Low performing rats model the inattentive subtype of adult ADHD in the 5-choice continuous performance task (5C-CPT)

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Introduction

- Disturbances in cognition; specifically sustained attention, vigilance and impulsivity are central features of the symptomatology of ADHD.
- The 5C-CPT measures vigilance in a way similar to the human CPT, and allows for the measurement of response disinhibition (false alarm rate), which is important when validating animal models of ADHD.
- Selection of rats from a "normal" population that display poor performance in the 5C-CPT may provide a more translational animal model of ADHD.
- **AIM: To investigate the effects of psychostimulant and non-stimulant drugs on attention, impulsivity and performance in adult rats divided into high and low performers in the 5C-CPT.**

Materials & Methods

- Female Lister-hooded rats were trained to criterion in the 5C-CPT. Standard training conditions included: variable inter-trial interval-ITI 5 s (average), stimulus duration 1 s, limited hold 5 s. 5C-CPT includes both no and no-go trials.
- After 60 trials animals were divided into two groups – 1.High performers 2.Low performers, based on their performance, using accuracy (sustained attention), % correct rejections (vigilance) and false alarm rate (response disinhibition).
- Rats then received atomoxetine (0.5, 1.0, 2.0 mg/kg; i.p.), methylphenidate (0.5, 1.0, 2.0 mg/kg; i.p.), or vehicle (0.9% saline i.p.) 20 - 30 min prior to testing in the modified 5C-CPT see below.
- On test days (challenge sessions) the 5C-CPT involved a variation in variable ITI from 5 s to 10 s within the session (all other parameters remained the same). Standard training sessions were interspersed between test days.
- The 5C-CPT attentional measures are expressed as % correct responding or % omission, % correct rejections, false alarm rate and sensitivity index. The impulsivity measures are expressed as the number of premature responses.
- Data were analysed using a linear mixed model analysis with treatment as fixed factor and subject as a random effect, followed by planned comparisons.

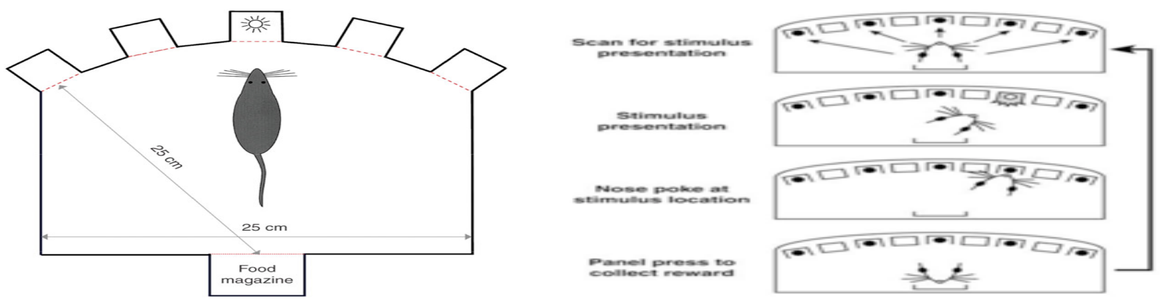


Figure 1: (A) **:** A schematic diagram of the 5-CSRTT chamber indicating the arrangement of the five response apertures and the food magazine. Image taken from (Bari et al 2008). (B) Schematic diagram of the correct performance of a trial presented to the animal during the 5-CSRTT. Image taken from (Amitai and Markou, 2010). The same apparatus are used in the 5C-CPT. When all the apertures are lit the animal must with-hold from nose-poking (responding).

Results

- Atomoxetine at the highest dose (2.0 mg/kg) produced a significant reduction ($p<0.05$) in impulsivity in low performers (figure 1B) as measured by the number of premature responses.
- Methylphenidate produced a significant increase impulsivity at the highest dose (2.0mg/kg) in high performers ($p<0.01$; figure 2A), and at 1.0mg/kg in low performers ($p<0.05$; figure 2B).

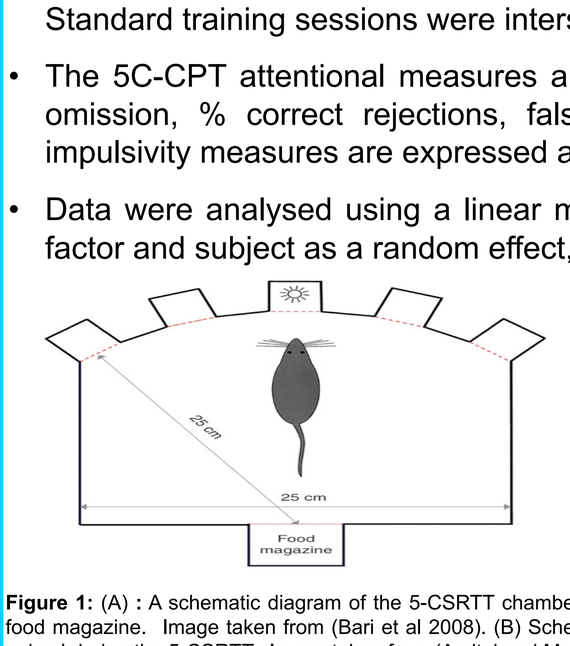


Figure 1A 2A: The number of trials, premature and perseverative responses in the 5C-CPT; ITI set at 10 s. All data are expressed as mean ± SEM (n=8).

Figure 1B, 2B: The number of trials, premature and perseverative responses in the 5C-CPT; ITI set at 10 s. All data are expressed as mean ± SEM (n=8).

Atomoxetine Results

In LOW performers, atomoxetine:

- significantly increased accuracy in low performers at 2.0 mg/kg ($p<0.05$; figure 3B).
- significantly decreased the false alarm rate at 1.0 and 2.0mg/kg, a measure of no-go trials incorrectly responded to - response disinhibition, ($p<0.05$, 0.01 respectively; figure 4E).
- significantly increased the sensitivity index, a measure of the ability to discriminate between go and no-go trials, at 1.0 and 2.0mg/kg ($p<0.01$, 0.05 respectively; figure 4F)

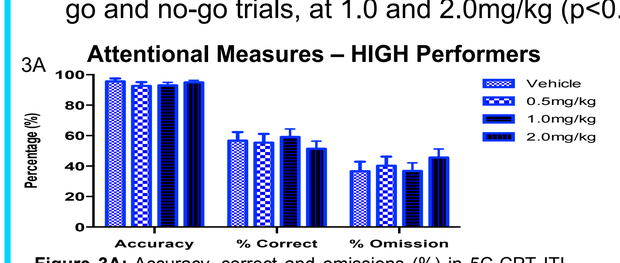


Figure 3A: Accuracy, correct and omissions (%) in 5C-CPT ITI set at 10 s. All data are expressed as mean ± SEM (n=8).

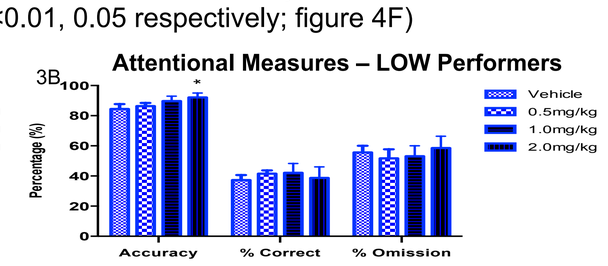
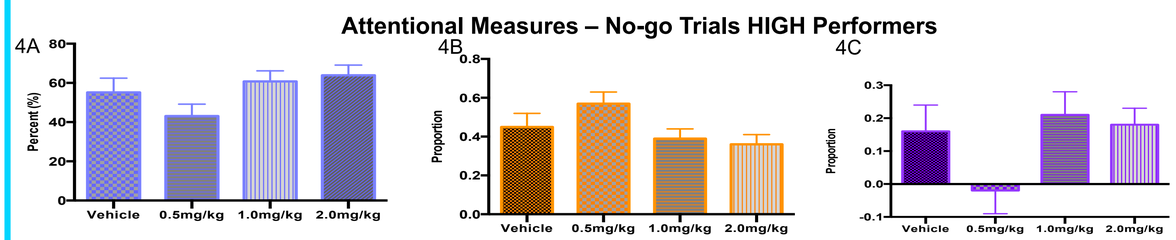


Figure 3B: Accuracy, correct and omissions (%) in 5C-CPT ITI set at 10 s. All data are expressed as mean ± SEM (n=8).



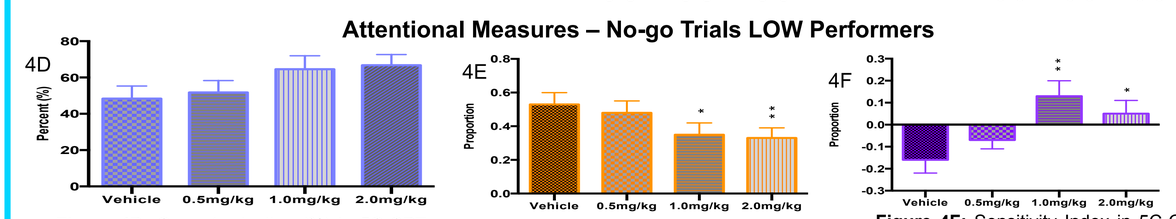


Figure 4D: Correct rejection (%) in 5C-CPT ITI set at 10 s. All data are expressed as mean ± SEM (n=8).

Figure 4E: False alarm rate in 5C-CPT ITI set at 10 s. All data are expressed as mean ± SEM (n=8).

Figure 4F: Sensitivity Index in 5C-CPT ITI set at 10 s. All data are expressed as mean ± SEM (n=8).

Methylphenidate Results

In LOW performers, methylphenidate:

- significantly increased accuracy at 1.0mg/kg and 2.0mg/kg ($p<0.05$, $p<0.01$; figure 5B).
- significantly increased correct rejections (%) at 1.0mg/kg ($p<0.05$;figure 6D).
- significantly reduced the false alarm rate at 1.0mg/kg ($p<0.05$; figure 6E).

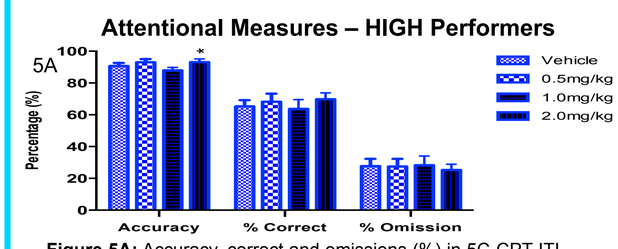


Figure 5A: Accuracy, correct and omissions (%) in 5C-CPT ITI set at 10 s. All data are expressed as mean ± SEM (n=8).

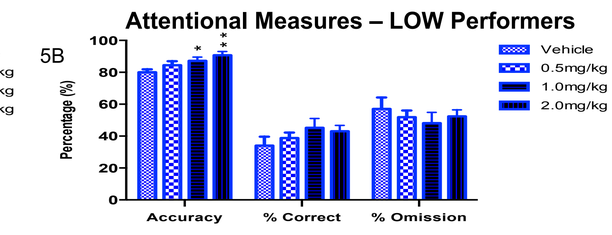
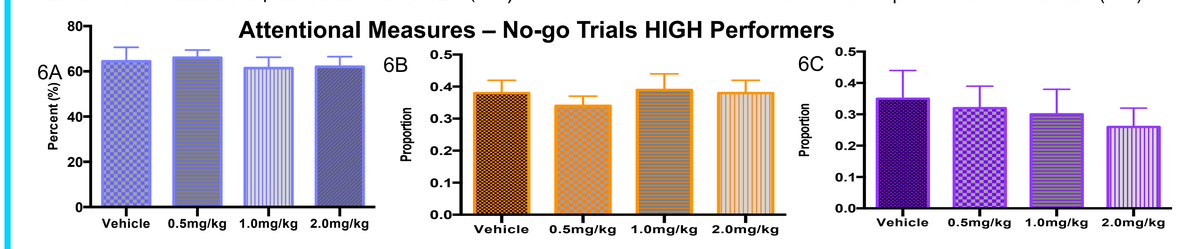


Figure 5B: Accuracy, correct and omissions (%) in 5C-CPT ITI set at 10 s. All data are expressed as mean ± SEM (n=8).



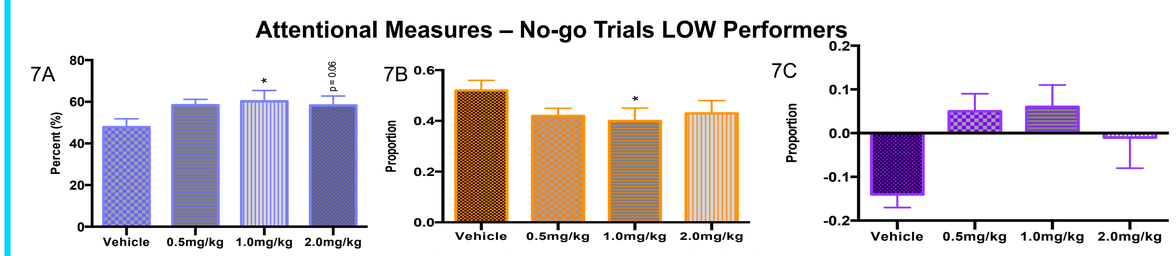


Figure 6D: Correct rejection (%) in 5C-CPT ITI set at 10 s. All data are expressed as mean ± SEM (n=8).

Figure 6E: false alarm rate in 5C-CPT ITI set at 10 s. All data are expressed as mean ± SEM (n=8).

Figure 6F: Sensitivity Index in 5C-CPT ITI set at 10 s. All data are expressed as mean ± SEM (n=8).

Conclusion

- This model utilises the 5C-CPT to select animals with reduced sustained attention and vigilance, in order to explore the efficacy of novel ADHD medication.
- Atomoxetine enhanced sustained attention in the go-trials in the poor performers only, and reduced impulsivity in the low performers. Methylphenidate enhanced sustained attention and vigilance in the low performers, but increased impulsivity in both the high and low performers.
- These data suggest that low performers are more sensitive to the effects of both stimulant and non-stimulant drugs, and could provide a putative animal model for the inattentive subtype of adult ADHD.

References

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There is no potential conflict of interest