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Bridging the gap between the neurocognitive lab and the addiction clinic

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HIGHLIGHTS

- There been an increase in new insights in neurocognitive mechanisms of addiction.
- A beginning has been made to transfer these recent insights to clinical practice.
- Usefulness of these neurocognitive insights for diagnosis and treatment is discussed.
- Current problematic issues and a future research agenda is provided.

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ABSTRACT

In the past decennium there has been an enormous increase in new insights in cognitive mechanisms of addiction and their neural substrates. These candidate neurocognitive mechanisms, particularly those associated with "drive" and "control" aspects of addiction, are clearly involved in substance use problems but do not yet provide a full explanation. The neurocognitive mechanisms addressed in the present perspective are attentional bias, reward processing (both drive aspects) and error-processing and cognitive control (both control aspects). The time has come to transfer these recent insights more consistently to clinical practice by studying their relevance for diagnosis and treatment in patient samples. The present perspective echoes the development of recent initiatives such as the RDoC system to integrate developments in neuroscience into clinical practice. The aim of this article is to open new vistas for addiction diagnosis and treatment and to discuss why and how these neurocognitive aspects of addictive behavior can be used in clinical practice. In addition, present problematic issues and a future research agenda are provided.

1. Introduction

The core of most addiction treatment programs consists of medication, (cognitive) behavioral treatment, psychoeducation and relapse prevention with additional stress reduction or coping interventions (APA, 1995). These interventions are either pharmacological as far as medication is concerned or primarily verbal. The application of the pharmacological treatments is often hampered by unwanted side effects that significantly reduce patient's compliance (Douaihy, Kelly, & Sullivan, 2013). The vast majority of our patients are low educated (Sheehan, Oppenheimer, & Taylor, 1988) with high rates of illiteracy and limited reflective capacity (Goldstein et al., 2009) paired with high rates of impulsivity (Verdejo-Garcia, Lawrence, & Clark, 2008). Too often we have seen in the addiction clinic that the highly educated addiction professional and the elaborated verbal interventions are not or only in part able to fit the cognitive and emotional capabilities of their patients with a substance use disorders (SUD). Based on our clinical and research experience we feel the need for an additional treatment and additional ways to diagnose and triage patients.

Recent neurocognitive studies (i.e., studies using neurophysiological measures during cognitive-task performance) have been providing valuable insights in brain mechanisms and neural circuitry underlying addictive behaviors. Using functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) methodology, the neurocognitive mechanisms associated with *drive* (*motivation*) and *control* (Volkow, Fowler, & Wang, 2003) have been unraveled partially. Goldstein and Volkow (2002, 2011) propose in their iRISA model that disrupted functioning of the prefrontal cortex leads to impaired response inhibition and salience attribution. This results in SUD patients in an attributing excessive salience to the drug and drug-related cues and a decreased ability to inhibit drug use behavior. This model has guided many neurocognitive studies in the field of addiction research.

This increase in knowledge goes hand in hand with recent criticism concerning the dichotomous diagnostic and classification systems of psychiatric diagnosis such as the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5). In the present paper, the

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potential usefulness of several neurocognitive markers for both diagnosing and treating addictive behaviors will be discussed, including usefulness of these markers for a more stratified treatment for addictive behaviors. The aforementioned current treatment interventions for addiction hardly make use of these recent scientific insights. New neurocognition-based diagnostics and new treatment interventions aimed at modulating particular brain circuitry by training hold the promise to enhance the results of current treatment strategies. We argue to bridge the gap between recent neurocognitive insights in addictive behaviors and clinical practice by a) exploring the usefulness of the concept of neurocognitive markers for the diagnoses of addictive behaviors, b) exploring the predictive validity of these markers for clinical outcome and c) exploring the idea of a modular stratified treatment which would be based on individual neurocognitive deficiency patterns. Furthermore, we propose to focus on those domains that are mentioned in the recently proposed the Research Domain Criteria (RDoC) system of the National Institute of Mental Health (NIMH; Casey et al., 2013; Cuthbert & Insel, 2013). These domains should be studied on the physiological (using EEG or fMRI), behavioral units of analysis in addition to the commonly used self-report assessment. We are convinced that the field would benefit from a more standardized approach to assess these neurocognitive constructs.

Instead of giving a systematic review of the field of neurocognitive problems associated with drive and control aspects – there are already a number of excellent overviews (e.g., Bechara, 2005; Ersche, Williams, Robbins, & Bullmore, 2013; Goldstein & Volkow, 2011; Smith, Mattick, Jamadar, & Iredale, 2014; Verdejo-Garcia et al., 2008; Volkow et al., 2010; Yucel & Lubman, 2007) – we discuss from a broad perspective why and how neurocognitive principles and techniques could be applied in clinical practice (see for a more systematic review, Marhe, Luijten, & Franken, 2014). At the moment this seems like a long way ahead, therefore we discuss some issues that we feel should be addressed along the way. After a brief description of some initial findings in this relative new area, we will discuss the issues which should be addressed in future studies before neurocognitive measures can be applied as routine in clinical practice.

2. The neurocognitive framework of drive and control in addictive behaviors

All substances of abuse share common neurobiological, behavioral, and (neuro)cognitive mechanisms (Volkow & Baler, 2013; Volkow, Fowler, & Wang, 2004). While several theories focus on an enhanced "drive", such as enhanced reward sensitivity and cognitive aspects of craving (Bava & Tapert, 2010; Blakemore & Robbins, 2012; Nixon & McClain, 2010). Other theories concentrate on decreased "control", targeting functions such as the role of reduced inhibitory control and impulsivity (Verdejo-Garcia et al., 2008), or emphasize both functions in interaction (such as the i-RISA model; Goldstein & Volkow, 2011; Volkow et al., 2004).

Previous studies have indeed indicated that substance abuse populations are characterized by alterations in a broad spectrum of cognitive problems characterized by drive (Dawe, Gullo, & Loxton, 2004; Volkow & Fowler, 2000) and control (Feil et al., 2010; Yucel & Lubman, 2007). Aberrations among adult SUD populations have been found in reward processing (Bühler et al., 2010; Franken, van den Berg, & van Strien, 2010; Martin-Soelch et al., 2001), attentional bias (Littel, Euser, Munafo, & Franken, 2012), error-processing (Franken, van Strien, Franzek, & van de Wetering, 2007), and inhibitory control (Luijten et al., 2014; Verdejo-Garcia et al., 2008). Some theories suggest that these drive and control aspects play an important role in the etiology and maintenance of substance abuse (Iacono, Malone, & McGue, 2008; Robbins & Everitt, 1999; Verdejo-Garcia et al., 2008; Volkow et al., 2010). Casey and Jones (2010) argue that adolescents show an imbalance between developing drive and cognitive control systems in the brain. This results in a relatively high sensitivity to rewarding stimuli (e.g., substance cues) that escape the control systems. All these theories have in common that these cognitive functions have a specific neurobiological substrate in the brain. Below, we will briefly discuss some of the neurocognitive deficits related to substance use disorders.

2.1. Attentional bias

The hyper-attentive focus of SUD patients on substances and substance-related stimuli is called attentional bias. In the past decade, experimental studies have indeed shown that SUD patients exhibit attentional processing biases for alcohol and drug-related stimuli (for reviews see Field, Munafo, & Franken, 2009; Franken, 2003). Attentional biases are thought to emerge because of the motivational and attention-grabbing properties of drug stimuli (Robinson & Berridge, 1993). Attentional bias in substance use is typically measured by variants of Emotional Stroop tasks. In these tasks persons have to name the color in which a word is printed, but ignore the content (which is substance-related or neutral). The difference between the latencies of both stimulus categories is an index of attentional bias. There have been several variants of this tasks used in previous studies, for example pictorial variants, and tasks in which manual responding is required. Substance-related attentional bias has been demonstrated in heroin and cocaine abusers, heavy alcohol drinkers, and smokers (see Field et al., 2009). The clinical importance of this enhanced processing has been demonstrated in several studies that found an association between attentional bias and relapse. Persons having higher degrees of attentional bias demonstrated higher relapse-rates (e.g. Marhe, Waters, van de Wetering, & Franken, 2013; Marissen et al., 2006), although some studies could not show such an association (see present issue Christiansen, Schoenmakers, & Field, 2015-in this issue). A study of Field and Eastwood (2005) demonstrated that increased attentional bias for alcohol-related stimuli increases the motivation to drink alcohol suggesting some causal role in drinking behaviors. Recently, the neurocognitive aspects of biased attentional processing in addiction have been studied using fMRI (Luijten et al., 2011; Luijten et al., 2012; Marhe, Luijten, van de Wetering, Smits, & Franken, 2013) and Event-Related Potentials (ERP) measures of the EEG (see for a review Littel et al., 2012). Particularly the fMRI studies suggest that the dorsal anterior cingulate cortex (dACC) is associated with attentional bias. Activation of the dACC was shown to predict treatment outcome in cocaine dependent patients (Marhe, Luijten, van de Wetering, Smits, & Franken, 2013). Moreover, several studies indicate that the brain dopamine system is involved in this attentional bias (Luijten, Field, & Franken, 2014). Other systems such as the GABA system seem also to be associated with attentional bias (Janes et al., 2013). However, systematic and large-scale research concerning the pharmacology of attentional bias is still lacking.

2.2. Reward processing

Risky decision-making is another hallmark characteristic of SUDs. For appropriate decision-making it is essential to determine the positive and negative outcomes rapidly to guide current as well as future actions. Disruption of this process may produce risk-prone behavior, where choice is driven by the positive short-term outcomes, despite possible detrimental long-term consequences (Bechara, Damasio, Damasio, & Anderson, 1994). A typical category of tasks to measure reward processing is a gambling task. In a typical gambling task, individuals have to make a choice between two or more stimuli upon which they receive a reward (gain) or punishment (loss). Neural responses to these rewards are one indication of reward processing. Adolescents are especially prone to risk-taking behaviors, which makes adolescence a period of heightened vulnerability to substance use (Casey & Jones, 2010). Non-addicted high risk (HR) persons show more activation in the ACC and caudate nucleus (CN) during gambling situations (Acheson, Robinson, Glahn, Lovallo, & Fox, 2009). Others found blunted