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Chronic amphetamine treatment affects collicular-dependent behaviour

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ABSTRACT

Distractibility can be defined as an attention deficit where orientation toward irrelevant targets cannot be inhibited. There is now mounting evidence that the superior colliculus is a key neural correlate of distractibility, with increased collicular-activity resulting in heightened distractibility. Heightened distractibility is reduced by amphetamine, which acutely suppresses collicular responsiveness. However, when amphetamine is used to treat distractibility, it is given chronically, yet no data exist on whether chronic amphetamine treatment affects the colliculus. Here, the effect of chronic amphetamine treatment was assessed in healthy hooded lister rats on two collicular dependent behaviours following a twenty-eight day treatment period: i) orienting to visual stimuli, and ii) height-dependent modulation of air-righting. We found no significant impact of amphetamine treatment on visual orienting despite showing dose-dependent decreases in orienting to repeated stimuli. However, we did find that treatment with amphetamine significantly reduced the ability to modulate righting according to the height the animal is dropped from – a function known to be dependent on the colliculus. We suggest that the results are in line with previous research showing acute amphetamine suppresses collicular activity and we speculate that the psychostimulant may increase receptive field size, altering time-to-impact calculations carried out by the colliculus during air-righting.

1. Introduction

Distractibility can be defined as an attention deficit where orientation toward irrelevant targets cannot be inhibited [1]. Heightened distractibility is associated with a variety of conditions, including Attention Deficit Hyperactivity Disorder (ADHD) [2,3] and schizophrenia [4], as well as healthy ageing [1,5]. The latter is thought to underpin a decline in various cognitive functions including speed of processing, selective attention, working memory, long term memory and problem solving, all of which can impact negatively on quality of life in healthy aging [6].

Despite the prevalence of heightened distractibility, and its potential impact on quality of life, attempts to understand fully its neurobiological basis have been limited and focussed on the prefrontal cortex and associated cortical networks [7,8]. However, converging evidence suggests that the superior colliculus (SC), which has intimate connections with the prefrontal cortex [1], is a key neural substrate for distractibility. The colliculus is responsible for orienting head and eye movements [9] and covert attention toward sensory stimuli [10]. It is highly conserved across species and work in a range of species shows that collicular lesions cause decreased distractibility [11–13] while removal of prefrontal cortex inhibitory control of the colliculus, leading to heightened activity in the structure, results in increased distractibility in humans [1]. Additionally, there is evidence that the colliculus may play a role in ADHD, a core symptom of which is heightened distractibility [12,14–21]. The ability of the colliculus to play a key role in distractibility arises because the SC is capable of specifying actions, which are thought to be processed by the brain in such a way that enhanced collicular activity puts in a stronger "bid" for behavioural selection into the basal ganglia, the central device for action selection [22,23]. In the case of the superficial layers of the SC, which process visual information, this can occur either via direct ascending projections to the thalamus and then forward to the neostriatum [24], or via a link in the deep layers of the SC [25], which also project to the thalamus [24]. A stronger bid for behavioural expression is more likely to win against competitors and therefore enhancing SC responses is likely to result in the probability of orienting eye and head movements (and covert attentional shifts) being increased, manifesting as 'distraction'. Conversely, by depressing responses in the SC, the probability of orienting movements and attentional shifts would be reduced [26].

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Increased distractibility is not always treated, but amphetamine has been found to be effective in reducing distractibility in ADHD [27,28] and in healthy subjects [29,30]. Although the psychostimulant is efficacious, it is not clear how the relevant effect is achieved, but 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 [26,31] and in rodent models of ADHD [32]. In addition, a role for dopaminergic projections in collicular visual orienting behaviour has been established [33], meaning that any drug altering dopamine transmission has the potential to impact on collicular dependent behaviours. However, pharmacotherapies for ADHD are administered chronically and despite evidence that acute amphetamine can influence the colliculus, to date no study has directly investigated the effects of chronic amphetamine on collicular-dependent behaviours. More specifically, no study to date has explored the possibility that chronic amphetamine administration may produce a lasting alteration in collicular function that could extend beyond the period of treatment, as has been shown for other structures where changes have persisted weeks and months after amphetamine treatment [34–36]. Several behavioural tasks are known to be dependent on the SC and, therefore, provide a suitable assay for assessing the effects of amphetamine on this key structure. Firstly, orienting behaviour can be measured by examining initial responses and subsequent habituation of the response to a visual stimulus [20,37,38] within an arena. Secondly, the air-righting reflex, produced when falling supine in the air prior to landing is modulated depending on the height at which the rat falls from [39]. This modulation is dependent on visual input and, in particular, on the SC, with SC-lesioned rats being unable to modulate the height at which righting is initiated [40]. Rats with an intact SC will increase the latency of righting if dropped from a greater height, whilst those with a lesioned SC right immediately upon release, irrespective of height [39]. We hypothesized that chronic treatment with amphetamine would suppress collicular activity resulting in reduced orienting to visual stimuli and a reduced ability to modulate air-righting according the drop height.

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) in advance. Work was also conducted with the authority of the appropriate U.K. 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" (NIH publication, 8th ed, The National Academies Press, Washington, 2011).

2.1. Subjects

Male Hooded Lister rats, bred in-house as part of an on-going breeding colony, and aged six weeks at the start of experiments were used. In all cases, the individual rat was deemed the experimental unit. Female rats from within the colony are used for different research and, therefore, there was no animal wastage. Animals were housed with bedding and tubing in groups of 2–3, with standard lab chow (RM3 diet, Special Diet Services, Witham, UK) and water available ad libitum within the home cages. Cages were kept in scantainers held at a temperature of 21–23 °C, and humidity of approximately 50%. The holding room was on a 12-hr reverse dark-light cycle with lights turning on at 8 p.m. All procedures were carried out in the dark phase and, therefore, at the time when rats are most active. All behavioural testing took place within five days of the end of chronic treatment. After behavioural work was complete, animals were used for other experiments prior to sacrifice, therefore ensuring that as much data was obtained as possible from the cohort.

2.2. Chronic drug treatment

Amphetamine (Sigma Aldrich, UK) was prepared as a stock solution in distilled water and frozen at ¯20 °C until use. Immediately prior to use it was defrosted and diluted 1:10 into apple juice (Just Juice, DME, Middlesex, UK) to give the final concentration for oral administration. Drugs were administered per os rather than by injection to more closely reflect how these drugs are taken by humans [41]. A vehicle control was also used, consisting of the same volume of distilled water, also previously frozen, diluted 1:10 into apple juice immediately prior to use. Dosing was achieved using a pipette [42], administering a volume of 1 μL/g (i.e. a rat of 100 g received 100 μL). This method of administration allows precise administration in the microlitre range, and has fewer health risks compared to oral gavage, which can result in damage to the oesophagus, or accidental drug delivery to lungs [43]. Prior to chronic treatment animals were habituated to oral administration using 200 μl of apple juice for 5 days. Drugs were then administered every day for 4 weeks (excluding weekends) for a total of 20 days [44]. 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 used: 10 mg/kg, 5 mg/kg, and 2 mg/Kg. These doses were selected to ensure some clinical relevance. Doses of amphetamine that are used clinically range from 5 to 60 mg [45,46] and these are thought to result in blood plasma concentrations between 120 and 140 ng/ml in people receiving treatment for ADHD [47,48]. When administered orally to rats, a dose 0.067 mg/ml gives a peak plasma concentration of 4 ng/ml [49] and, therefore, assuming a linear scaling, a dose of 2 mg/Kg would amount to a blood plasma level of approximately 120 ng/ml. It was on this basis that our lower dose was chosen. We then selected two higher doses to allow comparison with other existing literature. Whilst this approach makes assumptions about linear scaling, it is generally accepted that the use of blood plasma levels is preferable to extrapolation on a milligram per kilogram basis from clinical doses when translating from humans to laboratory animals [41]. The drug treatment was performed blind, with randomly assigned letters representing each group, and dose was only revealed after completion of all analyses.

2.3. Orienting behaviour

Orienting behaviour was assessed (N = 52, 224 ± 4.5 g; Vehicle N = 14, 2 mg/Kg = 13, 5 mg/Kg = 12 and 10 mg/Kg = 13) as outlined in previous studies [20,37,38] at the end of the treatment period with all habituation and testing completed within three days. All testing was carried out between the hours of 9am and 5pm and, therefore, in the dark active phase, in a dimly red-lit room in the presence of white noise. Olfactory cues were removed from testing equipment using alcohol between trials to remove any extraneous cues that could affect behaviour. Prior to testing, animals were habituated to the testing space, a circular plastic arena (2.5 m diameter) with a centrally located light (green LED, 20 mcd) sealed within a clear Perspex cylinder, for two days prior to testing. On each habituation day, the animal was placed in the arena for 15 min with the stimulus light remaining off for the entire period. Testing began on the third day with the animal placed in the arena and the video camera started. After 5 min, the light was remotely switched on for a period of 5 s. This was repeated for a total ten stimulus presentations. The stimuli occurred at 5-min intervals, randomised to jitter around the 5 min by ± 1 min to prevent the animal from anticipating stimulus onset. Behaviour was recorded throughout using a Samsung VP-HMX20C camcorder for later offline analysis. The 5 s during the light stimulus were analysed to determine whether an animal had oriented to the stimulus. An animal was deemed to have oriented if it physically interacted with the stimulus casing, oriented its head towards the stimulus or looked at the stimulus. In addition to whether a response occurred, the duration of any response to the

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