Drug and Alcohol Dependence 173 (2017) 151–158

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Review

The cerebellum in drug craving

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ARTICLE INFO

Article history:
Received 25 July 2016
Received in revised form 4 December 2016
Accepted 28 December 2016
Available online 20 February 2017

Keywords:
Craving
Cerebellum
Memory
Cue reactivity
Prediction
Expectations

ABSTRACT

Craving has been considered one of the core features of addiction. It can be defined as the urge or conscious desire to use a drug elicited by the drug itself, drug-associated cues or stressors. Craving plays a major role in relapse, even after prolonged periods of abstinence, as well as in the maintenance of drug seeking in non-abstinent addicts. The circuitry of craving includes medial parts of the prefrontal cortex, ventral striatal zones, ventral tegmental area, ventral pallidum, and limbic regions. Interestingly, the cerebellum shows reciprocal loops with many of these areas. The cerebellum has been linked traditionally to motor functions but increasing evidence indicates that this part of the brain is also involved in functions related to cognition, prediction, learning, and memory. Moreover, the functional neuroimaging studies that have addressed the study of craving in humans repeatedly demonstrate cerebellar activation when craving is elicited by the presentation of drug-related cues. However, the role of cerebellar activity in these craving episodes remains unknown. Therefore, the main goal of this review is to provide a brief update on craving studies and the traditional neural basis of this phenomenon, and then discuss and propose a hypothesis for the function of the cerebellum in craving episodes.

1. Introduction

Craving is a very relevant concept in the addiction field as it has been hypothesized to underlie drug seeking and relapse in addicts (O'Brien et al., 1998). It has always referred to an urge or conscious desire to take a drug though such conceptualization has been a matter of debate. Indeed, there are some authors that consider that craving may also occur unconsciously (Miller and Gold, 1994; Berridge and Robinson, 1995). Despite this disagreement, the importance of pavlovian associations with craving was recognized from the very beginning (Wikler, 1948). It is now accepted that drug-associated stimuli evoke drug memories, triggering craving and relapse (Robinson and Berridge, 1993; Robbins et al., 2008; Pickens et al., 2011).

Traditionally, craving has been associated with brain areas related to reward, motivation and memory, including prefrontal cortical areas (Grant et al., 1996); the striatum and ventral pallidum (Filbey et al., 2009; Wetherill et al., 2013); mesolimbic dopamine structures, such as the ventral tegmental area (Goudriaan et al., 2013); and reward memory areas like the amygdala or the hippocampus (Kilts et al., 2001; Volkow et al., 2004).

However, addiction literature has not paid much attention to the cerebellum until recently (Miquel et al., 2009, 2016; Moulton et al., 2014). The cerebellum is a hindbrain structure that contains more neurons than the rest of the brain (Herculano-Houzel, 2009). This structure presents some organizational similarities with the cerebral cortex (Herrup, 2000). During the last few decades, several findings have pointed to the possibility that other functions not linked to motor domains could require the cerebellum. Indeed, several studies have provided evidence of cerebellar involvement in some of the brain functions altered in addiction, such as memory (Sacchetti et al., 2004), prediction (Blakemore and Sirigu, 2003), and executive control (Bellebaum and Daum, 2007; see Miquel et al., 2016 for a recent review).

Other brain function related to craving and addiction in which the cerebellum has been involved is salience. Salience could be described as the property of a stimulus that makes it differentially relevant from the others within an environment (Uddin, 2015). The attribution of salience to the surrounding environmental stimuli is an essential process for survival that allows individuals to perform adaptive behavioral responses to approach beneficial goals or avoid threatening ones (Borsook et al., 2013). Of note, one of the most influential addiction theories posits that such disease is driven by the attribution of excessive incentive salience to drugs and drug-associated cues (Robinson and Berridge, 1993). Data showing cerebellar activations when salient stimuli or cues are presented no matter their valence point to the involvement of this structure in

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http://dx.doi.org/10.1016/j.drugalcdep.2016.12.028
0376-8716/

such process (Moulton et al., 2011; Killgore et al., 2003; Anderson et al., 2006). Moreover, resting-state functional connectivity studies have allowed to unravel a functional network termed as the "salience network", which showed responsivity to salient events with independence of the sensory modality (Downar et al., 2002). Posterior studies have confirmed functional connections between the cerebellum and the core components of this network, such as insula, anterior cingulate cortex and temporoparietal junction (Caulfield et al., 2015; Habas et al., 2009; Igelström et al., 2016; Moulton et al., 2011; Shinn et al., 2015).

Animal studies show the cerebellum to be reciprocally interconnected with the brain areas traditionally related to addiction. As a matter of fact, the presence of dopaminergic synaptic components in the cerebellum of primates and rodents has been repeatedly demonstrated (Melchitzky and Lewis, 2000; Carbo-Gas et al., 2014a). This finding is consistent with the observed reciprocal connections between the cerebellum and the ventral tegmental area (VTA), the main source of dopamine in the mesocorticolimbic system (Ikai et al., 1992). Striatal projections and limbic zones have also been shown to functionally connect to the cerebellum (Bostan et al., 2013). For example, basolateral amygdala inactivation prevents learning-induced cerebellar LTP (Zhu et al., 2011). Moreover, it is clear that the cerebellum is functionally associated with the prefrontal cortex (Kelly and Strick, 2003), as well as other motor and associative cortices (see Bostan et al., 2013; D'Angelo and Casali, 2013 for a review). Animal findings regarding cerebellar-cortical and cerebellar-subcortical connections have been confirmed in humans by neuroimaging studies. Notably, functional magnetic resonance imaging studies, including resting-state and task-related functional connectivity confirm cerebellar relationships between the cortical and subcortical areas involved in addiction, and specifically in craving. Concretely, co-activations and functional connections between cerebellum and cortical structures, such as dorsolateral prefrontal cortex (Habas et al., 2009; Leutgeb et al., 2016; Moulton et al., 2011; Sang et al., 2012), orbitofrontal cortex (Addis et al., 2016; Habas et al., 2009; Leutgeb et al., 2016), anterior cingulate cortex (Addis et al., 2016; Moulton et al., 2011; Sang et al., 2012; Zeng et al., 2012), insula (Addis et al., 2016; Habas et al., 2009; Moulton et al., 2011; Sang et al., 2012), and inferior frontal gyrus (Addis et al., 2016; Moulton et al., 2011; Tomasi and Volkow, 2011) have been reported. Other subcortical structures such as amygdala (Leutgeb et al., 2016; Sang et al., 2012; Zeng et al., 2012), hippocampus (Onuki et al., 2015; Sang et al., 2012; Zeng et al., 2012), ventral tegmental area (Carnell et al., 2014; Etkin et al., 2009; Kline et al., 2016; Kwon and Jang, 2014), dorsal striatum (Moulton et al., 2011; Sang et al., 2012; Tomasi and Volkow, 2011), and ventral striatum (Cauda et al., 2011; Cservenka et al., 2014; Koehler et al., 2013) also have demonstrated to be connected to the cerebellum.

In addition, there is growing evidence that addictive drugs induce direct effects on cerebellar functioning and plasticity. As an example, alcohol modifies Purkinje neuron firing rates (Freund and Palmer, 1997); and chronic exposure to this drug increases AMPA-dependent calcium signaling in these cells (Netzeband et al., 1999). It is noteworthy that cerebellar degeneration is a common feature in long-term alcoholics and has been linked to the emotional and cognitive deficits that these patients suffer (Fitzpatrick et al., 2008). Psychostimulants also affect the cerebellum. It has been demonstrated that cocaine-induced sensitization has a big impact on cerebellar plasticity, altering the balance of plasticity-related proteins (Vazquez-Sanroman et al., 2015a,b). The direction of plasticity changes depends on the length of the withdrawal period that precedes a new drug exposure (Vazquez-Sanroman et al., 2015a,b). Also, cocaine-induced preference conditioning selectively increases c-FOS expression (an early transcription factor which acts as a marker of neuronal activity) in the cerebellar cortex (Carbo-Gas et al., 2014a,b).

Numerous human neuroimaging studies have demonstrated activation in the cerebellum during the presentation of drug-associated cues (Anderson et al., 2006; Filbey et al., 2009; Grant et al., 1996). In almost every study, craving was elicited by the presentation of the cue. Nevertheless, in the absence of causal studies about the cerebellum's role in drug addiction, the functional significance of such cerebellar activation in craving episodes is unknown.

Given the aforementioned findings, the main goal of the present work is to review evidence about the involvement of the cerebellum in craving and to propose a hypothesis for its role. First, we present the current neurobiological model of craving. Then, we discuss craving-eliciting studies in which the activation of the cerebellum was shown. Finally, we suggest a working hypothesis to clarify the function cerebellar activation might play in the disturbing experience that craving assumes for an addict. We hope that the present review will help guide future experimental approaches to the subject.

2. The circuitry of craving

Research in both clinical and preclinical fields has provided knowledge about the brain areas and circuits that underlie the experience of craving. The reinstatement/relapse models have been the major contributors to elucidating the brain areas involved in animal craving. These models, which are able to elicit craving-like behaviors after the extinction of drug seeking in experimental animals, appear valid because the same stimuli that elicit craving-like behaviors in animals (Spanagel et al., 1998; Sanchis-Segura et al., 2006), also provoke craving in humans (Jaffe et al., 1989; Sinha et al., 1999; Grant et al., 1996). Basically, findings about the underlying circuitry parallel those derived from human research (see Bossert et al., 2013 for a recent review).

Brain correlates of human craving have been studied using the cue reactivity paradigm. Drug addicts are presented with drug-related cues under abstinence, while both craving levels and neurobiological parameters are evaluated (Carter and Tiffany, 1999). The frontal zones involved in craving seem to be the anterior cingulate cortex, orbitofrontal cortex, dorsolateral prefrontal cortex, and the inferior frontal gyrus (Grant et al., 1996; Bonson et al., 2002). The anterior cingulate cortex, a brain area related to self-control (Tang et al., 2015) and to reward-related cognitive processes (Shidara and Richmond, 2002) has been found to be active when drug-related cues are presented (Filbey et al., 2009; Myrick et al., 2004). Activity in the anterior cingulum seems to act as a predecessor of the onset of craving, being linked to the emotional response triggered by drug-related cues (Robbins et al., 2008; Wexler et al., 2001). Orbitofrontal cortex activity during craving episodes (Bonson et al., 2002) appears to be more related to salience attribution and expectation (Volkow and Baler, 2015). Also, consistent activation of the dorsolateral prefrontal cortex has been involved in the acquisition and storage of drug-conditioned memories, as well as in the formation of drug-related short-term working memory that drives behavior (Tang et al., 2015).

When addicts are exposed to drug-related cues, the inferior frontal gyrus is activated (Grant et al., 1996; Tomasi et al., 2015). This region exerts an inhibitory effect on drug seeking (Goldstein and Volkow, 2011; Tang et al., 2015). Importantly, craving suppression was inversely correlated with the activity of this prefrontal area (Volkow et al., 2010). Moreover, gray matter in this area correlated with striatal D2/D3 receptor availability in methamphetamine users (Morales et al., 2015).

Subcortical activity during craving experience has been described in brain areas traditionally related to emotional mem-