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The Brain-Behavioral Connection in Substance Use Disorders and Effects Associated with Injectable Opioid Prescription

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I. THEORETICAL SECTION

1 Introduction

Substance use disorders (SUD), especially the compulsive state of substance use – commonly known as 'addiction' and clinically defined as substance dependence – have become a subject of great interest not only among clinicians and researchers but also in the media and the public. Once attributed to everything from imbalances in bodily humors to failure of morals, character defect or weakness of willpower (London, 2005; Saunders, 2006) substance dependence, on the basis of accumulated scientific evidence, is nowadays understood to be a chronic brain disorder characterized by overwhelming drug cravings and relapses, despite the awareness of negative consequences (Leshner, 1997; Wise, 2002).

1.1 Moralism impedes appropriate SUD treatment

However, the concept of moral failure or character flaws is by no means absent from the discussion of SUD (Hyman, 2007), as evidenced by Switzerland's investment in criminal justice rather than treatment, including the denial of invalidity pension for substance-dependent patients, following a court ruling that compulsive substance use is 'willful misconduct', not a disease. Ironically, this political denial continues at a time when our understanding of the neurobiology of compulsive substance use offers new treatment options for SUD. The ignorance of scientific data and the bias against compulsive substance users, however, is highlighted most vividly by claims of conservative politicians, and widespread policies of health care professionals (e.g. limitation of treatment places and treatment duration, waiting lists, visiting restrictions, disciplinary sanctions or treatment cessation in case of relapse or other SUD-related behaviors), implying that SUD are simply bad habits or moral weakness which need corrective measures.

In most areas of medicine, pharmacological interventions which make patients feel better are desirable – but this is often not the case in SUD. Despite the weight of scientific evidence many treatment providers, for instance, persist in refusing to offer heroin-dependent patients high-dose, indefinite methadone maintenance (Caplehorn et al., 1998; Magura & Rosenblum, 2001; O'Connor, 2000; Pollack & D'Aunno, 2008). Others have been complicating access to treatment supposing this may constitute a sort of motivation test (Novick & Kreek, 2008; Vignau et al., 2001) even though many studies have failed to show any kind of association of readiness to change with treatment outcome (West, 2005) as postulated by the transtheoretical model of change (DiClemente & Prochaska, 1982). Moreover, one of the most widely accepted drugs in the treatment of alcohol dependence is disulfiram (Antabus®), which can induce severe and even life-threatening complications, or – at least – may make patients who drink while taking it wish they were dead (Fuller & Gordis, 2004; Suh et al., 2006). This medication, which relies on psychological threat to avoid the disulfiram-ethanol reactions, has been on the market for alcoholism treatment since 1951 (Suh et al., 2006). However, it does not substantially improve recovery rates since 'poorly motivated' alcohol-dependent patients stop taking it if they crave alcohol (Fuller & Gordis, 2004; Garbutt et al., 1999; Mann, 2004; Suh et al., 2006). As a consequence, many researchers and clinicians have turned to supervised ingestion of disulfiram to improve treatment outcome (Fuller & Gordis, 2004; Suh et al., 2006). While such a shift may increase the response rates in certain subgroups of alcohol-dependent patients there are other medications available with proven effectiveness but without any aversive or 'punishing' effects. Such examples of common practice suggest that the greatest difficulty in the field of SUD treatment is the misunderstanding of compulsive substance use and the unawareness of the underlying moralism that pervades this view.

1.2 Neuroscience challenges common-sense conceptions of SUD

The brain-based conception of substance dependence calls into question folk-psychological views on the voluntary control of behavior, assuming for the

most part, that we regulate our actions based on 'conscious' reasons (Haggard, 2005; Libet, 1999; Wegner, 2003a). However, even in health matters, critical processes that intervene between sensory inputs to the brain and the execution of actions, including processes that permit 'top-down' or 'cognitive' control of behavior, do not appear to depend upon conscious exertion of will (Roth, 2001; Wegner, 2003b). A profoundly influential series of experiments by Libet and co-workers (Libet, 1965, 1982; Libet et al., 1983a; Libet et al., 1982, 1983b) suggests that conscious intention arises as a result of brain activity. In their now classical study on conscious awareness of voluntary motor actions, Libet et al. (1983b) have shown that electrical brain activity, the so-called readiness potential, precedes the conscious awareness of intention to act by around 350–400 milliseconds. This finding introduces the idea that there are certain constraints on the potentiality for conscious generation and control of voluntary behavior, contrasting with traditional concepts of free will in which the mind is ahead of the brain (Haggard et al., 2002). The work of Libet and colleagues has since been replicated and improved by others (Haggard & Eimer, 1999; Maidhof et al., 2009; Sirigu et al., 2004; Soon et al., 2008). Haggard & Eimer (1999), for example, have further examined the relation between neural events and the perceived time of voluntary motor actions, or the perceived time of initiating those actions, concluding that conscious awareness of intention is linked to the choice or selection of a specific action, and not to the earliest initiation of action processes. Recent findings obtained by Soon et al. (2008) go substantially further than those of previous studies. Using functional magnetic brain imaging, Soon et al. (2008) have shown that the earliest predictive information of a motor decision is encoded in specific regions of the prefrontal and parietal cortex up to 10 seconds before it enters awareness. This preparatory time period in high-level control regions is much longer than that reported for lower-level motor-related brain regions (Haggard & Eimer, 1999; Libet et al., 1983a).

Neurobiological research findings thus cast reasonable doubt on whether conscious processes cause actions. The data, however, may remain compatible with the idea that conscious processes might nonetheless exert some effect over actions by modifying the brain process already in progress (Libet & Haggard, 2001). The fact that conscious awareness of intention precedes the action by several hundred milliseconds means that a person could still inhibit cer-

tain actions from being made. Or as Libet (1999) puts it: "The volitional process is therefore initiated unconsciously. But the conscious function could still control the outcome: it can veto the act" (p. 47). One might call it 'free won't' as opposed to 'free will'. A recent study (Brass & Haggard, 2007) has strongly illuminated this very important aspect of cognitive control: the ability to hold off doing something after we have already developed the intention to do it. The capacity to withhold an action that we have prepared but reconsidered is viewed as a crucial distinction between intelligence and impulsive behavior. Brass & Haggard (2007) have shown that the area of the brain responsible for self-control, where the decision not to do something, i.e. 'to veto the act', is separate from the area involved in taking the action. Moreover, their data not only identify a brain basis for inhibiting intentions, thus providing a potential neural correlate of the decision to do or not to do (i.e. 'veto the act'), but they also indicate that the initiation of inhibition may be unconscious; this conflicts with Libet's concept of 'free won't'. Hence, compulsive substance use in which the core symptoms reflect changes in the underlying neural systems, such as alterations in incentive-motivational processes, in impulse control or in decision making, challenges common-sense concepts of cognitive behavior control profoundly (Hyman, 2007; Kalivas & Volkow, 2005; Montague et al., 2004; Patrick, 2007).

The neuroscientific view of compulsive substance use further calls into question the popular theory of Cartesian dualism in which mind is conceptualized as a distinct, non-physical entity separate from material, which is not spatially extended and not subject to causal laws. This dualistic approach to the mind/body problem clearly stands in contrast to the view of the American Psychiatric Association (2000), which explicitly rejects the notion of a division between mind and body in its definition of mental disorder: "[T]he term *mental disorder* unfortunately implies a distinction between 'mental' disorders and 'physical' disorders that is a reductionistic anachronism of mind/body dualism. A compelling literature documents that there is much 'physical' in 'mental' disorders and much 'mental' in 'physical' disorders" (p. xxx). Unfortunately, the current edition of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2000), better known as DSM-IV, specifies no framework for conceptualizing interactions among cognitive, emotional, and behavioral processes in mental disorders.

1.3 The conceptualization of SUD

The concepts of SUD and the terminology used in this work require some comment. SUD represent a diagnostic subgroup in which the two internationally accepted classification systems of mental disorders, the International Classification of Diseases (ICD) of the World Health Organization (1992) and the DSM-IV of the American Psychiatric Association (2000), agree in most generalities and many particulars (Jaffe, 1995; Rounsaville, 2002; Saunders, 2006).

Both systems are based on the 'alcohol dependence syndrome' construct by Edwards and Gross (1976) which was later broadened to include other substances producing the 'drug dependence syndrome' (Edwards, 1986; Edwards et al., 1981). Edwards et al. (1981) thereby define syndrome as a "[…] clustering of phenomena so that not all components need always be present, or not always present with the same intensity" (p. 230). The dependence syndrome theory of Edwards (1986) poses three testable propositions: (1) the syndrome elements representing neuroadaptation, behavioral conditioning and cognitive schema comprise a coherent unidimensional syndrome, (2) the syndrome is relatively independent of, or even uncorrelated to medical, psychological, legal or social consequences of substance use, and (3) the syndrome is arrayed along a continuum of severity and is not a categorical or bimodal construct. The clinical guidelines of ICD-10 and DSM-IV encompass the dependence syndrome construct in two ways (see Table 1 and 2). First, both classification systems include a 'dependence' diagnosis that consists of a virtually similar subset of clinical phenomena taken from the original syndrome. In DSM-IV, however, the word 'syndrome' is not added to the diagnostic terms.

Table 1. Substance dependence criteria according to DSM-IV

A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by three or more of the following, occurring any time in the same 12-month period:	
1) a) b)	tolerance, as defined by either of the following: a need for markedly increased amounts of the substance to achieve intoxication or the desired effect; markedly diminished effect with continued use of the same amount of the substance;
2) a) b)	withdrawal, as manifested by either of the following: the characteristic withdrawal syndrome for the substance; the same (or closely related) substance is taken to relieve or avoid withdrawal symptoms;
3)	the substance is often taken in larger amounts or over a longer period than intended;
4)	there is a persistent desire or unsuccessful efforts to cut down or control substance use;
5)	a great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), using the substance (e.g., chain smoking), or recovering from its effects;
6)	important social, occupational, or recreational activities are given up or reduced because of substance use;
7)	continued substance use despite knowing that a persistent physical or psychological problem is likely to have been caused by, or will be exacerbated by the substance (for example, current cocaine use despite recognition of cocaine-related depression or continued drinking despite recognition that an ulcer was made worse by alcohol consumption).

Only one component differs substantially across the two systems: ICD-10, but not DSM-IV, specifically mentions the condition "a strong desire or sense of compulsion to take the substance" (Hasin et al., 2006; World Health Organization, 1992, p. 75). In addition, DSM-IV puts more weight on the concepts of 'preoccupation' (time spent, give up or reduce alternative pleasures or interests) and 'impaired control' (use more, cut down) by including two criteria

representing these elements where ICD-10 integrates these pairs into a single feature (Rounsaville, 2002). However, the ICD-10 and DSM-IV dependence diagnoses are both psychometrically robust with strong reliability and validity evidence despite small differences in formulations between the two systems (Hasin et al., 2006; Rounsaville, 2002; Saunders, 2006).

Table 2. Criteria for dependence syndrome in the ICD-10 guidelines

A definite diagnosis of dependence should usually be made only if three or more of the following have been present together at some time during the previous year:	
1)	a strong desire or sense of compulsion to take the substance;
2)	difficulties in controlling substance-taking behaviour in terms of its onset, termination, or levels of use;
3)	a physiological withdrawal state when substance use has ceased or been reduced, as evidenced by the characteristic withdrawal syndrome for the substance; or the use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms;
4)	evidence of tolerance: requiring increased doses of the psychoactive substances in order to achieve effects originally produced by lower doses (clear examples of this are found in alcohol- and opiate-dependent individuals who may take daily doses sufficient to incapacitate or kill nontolerant users);
5)	progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain or consume the substance, or to recover from its effects;
6)	persisting in substance use despite clear evidence of overtly harmful consequences, such as harm to the liver through excessive drinking, depressive mood states consequent to periods of heavy substance use, or drug-related impairment of cognitive functioning; (here, efforts should be made to determine what the user was actually, or could be expected to be aware of regarding the nature and extent of the harm).

Both diagnostic systems further contain a separate diagnosis based on the consequences of substance use, when criteria for dependence are not met. In ICD-10, the category 'harmful use' is defined by clear-cut medical or psy-

chological consequences of substance use in the absence of dependence. In contrast, the DSM-IV diagnosis 'abuse' puts particular emphasis on social and legal consequences in the absence of dependence. Accordingly, both systems include the second concept of the dependence syndrome construct – the orthogonal nature of dependence and consequences. However, the ICD-10 guidelines differ considerably from the DSM-IV criteria (Rounsaville, 2002; Saunders, 2006); 'harmful use' and 'abuse' thus do not represent identical disorders (Jaffe, 1995; Maddux & Desmon, 2000). This is critical for several reasons and should be addressed when developing future editions of ICD and DSM guidelines especially since reliability is rather low for both diagnoses, although better for abuse, which on the other hand has the disadvantage of being defined essentially by social criteria that are highly culture-dependent (Rounsaville, 2002; Saunders, 2006). For future revisions, dropping both separate diagnoses and integrating the constructs 'harmful use' and 'abuse' into the dependence diagnosis should be considered. In both ICD-10 and DSM-IV one of the dependence criteria already incorporates the concept of continued use despite harmful medical or psychological consequences. Meeting a lower number of diagnostic criteria could thus be specified as 'mild dependence'. This suggestion fits well with several factor-analytic studies, which, however, fail to show a clear orthogonal relationship between the criteria for harmful use/abuse and dependence (Feingold & Rounsaville, 1995; Fulkerson et al., 1999; Nelson et al., 1999). According to Rounsaville (2002, p. 87) arguments against such a move, however, point out the high severity diagnosis implied by being labeled 'dependent' on substances when only a few criteria are met.

1.4 Dependence or addiction?

Consistent with the third concept of Edwards' dependence syndrome (1986), there is agreement among most clinicians and researchers that different stages of severity exist ranging from occasional substance use to a more harmful, but moderately severe state called 'harmful use' (ICD-10) or 'abuse' (DSM-IV), to a severe and compulsive state known as 'dependence' or 'addiction'. There is disagreement, however, on the usefulness of the term 'addiction' to denote the compulsive state of substance use that occur only in the minority of users

who show an immoderate pattern of substance use with a chronic relapsing course despite harmful consequences. The DSM-III-Revision Committee in agreement with the recommendation of the WHO Expert Committee on Addiction-Producing Drugs (1964, later renamed as WHO Expert Committee on Drug Dependence) voted to substitute the term 'drug dependence' for the formerly used term 'addiction' because of its pejorative connotations but also because of its trivialisation (O'Brien et al., 2006). "'Addiction' is unscientific, overused, misunderstood (e.g. addicted to my cell-phone), and clinically inaccurate (e.g. addicting anti-depressants)" (Erickson & Wilcox, 2006, p. 2015). Or as Jaffe (1995) formulates it: "The words 'addict' and 'addiction' […] are frequently used to refer to ordinary activities, such as exercising and solving crossword puzzles" (p. 934). Most interestingly, Rippere (1978) has shown by means of semantic differential data from native English-speaking individuals that the connotations of the verbal concept 'drug dependence' are significantly less negative than those of 'drug addiction'. It thus appears that replacing the term 'addiction' by 'dependence' may have produced the desired shift toward less emotive discourse in the public.

The other point of view is that the term 'dependence' creates confusion because it is already used to designate the physiological state marked by substance-specific withdrawal symptoms that normally occur when regular substance use is suddenly ceased or too rapidly reduced. It has therefore been argued that addiction may more clearly suggest a neurobehavioral disorder than dependence does, and it is less likely to be confused with physical dependence (Maddux & Desmon, 2000; O'Brien et al., 2006). Indeed, most preclinical researchers define the dependence syndrome as 'addiction' to distinguish 'normal' physiological adaptations from compulsive substance use behaviors (Sanchis-Segura & Spanagel, 2006). However, the Expert Committee on Drug Dependence (1993) recommended against efforts to differentiate between 'physical dependence' and 'psychic dependence', because it felt that all substance effects on the individual are potentially understandable in neurobiological terms. Others again have argued that patients receiving opioids for chronic pain management often reveal signs of tolerance and withdrawal symptoms without presenting any behaviors that could be categorized as compulsive; thus, they would be stigmatized if they were diagnosed as dependent (Fainsinger et al., 2006; Portenoy & Payne, 1997). Further, clinicians

who are confused by dependence defined as a 'normal' physiological response and dependence as a disorder might mistakenly withhold pain medication to prevent opioid dependence: "Pain patients in need of opiate medications may forgo proper treatment because of the fear of dependence which is self-limiting by equating it with addiction" (O'Brien et al., 2006, pp. 764–65).

From a clinical point of view, however, these arguments lack a sound foundation. Many pain patients prescribed opioids over a longer period of time may indeed experience or exhibit signs of tolerance and withdrawal but they do not meet any of the other criteria necessary to fulfill the diagnosis of opioid dependence as listed in ICD-10 and DSM-IV; at least three within a 12-month period are required by both. Study findings indicate that only an extremely small percentage of patients treated with opioids for pain will actually become compulsive users (Edlund et al., 2007; Pletcher et al., 2006). Accordingly, the WHO Expert Committee on Cancer Pain Relief and Active Supportive Care (1996) points out that opioid dependence occurs rarely in cancer patients: "Consequently, the risk of [substance] dependence should not be a factor in deciding whether to use opioids to treat the cancer patient with pain" (p. 58). The WHO Expert Committee on Drug Dependence (1993) also noted the potential for confusion between the terms 'physical dependence' and 'substance dependence' and opted to use the term 'withdrawal syndrome' instead of 'physical dependence'. This is consequential because 'physical dependence' occurs not only with substances having reward potential, such as alcohol, benzodiazepines, and opioids, but also with those having little or no 'addictive' potential, such as tricyclic antidepressants, selective serotonin reuptake inhibitors, and alpha-2 adrenergic agonists (Erickson & Wilcox, 2006; Lader, 2007; van Geffen et al., 2005). Others have criticized the term 'dependence' as misleading since dependence also has a long-standing use as a personality disorder descriptor completely unrelated to substance use (O'Brien, 1996). However, personality disorders are used with the qualifier 'personality' to refer to the construct of personality disorders, which is completely distinct from DSM-IV Axis I disorders, such as SUD, major depression, or schizophrenia.

In this work, clinical terminology will be followed, despite the variance and inconsistency in the use of the terms 'dependence' and 'addiction' not only in the research field of SUD, but also in the clinical literature (Jaffe, 1995; Maddux & Desmon, 2000). The words 'addiction' and 'addictive' will generally

be avoided because until now they have no agreed definitions and only limited value in clinical settings (World Health Organization, 1994). These labels are used in this work only if they appear in a quotation or in a collocation and form a common expression, such as 'addictive potential' or 'addiction research'. Furthermore, the word 'misuse' instead of 'abuse' concerning non-medical substance use has been favored in this work, at least when not referring to the abuse concept in DSM-IV. Numerous journals (e.g. 'Substance Use and Misuse' or 'Child Abuse and Neglect') are now advising this change in terminology since 'abuse' in English refers to maltreatment of living creatures, such as 'child abuse' or 'animal abuse'. Here too, the implicit moralism that underlies most conceptualizations of SUD may have led to a labeling which implies that substance-misusing individuals would intentionally damage themselves and/or the society.

2 Brain-Behavioral Connections in SUD

Once thought to produce global, nonspecific brain injury, recent research clearly shows that substances prone to misuse produce selective neuroadaptations in particular brain regions (Kalivas et al., 2005; Nestler, 2004; Shaham & Hope, 2005; Volman, 2007; Weiss et al., 2001). During recent years, the increasing insight into neural and molecular mechanisms as well as brain region-specific neuronal changes connected with compulsive substance use has shed considerable light on substance-induced brain dysfunction, correlating with measurable changes in behavior (Baker et al., 2003; Chao & Nestler, 2004; Eisch & Harburg, 2006; Everitt et al., 2001; Self, 2004). It is far from clear, however, how continued substance use alters brain structure and function, and which neuromodulatory mechanisms and neural systems are responsible for compulsive behavior and its persistence (Everitt & Robbins, 2005; Hyman, 2005; Robinson et al., 2002). Thus, exactly what drives compulsive substance use and why abstinence can be so difficult to maintain for individuals who were previously dependent remains vague, even though a plethora of recent research has advanced understanding of the neurobiological factors involved

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