Chronic amphetamine treatment affects collicular-dependent behaviour

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Highlights

Visual orienting to a novel stimulus is unaffected by amphetamine.

Orienting to a repeated visual stimulus may decrease with amphetamine treatment.

Air-righting and static righting are unaffected by amphetamine.

Height-dependent modulation of air-righting is impaired by amphetamine.

Collectively this suggests amphetamine suppresses collicular-dependent behaviours.

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.

Keywords

Amphetamine, distractibility, orienting, air-righting, superior colliculus

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].

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 pm. 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 minutes 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 minutes, 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 stimulus during the 5 s in which it was on was measured for each of the ten stimuli. As well as examining behaviour within the 5 s while the stimulus was on, the 5 s pre- and post-stimulus periods were also examined to assess whether the animals were affected by the stimulus when it was not actually on. That is, if their behaviour was a general behaviour directed towards the stimulus object rather than a response to the sensory stimulus itself (i.e. the light), that is a result of arousal rather than attention.

2.4 Air-righting

To test air-righting, each rat (N=50, 219 ± 4.9 g; Vehicle N=14, 2 mg/Kg = 13, 5 mg/Kg = 11 and 10 mg/Kg = 12) was dropped onto a soft cushion from heights of 50 and 10 cm. Drops were repeated 4 times at each height and heights were alternated to prevent the rats from using tactile landing cues to judge the appropriate righting speed, and ensuring only visual cues are used for modulating righting speed [39]. Prior to being dropped, the animals were held by the shoulders and pelvis in a supine position and were not released until they ceased struggling. All trials were recorded using a Samsung VP-HMX20C camcorder at a frame rate of 50 fps. The footage was then analysed frame by frame to obtain: i) the number of trials for which each animal could successfully right at each drop height ii) the average latency from the animals' release to successful air-righting across the four trials at each height, and iii) the plane in which the rotation took place (whether the animals turned longitudinally or

laterally). Plane was included as a dependent variable because previous studies in animals with different types of SC lesion revealed variation in the plane of righting [50].

To ascertain whether any differences in air-righting reflexes between groups were specific to air-righting, as opposed to differences in reflex behaviour between the drug groups, static supine reflexes were also assessed. For this assessment, animals were held supine against a flat surface and released. This test was repeated 4 times for each animal. As with the air-righting, all trials were digitally recorded using a Samsung VP-HMX20C camcorder. The same measures were collected i.e. whether the animal could right, the plane of righting and the latency to right. Both measures of righting were collected within three days of the end of the treatment period.

2.5 Statistical analysis

Specific statistical tests are detailed in the results section. In all cases where parametric tests were used, data was confirmed as suitable using Kolmogorov-Smirnov test and measures of skewness and kurtosis prior to analysis. In reporting the outcome of statistical tests, we have provided both the effect size and observed power in addition to statistical significance. The effect size provides a measure of the magnitude of the difference between groups in an analysis and it can be considered the main finding of a quantitative study [51]. The p-value provides information about whether an effect exists but the effect size reveals the size of the effect and it is becoming increasing recognised that both values should be reported [51, 52]. In the present study phi (φ) is reported for Chi-Square analyses, where a value of 0.1 is considered a small effect, 0.3 a medium effect and 0.5 a large effect, corresponding to 15%, 33% and 47% of non-overlap between groups respectively. For ANOVA

analyses, partial-eta squared (η^2) is provided for effect size where values of 0.01, 0.06, and 0.14 indicate small, medium, or large effects and the overlaps outlined above. Observed statistical power is provided to show the probability of rejecting a false null hypothesis. It is generally accepted that power should be at least 0.8.

3. Results

3.1 Orienting behaviour

Chi-Square analysis revealed that there was no significant relationship between the dose given (Vehicle N=14, 2 mg/Kg = 13, 5 mg/Kg = 12 and 10 mg/Kg = 13) and whether the animal responded to the first stimulus (χ^2 (3) = 1.46; p=0.691; φ = 0.168, Observed power = 0.82). This indicates that initial visual responsiveness i.e. response to a novel stimulus, was unaffected by treatment with amphetamine. To examine whether there was a difference in the number of stimuli oriented towards, we calculated the number of stimuli responded to before the animal ceased orienting to the visual stimulus. These data were analysed using a One-Way ANOVA. As shown in Figure 1 there was a dose-dependent decrease in the number of stimuli oriented towards, indicating amphetamine was suppressing this behaviour, however, this trend failed to achieve significance (F(3, 48)=1.44; p=0.244; η^2 = 0.082, Observed power = 0.36). In the 5 s periods either side of the stimulus light being on, animals were not responsive to the stimulus object and this remained the case for all stimulus

presentations.

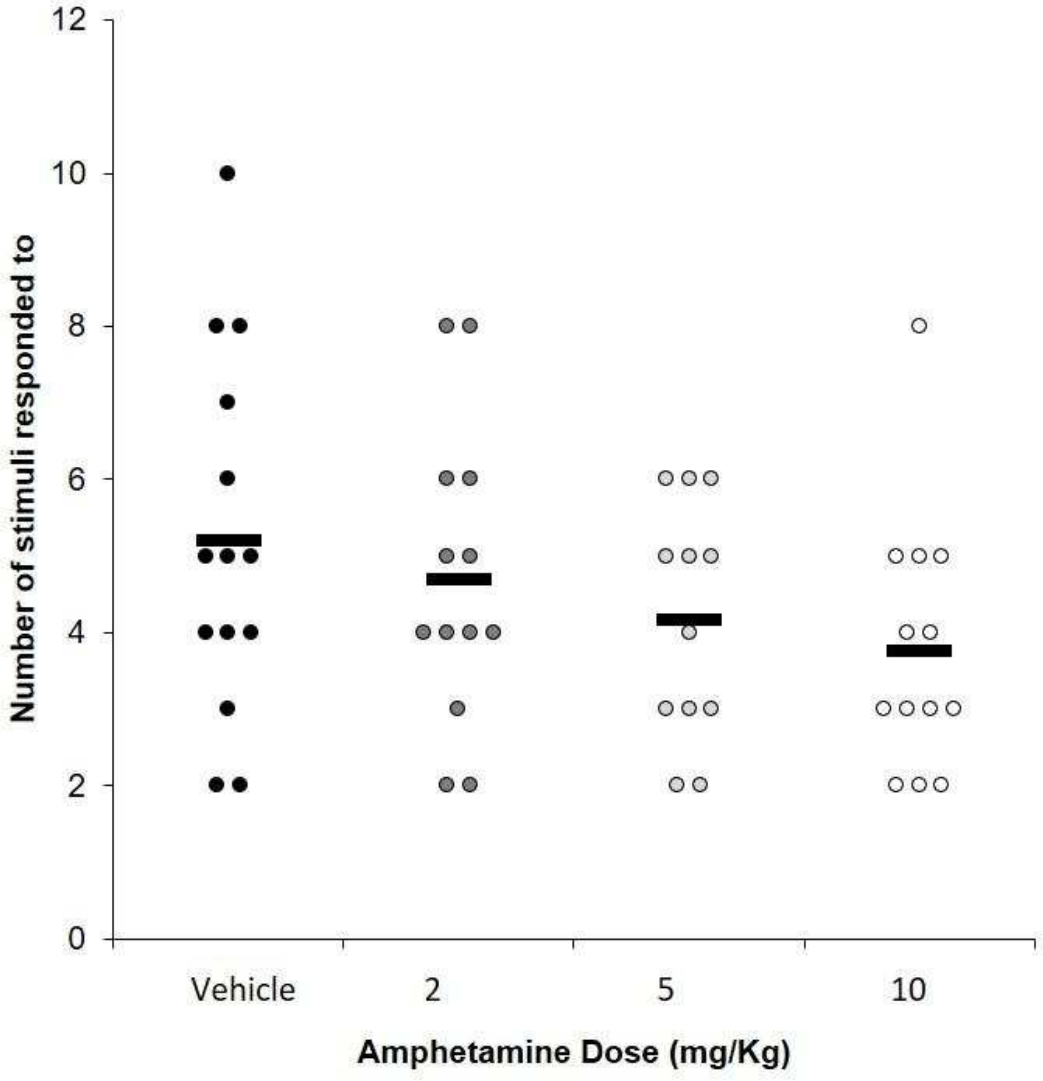

Figure 1: A univariate scatter plot showing the number of stimuli responded to for individual animals in each of the four groups. The black bar represents the mean in all cases.

Response duration data were then analysed with a Mixed Measures ANOVA with STIMULUS PRESENTATION as the within-subjects variable and DOSE as the between-subjects variable. There was a main effect of STIMULUS PRESENTATION ($F(9, 432)=3.08$; $p=0.001$; $\eta^2 =0.06$, Observed power = 0.976) as response duration decreased with repeated stimulus presentation (Figure 2). There was, however, no

significant main effect of DOSE ($F(1, 3)=0.44$; $p=0.726$; $\eta^2 =0.03$, Observed power = 0.132) or interaction effect ($F(27, 432)=0.88$; $p=0.644$; $\eta^2 =0.05$, Observed power = 0.779).

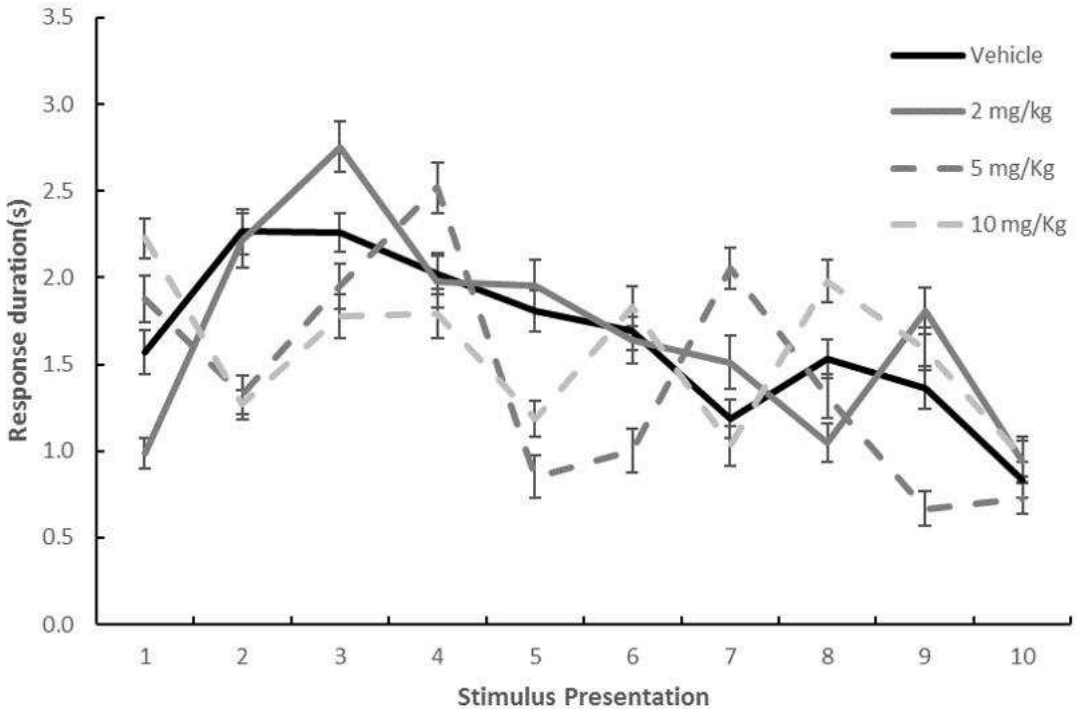

Figure 2: Response duration across stimulus presentation given as mean ± SEM.

3.2 Air-righting

All animals successfully air-righted when dropped from 50 cm for every trial, so no inferential statistics were conducted on these data. At the 10 cm height, there was a reduction in the percentage of trials where righting was successful (Figure 3) but a Chi-Square analysis revealed that there was no significant relationship between the dose received (Vehicle N=14, 2 mg/Kg = 13, 5 mg/Kg = 11 and 10 mg/Kg = 12) and the ability to right at a 10cm drop height (χ^2 (12) = 10.33; $p=0.587$; $\varphi = 0.262$, Observed power = 0.83).

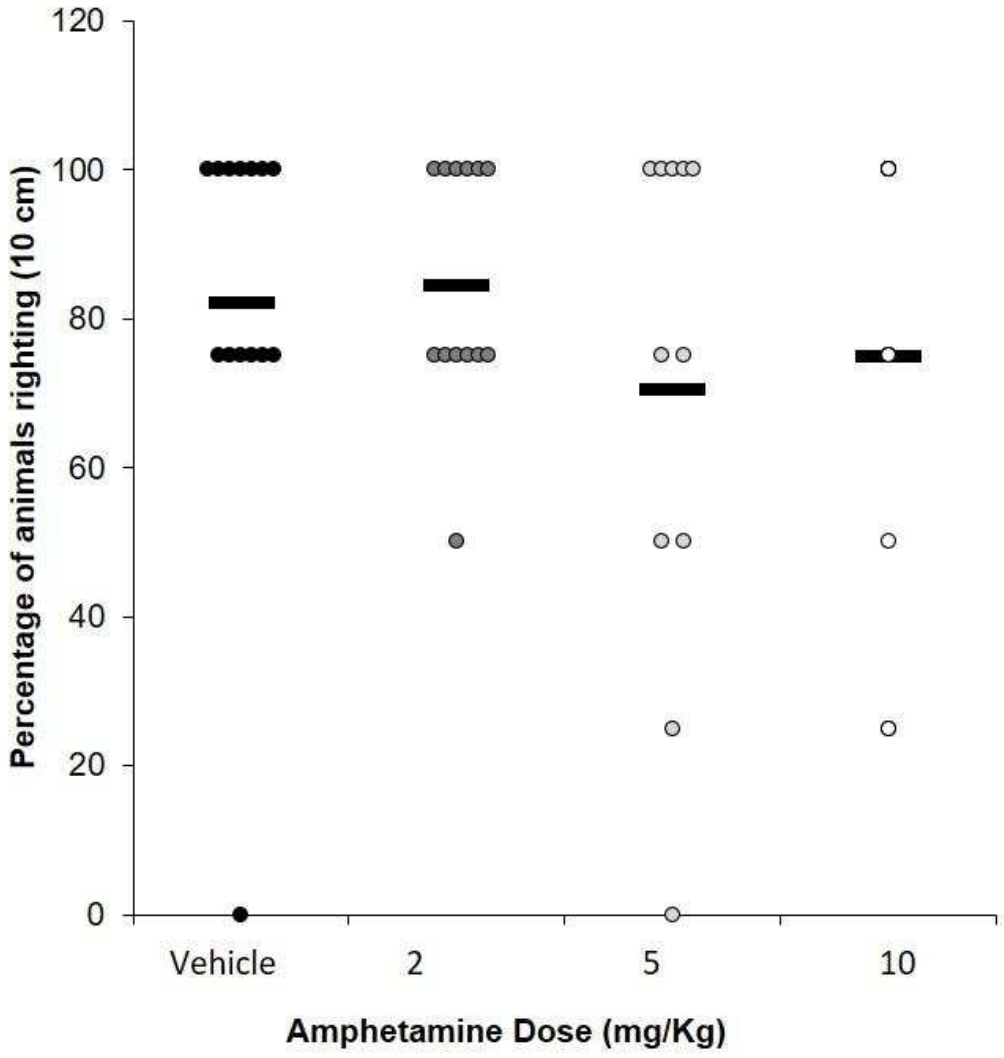

Figure 3 A univariate scatter plot showing the percentage of trials each animal righted successfully on for the different groups. The black bar indicates the mean percentage for the group.

All animals righted in the longitudinal plane and, therefore, no inferential statistics were conducted. Latency data were analysed with a Mixed Measures ANOVA with HEIGHT as the within-subjects variable and DOSE as the between-subjects variable. The analyses revealed a significant main effect of HEIGHT ($F(1, 44)=127.69$; $p<0.001$; $\eta^2 =0.744$, Power=1.00) with, unsurprisingly, animals dropped from the greater height having a longer latency to right overall (see Figure 3). There was also a significant main effect of DOSE ($F(3, 44)=4.03$; $p=0.013$; $\eta^2 =0.215$, Observed power

= 0.81). Post-hoc Tukey tests revealed there was a significant difference between the 2 mg/Kg and 10 mg/Kg doses (p=0.01), with the latter having a shorter latency to right. Finally, there was a significant HEIGHT x DOSE interaction ($F(3, 44)=5.09$; $p=0.004$; $\eta^2 =0.258$, Observed power = 0.90). To establish what drove this interaction we conducted a series of restricted Mixed Measures ANOVAs using just the vehicle group and one amphetamine dose. A significant interaction was found for the vehicle and 10 mg/Kg comparison ($F(1, 23)=12.13$; $p=0.002$; $\eta^2 =0.345$, Observed power = 0.92). However, there was also a trend towards significance for the vehicle and 5 mg/kg interaction ($F(1, 21)=3.54$; $p=0.075$; $\eta^2 =0.144$, Observed power = 0.44). Notably this comparison had lower power, which may explain why significance was not reached. Examination of the data in Figure 4 confirm that the animals treated with 10 mg/Kg amphetamine are less able to modulate the latency of their righting by height compared with the vehicle group, in line with our hypothesis. The 5 mg/Kg had an intermediate ability to modulate their latency between the vehicle and 10 mg/Kg group.

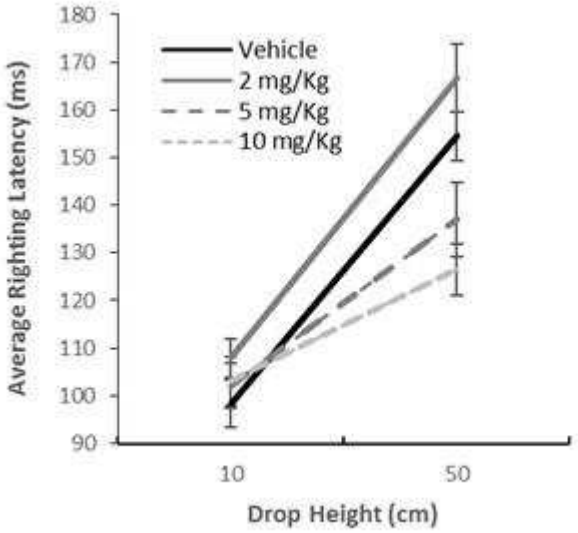

Figure 4: Latency to right from the different heights shows that animals treated with 10 mg/kg amphetamine are less able to modulate their righting latency by height.

Analysis of static righting behaviour revealed that all animals successfully righted on every trial and in the longitudinal plane and, therefore, no inferential statistics were conducted on these measures. Latency to right data was deemed suitable for parametric tests and then analysed with a One Way ANOVA, which showed that there was no significant difference between the groups ($F(3,49)=0.796$, $p=0.503$, $\eta^2 = 0.049$, Observed power = 0.70).

4. Discussion

We reasoned that heightened activity in the SC was linked to increased distractibility and that chronic treatment with amphetamine, known to reduce distractibility, would impact on collicular activity and that this would result in a change to collicular-dependent behaviour. Specifically, we hypothesized that treatment with amphetamine would reduce orienting to repeated visual stimuli and reduce the ability to modulate air-righting according the drop height. The results of the present study partially support this hypothesis.

On the orienting task we found no difference between the treatment groups in terms of the initial response to visual stimuli. This is consistent with previous visual orienting research using acute amphetamine administration [53]. Our hypothesis focussed on the subsequent reduced orienting and the present study showed a dose-dependent decrease in the number of stimuli responded after the initial response. Whilst this dose-dependent effect did not reach statistical significance, the analyses indicated a medium-to-large effect size and reduced power, suggesting that there may be

differences between the groups but that the power of the analysis prevented this reaching significance. Certainly, the overall pattern of results were in line with studies showing a decrease in collicular activity in the presence of amphetamine [26, 31, 32]. Previous research has shown that with very salient stimuli, orienting behaviours can occur in the presence of collicular lesions [53]. Whilst this seems unlikely here because the previous stimuli classed as salient were moving (ours were not), it is possible that our stimulus was too salient to see significant suppression of the response in the presence of the selected doses of amphetamine. Another possible explanation for the lack of effect of amphetamine on the number of orienting responses is that when administered chronically, cortical effects mask those within the colliculus itself. Previous research has shown that acute systemic amphetamine, whilst depressing visual responses in the colliculus [31, 32] also causes cortical desynchronization [54] which would have a faciliatory effect on the colliculus, thus potentially counteracting the direct depressive effects. However, to date, no one has investigated whether such cortical effects occur with chronic amphetamine administration and this may, therefore, warrant further investigation. It is also possible that with repeated administration the SC effectively desensitized to the depressive effects of amphetamine. This would seem unlikely given the known sensitization that occurs to repeated administration of amphetamine in other paradigms [55] but it cannot be ruled out without further investigation.

As expected the duration of response did decrease with repeated stimulus presented, with results indicating a significant difference over time and a medium effect size. There were no significant differences between the different doses, and the effect size indicated only small effect size but also a low power. There was also no significant

interaction, found between stimulus presentation and dose, despite reasonable statistical power. These results indicate that the duration of the response is unaffected by amphetamine administration in the current paradigm, but these duration measures could, of course, be impacted by cortical activation or desensitization as outlined above.

Data from the air-righting experiment revealed that all animals, irrespective of dose received, were equally capable of righting from both heights. This is perhaps not surprising given the ability to right per se is not dependent on the SC, only the ability to modulate righting by height is. Rather the vestibular system is responsible for overall righting [39] and there is evidence that amphetamine does not impact on this system [56]. In addition, there was no alteration to the plane in which righting occurred. Previous work with SC-lesioned animals suggested plane changes do occur in these circumstances [50]. The fact that they were not apparent in the present study is perhaps unsurprising given that the colliculus was not removed, rather its activity was just likely suppressed by amphetamine [31, 32, 57].

In line with previous studies, we found that animals dropped from a lower height righted with a shorter latency [21, 39, 40, 50]. This relationship was similar for all drug doses. However, in support of our hypothesis, animals treated with a high dose of amphetamine were unable to modulate their righting latency according to height as effectively as those in the control group– a key collicular-dependent behaviour. This effect was shown to be large for both the 5 mg/Kg and 10 mg/Kg group (effect sizes of 0.144 and 0.345 respectively), although only the latter reached statistical significance. This is likely to be due to the reduced power of the analysis for the 5 mg/Kg group., although cortical activation countering collicular effects, as described

above, cannot be ruled out. The fact that we do see effects of the drug on the ability to modulate righting by height does suggest there is still an impact on the colliculus at the higher dose at least, indicating desensitization is unlikely to explain the lack of effects on orienting. There was no effect for the 2 mg/Kg dose, which is the most closely associated with typical therapeutic doses of amphetamine. This could suggest that the action of amphetamine reported here is unlikely to underlie the therapeutic effects of amphetamine. However, to be sure of this further research, with additional dose validation using blood plasma levels is necessary.

It is unclear exactly how suppression of activity in the colliculus by amphetamine would impact on the height-dependent modulation, however, it is possible to speculate that amphetamine is affecting the time-to-impact calculation that is believed to be computed in the colliculus [58, 59]. The details of such a calculation are unclear but it is suggested that it involves binocular collicular cells in other species [59] and such cells are known to exist in rats [60-63]. Furthermore, acute injections of amphetamine have been shown to alter receptive field size in the visually-responsive layers of the SC [64]. When administered acutely, the amphetamine-induced changes in the receptive field diminished after eight hours [64]. However, it is plausible that, following a chronic treatment schedule, effects on the receptive fields would be longer lasting. It is therefore possible to speculate that amphetamine induced increases in receptive field size result in an impaired calculation and reduced ability to right in a height-dependent manner. Such longer lasting effects are in line with research investigating the impact of similar amphetamine treatment on other brain structures, where changes are found to persist for 3.5 months after treatment cessation [35, 36]. This research also suggests that chronic amphetamine treatment can increase dendritic

spines and branching, something which has been positively correlated with receptive field size in the colliculus [65]. It may be helpful to next examine exactly how long after treatment stops these changes persist for because clinical literature is currently unclear about the presence and timing of a possible rebound effect, i.e. the return of symptoms after stopping amphetamine treatment in ADHD [66].

Despite the findings showing that chronic treatment with amphetamine can impair some collicular-dependent behaviours, it is important to acknowledge the limitations of the present study. Firstly, whilst every effort has been made to ensure doses are therapeutically relevant and administered using an appropriate method to best mirror human use, we did not measure blood plasma levels, something that should be considered in future research. Secondly, for some of the reported analyses the observed power was less than the recommended 0.8. Specifically, this affected our analysis of the orienting task for the number of stimuli oriented to (Observed power = 0.36), and the main effect of dose (Observed power = 0.132) and interaction effect in the response duration (Observed power = 0.779), although the latter was only just short of the required power. In the air-righting analyses, all key comparisons for testing the hypothesis were sufficiently powered, except for the restricted ANOVA comparing the control and 5 mg/Kg in terms of their ability to modulate their righting by height. Given the lower power on these analyses, there is an increased risk of Type II errors, and therefore an increased possibility of the null hypothesis being false, but not rejected. As such, the lack of power does not negate the study results but rather indicates, we may have underestimated the impact of amphetamine on the collicular dependent behaviours. Finally, we have suggested that the effect of air-righting may be underpinned by changes in the receptive field size. This explanation is based on

current literature and future research may consider direct measuring of receptive fields in animals chronically treated with amphetamine.

5. Conclusions

Heightened distractibility is associated with several conditions and is most notably a core symptom of ADHD where it is often treated with psychostimulants including amphetamine. In the present study we have demonstrated that chronic treatment with amphetamine can alter collicular-dependent modulation of air-righting in the days following treatment cessation in a manner consistent with amphetamine's acute ability to suppress activity in the visually-responsive superficial layers of the colliculus. We suggest that the mechanism of this effect may be increased receptive field size, altering the collicular time-to-impact calculations.

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