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Methamphetamine-associated difficulties in cognitive control allocation may normalize after prolonged abstinence

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ABSTRACT

Chronic heavy methamphetamine use likely causes dopaminergic neurotoxicity, which is commonly thought to result in cognitive control deficits. Both of these alterations may persist even after the use is discontinued, but tend to (partly) improve with increasing duration of abstinence. While several studies have demonstrated that the reinstatement of comparatively normal dopaminergic signaling may take months, if not years, the amelioration of cognitive deficits has predominantly been investigated in much shorter intervals of several weeks to less than half a year. Against this background, we set out to investigate the effects on prolonged abstinence in n = 27 abstinent former methamphetamine users in a cross-sectional design using behavioral and neurophysiological measures of cognitive control.

Our behavioral results suggest that former users struggled to identify and adapt to different degrees of cognitive control requirements, which made their behavioral performance less expedient than that of healthy controls. On the neurophysiological level, this was reflected by reduced modulations of the N2-N450 amplitude in response to high vs. low cognitive control requirements. Yet, those effects could only be observed in methamphetamine users who had been abstinent for a relatively short time (mean 9.9; max. 18 months), but not in former users who had been abstinent two years or longer.

While this finding alone does not allow for causal inferences, it suggests that the amelioration of control deficits may take longer than what is commonly investigated (1–6 months). Hence, some of the statements about permanent/irreversible dopamine-dependent executive dysfunctions in former methamphetamine users should be interpreted with caution.

1. Introduction

Second to cannabis, amphetamines have become one of the most commonly used class of illicit drugs worldwide, with methamphetamine being on the rise in several regions of the world (Morley et al. 2017; United Nations Office on Drugs and Crime 2017). While the initial effects of small doses on mood, cognition and behavior may still be rather beneficial (Hart et al. 2012), dependence is commonly assumed to develop rather rapidly (Aarde and Taffe 2017; Kohut et al. 2016; Miliano et al. 2016; Quinton and Yamamoto 2006; Simmler et al. 2013). Continuous illicit consumption of larger doses is associated with a heightened risk of developing cardiovascular problems, mood disturbances, psychosis and cognitive impairments, which seem to be most pronounced in the domain of executive functions (EFs) and cognitive control (Cruickshank and Dyer 2009; Darke et al. 2008; Farhadian et al. 2017; Hart et al. 2012; Parrott 2015).

A large proportion of these consequences is commonly attributed to a potent increase in dopamine (DA) and noradrenaline (NE) signaling as well as a much smaller increase in serotonin (5-HT) signaling in various parts of the brain, including the striatum (Fowler et al. 2008). This effect may be attributed to the finding that (meth)amphetamines impair normal monoamine transporter function, leading to reduced presynaptic reuptake as well as increased release of monoamines into the cytoplasm of presynaptic neurons (Sandoval et al. 2001; Sofuoglu and Sewell 2009; Vasan and Olango 2018). While the acute effects of a single recreational dose are best characterized by the increase in presynaptic DA and NE release and thus in postsynaptic receptor binding, prolonged use has been shown to strongly decrease endogenous monoamine release and postsynaptic receptor binding due to substantial reductions in presynaptic monoamine transporters as well as postsynaptic monoamine receptors (Ashok et al. 2017; Madras and Kuhar 2014; Volkow et al. 2001). These neurobiochemical alterations are likely most pronounced in DA rich areas (i.e. fronto-striatal brain regions) and tend to persist even after the use of methamphetamine is

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terminated (Cruickshank and Dyer 2009; Salo et al. 2009b).

Both DA deficiency and cognitive impairments associated with methamphetamine use tend to improve with increasing abstinence duration (Ashok et al. 2017; Farhadian et al. 2017; Hart et al. 2012; Volkow et al. 2001), but it is still debated whether some of the methamphetamine-induced cognitive deficit may be irreversible (e.g. Farhadian et al. 2017; Wang et al. 2004). Several studies have demonstrated that the reinstatement of comparatively normal DA signaling may take months, if not years (Salo et al. 2011a; Volkow et al. 2001). Yet still, the amelioration of potential cognitive deficits has predominantly been investigated in much shorter intervals of several weeks to less than half a year (Farhadian et al. 2017; Hart et al. 2012). Against this background, we set out to investigate the effects of protracted abstinence on EFs in former methamphetamine users. While the effects of consumption and abstinence duration on EFs have not yet been adequately investigated (Farhadian et al. 2017), some studies have reported correlations of cognitive control performance with these factors (e.g. Salo et al. 2011c). We hence hypothesized that the size of behavioral and neurophysiological methamphetamine-associated changes should be positively correlated with use duration and negatively correlated with abstinence duration.

EFs and cognitive control are heavily modulated by DA and are commonly assumed to show the strongest and most reliable methamphetamine-induced effects (Farhadian et al. 2017; Hart et al. 2012). Cognitive control is usually considered to play a pivotal role in overcoming addiction (McKim et al. 2016), but it is also effortful and has been suggested to deplete brain DA levels if continuously exerted (Jongkees et al. 2015). Against this background, the ability to carefully decide in which situations control is required and when this valuable resource may be spared is an important, but often underestimated faculty. In order to assess both cognitive control capacities and situation-based strategic adaptation of control allocation, we asked abstinent former methamphetamine users and controls matched for age, sex and education to perform a modified experimental paradigm originally proposed by Bocanegra and Hommel (2014). It comprises two complementary tasks: One requires high amounts of cognitive control, while the other requires low levels of control. Investigating just the first may provide information about how well participants cope with high control requirements. But only comparing the two tasks provides information about how well a person is able to allocate his/her control resources based on the actual task requirements. While stimulant-induced increases in DA signaling may help to better differentiate and adapt to high vs. low control requirements (Berman et al. 1999), DA down-regulation or deficiency may render affected individuals largely unable to efficiently shift between states of high and low cognitive control, which ultimately impairs their ability to process conflicts and thus correctly identify the need for cognitive control (Bluschke et al. 2017; Willemssen et al. 2011). Based on these findings, we hypothesized that the supposedly DA-deficient abstinent methamphetamine users might not only show executive deficits (i.e. generally not be able to sufficiently control their behavior), but should also struggle to adapt to differences in control requirements. While a general executive deficit should result in group differences (i.e. worse performance in the user group than in controls), the latter should result in a less pronounced performance difference between the high and low demand tasks in the user group as compared to controls.

While the DA system and has received much more attention than the NE system, the latter is similarly modulated by methamphetamine (Fowler et al. 2008) and could therefore be subject to the same downregulation as the DA system, even though there are currently no PET studies or the like to sufficiently substantiate this claim. NE has repeatedly been shown to modulate cognitive control functions by increasing attention and saliency-dependent stimulus detection (e.g. Mückschel et al. 2017; Nieuwenhuis et al. 2005). It has furthermore been associated with methamphetamine-associated increases in arousal, attention, mood and vigilance (Sofuoglu and Sewell 2009), so that those functions might be reduced during withdrawal and after prolonged periods of substance use. Given that our paradigm was however designed to primarily assess cognitive effects of DA and does not require high levels of attention or arousal, we are skeptical whether changes in the NE system would be adequately reflected by the experimental paradigm used in this study.

During task performance, we recorded an EEG because neurophysiologic measures like event-related potentials (ERPs) allow to dissociate and investigate several cognitive sub-processes with high temporal resolution and have furthermore been shown to be potentially more sensitive to drug-related changes in cognition than behavior alone (Gevins et al. 2002).

When investigating cognitive control, the fronto-central N2 and N450 components are the potentially most interesting ERPs. They reflect conflict detection and monitoring, which is crucial for goal-directed response adaptation and thus for cognitive control (Beste et al. 2010; Gajewski et al. 2012; Larson et al. 2014). Larger amplitudes usually reflect greater conflict monitoring, which should allow for greater adaptation to perceived task difficulties and control requirements (Larson et al. 2014). Matching this, a previous study employing almost the same experimental paradigm found larger N450 amplitudes in case of larger control requirements (Stock et al., 2016). General control deficits might hence be reflected by overall lower N2 and N450 amplitudes. If our hypothesis was true and abstinent methamphetamine users experienced problems in adapting their level of control to the actual task requirements, we would expect to see smaller amplitude differences between the high and low demand task. Importantly, this hypothesis might be supported by a previous study that also showed a lack of conflict-dependent N2 and N450 amplitude modulations (Bluschke et al. 2017).

The parietal P3b, which is commonly thought to reflect the process of mapping appropriate responses onto perceived task-relevant stimuli (Stock et al. 2014, 2017; Verleger et al. 2005, 2015), is another potentially interesting ERP. Several studies have suggested that the S-R mapping reflected by the P3b may be modulated by DA. Furthermore, DA deficiency may reduce the amplitude of the response-locked P3b, but not of the stimulus-locked P3b (Verleger et al. 2013). A previous study employing almost the same experimental paradigm found smaller response-locked P3 amplitudes in case of larger control requirements (Stock et al., 2016). Matching this, larger P3 amplitudes have been suggested to reflect residual control resources left over by the primary task (Polich 2007; Schubö et al. 2001). We would hence expect impaired stimulus-response mapping and diminished task set processing capacities, as reflected by smaller response-locked P3 amplitudes, in the methamphetamine group. It should however be noted that the P3 amplitude has also been shown to be modulated be NE (e.g. Mückschel et al. 2017; Nieuwenhuis et al. 2005), so that changes in this component may not solely be attributed to the DA system.

In order to provide a more comprehensive picture including several commonly investigated ERPs, we also assessed early attentional stimulus processing, as reflected by the visual P1 and N1 (Luck et al. 2000). But while methamphetamine abstinence has repeatedly been associated with attentional deficits (Birath et al. 2017; Farhadian et al. 2017), this terminology usually refers to the top-down allocation of attention though anterior brain regions (e.g. Salo et al. 2011b). Furthermore, those ERPs are usually not modulated by comparable DA deficiencies (Arnsten 2011; Ashok et al. 2017; Bluschke et al. 2017; Mazei-Robinson and Blakely 2006). Hence, we did not expect any relevant modulation of these ERPs.

2. Experimental procedures

2.1. Sample

We recruited n = 32 adult former/abstinent methamphetamine consumers using the following inclusion criteria: Participants should