et al., 2006).

8. Conclusion

This chapter is unique compared to other papers reviewing the relationship between anatomical and functional changes in the prefrontal cortex, executive abilities, and substance

dependence (Feil et al., 2010; Goldstein & Volkow, 2002; Fernandez-Serrano et al., 2011; Schoenbaum et al., 2006). This chapter emphasizes the breadth of this topic by describing this relationship across multiple classes of drugs and polysubstance dependence. In addition, it examines this relationship across the vulnerability to develop substance dependence, the impairment observed among addicts, and the persistence and recovery of executive functions during abstinence and as a function of treatment.

Several conclusions can be drawn from this literature review. Pre-existing variability in executive function and the effects of drug use itself are among the variables which influence an individual's risk of developing substance dependence. A significant body of literature shows that substance dependent individuals are impaired across multiple domains of executive functioning, and possess decreased grey matter and impaired activity within the prefrontal cortex. Moreover, multiple studies combining brain imaging and neuropsychological measures link impairment of performance on tests of executive function with anatomical and functional impairments of the prefrontal cortex. The persistence of executive deficits across time is highly variable, however research suggests that following short-term and long-term abstinence many individuals show recovery of executive functions which appears to be related to their ability to maintain abstinence across time. A growing body of research suggests specific treatments focused on augmenting activity within the prefrontal cortex or strengthening executive abilities may represent viable treatment approaches. While some differences in impairment of executive abilities have been observed across drugs, there are remarkable similarities in the executive deficits observed among drug addicts.

There are several limitations of this review. The purpose of this chapter is to illustrate the role of executive dysfunction in substance dependence, however it does not represent an exhaustive review of this topic. The research described here illustrates the major findings of studies in this area but does not emphasize results that were not consistent with the premise of this review. Based on this review it is evident that specific areas of the prefrontal cortex appear to show a greater degree of impairment than others (orbitofrontal, anterior cingulate, and dorsolateral regions) and that substance dependent populations appear to show greater deficits on certain executive domains (response inhibition, impulsivity, working memory); this chapter did not systematically evaluate these differences. This review focussed on the role of prefrontal cortical regions and executive dysfunction in addiction. Regions of the prefrontal cortex have also been implicated in other addiction related processes including craving, reward, and withdrawal (Goldstein & Volkow, 2002), however, a broader neural circuitry and associated behavioral dysregulation is likely involved in drug dependence.

The typical definition of a "disease" emphasizes that it involves abnormal structure and function of the body (Leshner, 1997). This chapter argues that according to this broad conceptualization, substance dependence should be considered a disease given its association with deficits in cortical function and related executive abilities. Addiction also shows several similarities with other chronic conditions considered diseases, such as a similar vulnerability toward relapse (Leshner, 1997). While these deficits are not unique to drug addiction (Rogers et al., 1999), in combination with compulsive drug use and other neurobiological markers this body of research strengthens the argument for defining addiction as a disease.

9. References

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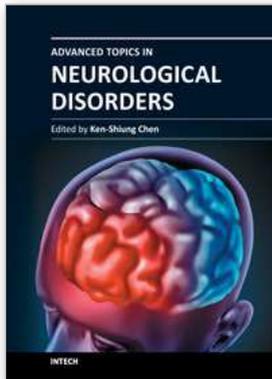
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Advanced Topics in Neurological Disorders

Edited by Dr Ken-Shiung Chen

ISBN 978-953-51-0303-5

Hard cover, 242 pages

Publisher InTech

Published online 16, March, 2012

Published in print edition March, 2012

This book presents recent advances in the field of Neurological disorders research. It consists of 9 chapters encompassing a wide range of areas including bioengineering, stem cell transplantation, gene therapy, proteomic analysis, alternative treatment and neuropsychiatry analysis. It highlights the development of multiple discipline approaches in neurological researches. The book brings together leading researchers in neurological disorders and it presents an essential reference for researchers working in the neurological disorders, as well as for students and industrial users who are interested in current developments in neurological researches.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

William Meil, David LaPorte and Peter Stewart (2012). Substance Dependence as a Neurological Disorder, *Advanced Topics in Neurological Disorders*, Dr Ken-Shiung Chen (Ed.), ISBN: 978-953-51-0303-5, InTech, Available from: <http://www.intechopen.com/books/advanced-topics-in-neurological-disorders/substance-dependence-as-a-neurological-disorder>

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