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Chronic amphetamine enhances visual input to and suppresses visual output from the superior colliculus in withdrawal

Amy C. Turner [a], Igor Kraev [a], Michael G. Stewart [a], Agata Stramek [a], Paul G. Overton [b], Eleanor J. Dommett [a, c, *]

[a] School of Life, Health and Chemical Sciences, The Open University, Milton Keynes, MK7 6AA, UK
[b] Department of Psychology, University of Sheffield, Western Bank, Sheffield, S10 2TN, UK
[c] Department of Psychology, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, SE1 1UL, UK

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ABSTRACT

Heightened distractibility is a core symptom of Attention Deficit Hyperactivity Disorder (ADHD). Effective treatment is normally with chronic orally administered psychostimulants including amphetamine. Treatment prevents worsening of symptoms but the site of therapeutic processes, and their nature, is unknown. Mounting evidence suggests that the superior colliculus (SC) is a key substrate in distractibility and a therapeutic target, so we assessed whether therapeutically-relevant changes are induced in this structure by chronic oral amphetamine. We hypothesized that amphetamine would alter visual responses and morphological measures. Six-week old healthy male rats were treated with oral amphetamine (2, 5 or 10 mg/kg) or a vehicle for one month after which local field potential and multiunit recordings were made from the superficial layers of the SC in response to whole-field light flashes in withdrawal. Rapid Golgi staining was also used to assess dendritic spines, and synaptophysin staining was used to assess synaptic integrity. Chronic amphetamine increased local field potential responses at higher doses, and increased synaptophysin expression, suggesting enhanced visual input involving presynaptic remodelling. No comparable increases in multiunit activity were found suggesting amphetamine suppresses collicular output activity, counterbalancing the increased input. We also report, for the first time, five different dendritic spine types in the superficial layers and show these to be unaffected by amphetamine, indicating that suppression does not involve gross postsynaptic structural alterations. In conclusion, we suggest that amphetamine produces changes at the collicular level that potentially stabilise the structure and may prevent the worsening of symptoms in disorders like ADHD.

1. Introduction

Distractibility is defined as an attentional deficit where orientation toward irrelevant targets cannot be inhibited (Gaymard et al., 2003). Heightened levels of distractibility are found within a variety of psychiatric conditions, including Attention Deficit Hyperactivity Disorder (ADHD) (Douglas, 1983; Thorley, 1984) and schizophrenia (Grillon et al., 1990). It is also found within healthy ageing (Gaymard et al., 2003; Mishra et al., 2014) where it is believed to underpin a decline in various cognitive functions, therefore impacting negatively on quality of life in otherwise healthy people (Kim et al., 2007). Despite the high prevalence of heightened distractibility, limited attempts have been made to understand its basis within the brain, with focus almost exclusively on the prefrontal cortex and associated cortical networks (Campbell et al., 2012; Chadick et al., 2014). However, converging evidence implicates the superior colliculus (SC) as a key neural substrate for distractibility. The colliculus is responsible for orienting head and eye movements (Grantyn et al., 2004) and covert attention toward sensory stimuli (Rizzolatti et al., 1987). It is highly conserved across species and work in a range of species shows that collicular lesions cause decreased distractibility (Goodale et al., 1978; Milner et al., 1978; Sprague and Meikle, 1965), while removal of prefrontal cortex inhibitory control of the colliculus, leading to heightened activity in the structure, results in increased distractibility in humans (Gaymard et al., 2003). Additionally, there is evidence that the

* Corresponding author. Department of Psychology, Institute of Psychiatry, Psychology and Neuroscience, King's College London, 2nd Floor Addison House, London, SE1 1UL, UK.
E-mail address: Eleanor.dommett@kcl.ac.uk (E.J. Dommett).

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colliculus may play a role in ADHD, a core symptom of which is heightened distractibility (Brace et al., 2015a; b; Dommett et al., 2009; Dommett and Rostron, 2011; Klein et al., 2003; Milner et al., 1978; O'Driscoll et al., 2005; Swanson et al., 1991).

A key role for the colliculus in distractibility is possible because of intricate connections to the basal ganglia, a series of nuclei believed to act as the central device for action selection (Gurney et al., 2001; Redgrave et al., 1999). The colliculus makes direct connections to dopaminergic neurons in substantia nigra pars compacta and the ventral tegmental area (Comoli et al., 2003; Dommett et al., 2005; Takakuwa et al., 2017). In turn the structure also receives dopaminergic input (Bolton et al., 2015; Perez-Fernandez et al., 2017; Rolland et al., 2013). As well as this dopaminergic input, the colliculus receives extensive GABAergic input from the substantia nigra pars reticulata (Hikosaka, 2007; Kaneda et al., 2008). Recent research suggests that when this GABAergic input is reduced, the effects of dopamine on the colliculus are revealed such that reduced dopamine activity is associated with enhanced visual responses (Rolland et al., 2013). As well as these connections with the basal ganglia both the superficial and deep layers of the SC have direct ascending connections to the thalamus. In the case of the superficial layers of the SC, which process visual information, this is to the lateral posterior nucleus and the pulvinar and then forward to the neostriatum (McHaffie et al., 2005), or via a link in the deep layers of the SC (Lee et al., 1997), which project to the rostral intralaminar regions of the thalamus on route to the neostriatum (McHaffie et al., 2005). Where collicular activity is enhanced, via these connections the structure can make a stronger bid for behavioural expression and is therefore more likely to win against competitors resulting in an increased probability of orienting eye and head movements (and covert attentional shifts) which can manifest as 'distraction'. Conversely, by depressing responses in the SC, the probability of orienting movements and attentional shifts would be reduced (Dommett et al., 2009).

Increased distractibility is not always treated, but amphetamine has been found to be effective in reducing distractibility in ADHD (Brown and Cooke, 1994; Spencer et al., 2001) and in healthy subjects (Agmo et al., 1997; Halliday et al., 1990). Although the psychostimulant is efficacious, it's therapeutic mechanism of action is still unknown. However, there is now mounting evidence that the colliculus could be a key site of action. For example, acute amphetamine has been shown to suppress activity in the visually responsive superficial layers of the SC in healthy animals (Dommett et al., 2009; Gowan et al., 2008) and in rodent models of ADHD (Clements et al., 2014). In addition, we have recently demonstrated that chronic treatment with orally-administered amphetamine selectively alters collicular-dependent behaviour in a manner consistent with suppression of activity in the area (Turner et al., 2018a). Furthermore, amphetamine is known to act on dopaminergic neurons to increase synaptic dopamine levels, and based on previous research (Rolland et al., 2013) we can infer that this should suppress visual responses in the colliculus. Evidence suggests that chronic treatment with amphetamine (or methylphenidate) in patients prevents the worsening of ADHD symptoms that occurs on a short time scale in a proportion of placebo-administered controls (Faraone et al., 2002), hence chronic drug treatment for ADHD clearly leads to changes that assist the therapeutic process. However, the nature of those changes and their location is currently unknown.

To assess whether therapeutically-relevant changes occur at the level of the SC following chronic psychostimulant administration, we chronically administered amphetamine orally to rats at a range of doses and examined the impact of the drug on visual processing and structural characteristics in the two-week period immediately after drug treatment, which we considered to be when the animal is in withdrawal. Research has consistently shown that chronic amphetamine treatment impacts on spine density and dendritic remodelling elsewhere in the brain (Robinson and Kolb, 1997, 1999; Selemon et al., 2007) and that these changes can be detected within 2 weeks and persist for several months (Acerbo et al., 2005; Kolb et al., 2003; Li et al., 2003; Robinson and Kolb, 1997, 1999). In line with this, there is evidence of altered expression of synaptophysin, a synaptic protein involved in regulation of vesicular exocytosis (Bergmann et al., 1993; Grabs et al., 1994), following amphetamine administration in several structures (Bisagno et al., 2004; Rademacher et al., 2006, 2007; Stroemer et al., 1998). Based on this previous research, we hypothesized that chronic treatment with amphetamine would alter visual responses in the colliculus and dendritic and synaptic measures within the structure.

2. Methods and materials

All experiments were approved by the Institutional Ethical Review Committee at the Open University, where work took place (The Animal Welfare and Ethics Board). Work was also conducted with the authority of the appropriate UK Home Office Licenses and adhered to guidelines set out in the Animals [Scientific Procedures] Act (1986), EU Directive 86/609/EEC, and the "Guide for the care and use of Laboratory Animals" (Council, 2010).

2.1. Subjects

Male Hooded Lister rats, bred in-house and housed in standard conditions as previously described (see Supplementary Material 1 (Turner et al., 2018a; b) were used in all experiments. All procedures were carried out in the dark phase and, therefore, when rats are most active.

2.2. Chronic drug treatment

Oral administration of amphetamine (Sigma Aldrich, UK) or vehicle in apple juice was conducted as previously described (Turner et al., 2018a; b; Wheeler et al., 2007) and is therefore detailed in the Supplementary Material 1. Drugs were administered daily for 4 weeks (excluding weekends) for a total of 20 days (Kuczenski and Segal, 2002). All treatment took place in the holding room, after daily weighing of the rats (to determine dose and monitor health status), at the start of the dark phase. Three doses of amphetamine were selected (10 mg/kg, 5 mg/kg, and 2 mg/kg) to ensure some clinical relevance and included those that have previously been shown to impact on collicular-dependent behaviours (Turner et al., 2018a). The final day of treatment fell on a Friday and in all cases subsequent procedures were conducted between 3 and 14 days after treatment end are summarised in Fig. 1. Previous work has demonstrated that some effects associated with amphetamine withdrawal can be found as within 24 h after treatment cessation (Barr et al., 2010, 2013) and can persist for over 14 days (Hitzemann et al., 1977; Onn and Grace, 2000; Renard et al., 2014; Robinson and Kolb, 1997). The exact duration of any effect is likely to depend on the exact treatment regime and effects on some measures may persist for longer than others. The 3–14 day period selected here was chosen because existing literature suggested effects of withdrawal would be present for this whole period and it allowed sufficiently-sized cohorts to be used, bearing in mind the time consuming nature of some of the techniques, especially the *in vivo* electrophysiology.