Effect of modulating dopaminergic and noradrenergic neurotransmission on attention and impulsivity

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Introduction. Clinical studies suggest that an individual's response to drug administration changes according to his or her baseline rates of behaviour (*rate dependence*). However, factors such as regression to the mean and mathematical coupling can also contribute to rate dependence and these are often unrecognised in drug studies. Oldham's method (Oldham, 1962) controls for these factors on rate dependence. Here, we compared simple correlations to Oldham's method to determine if the performance changes following drug administration (Atomoxetine or GBR12909) depend on baseline rate of behaviour.

Method. 28 Lister-Hooded female rats (240±10g at the start of training) were trained to target (>70% accuracy, < 30% omission and < 40% false alarms) in a standard 5C-CPT task (Fig. 1). 5C-CPT performance was then tested under Atomoxetine (0.5, 1 and 2mg/kg) which is a selective noradrenaline reuptake inhibitor or GBR12909 (0.25, 0.5 and 1mg/kg) which is a selective dopamine reuptake inhibitor administered using a Latin-square within-subjects design. Three methods were used to assess rate dependence: 1) Common basic method to correlate baseline and parameter change. 2) Oldham's method, which correlates between the average of pre and post treatment and the parameter change. 3) Retest Reliability method, which correlates adjusted baseline value with behavioural change.

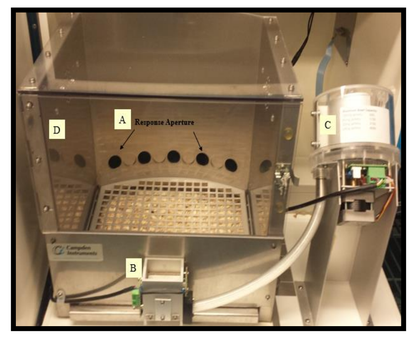

Figure1. **5C-CPT chamber**. **A** Response apertures, **B** reward tray, **C** Reward dispenser and **D** House light

Results 1. Atomoxetine improves sustained attention (d') and waiting impulsivity (premature response) in a baseline-dependent manner

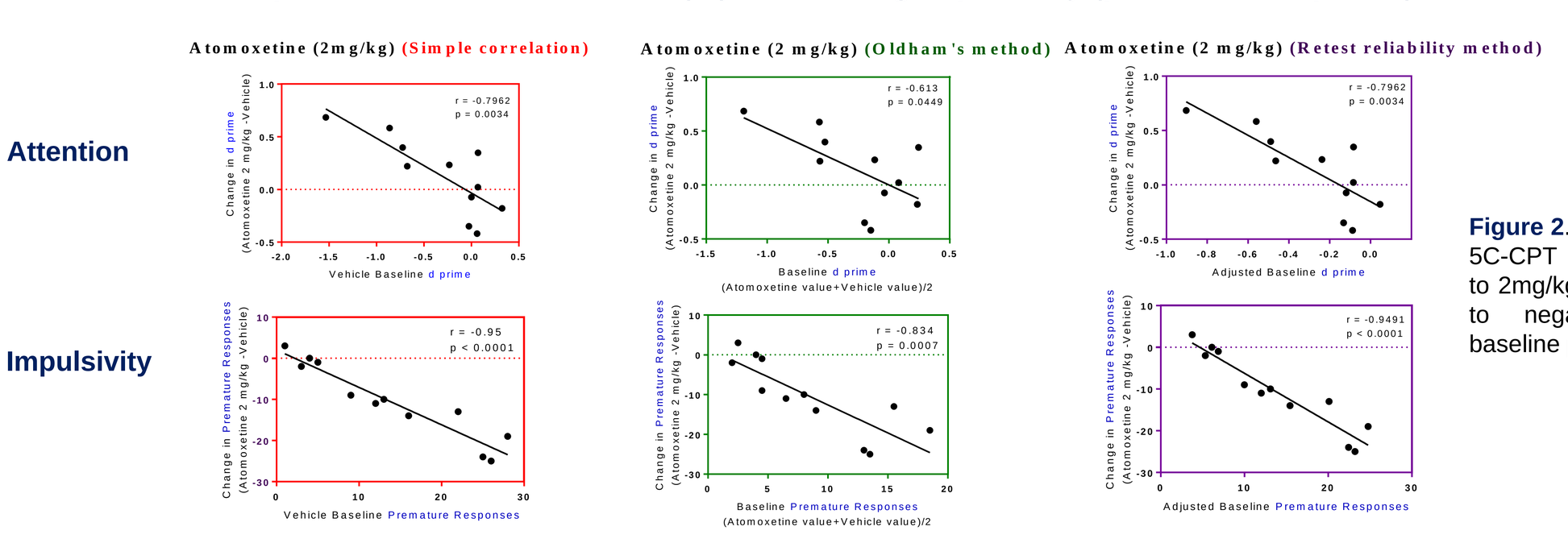

Figure 2. Effect of atomoxetine on 5C-CPT performance. Response to 2mg/kg atomoxetine was found to negatively correlate with baseline performance

Results 2. GBR12909 improves selective attention (accuracy) and promotes waiting impulsivity in a baseline-dependent manner

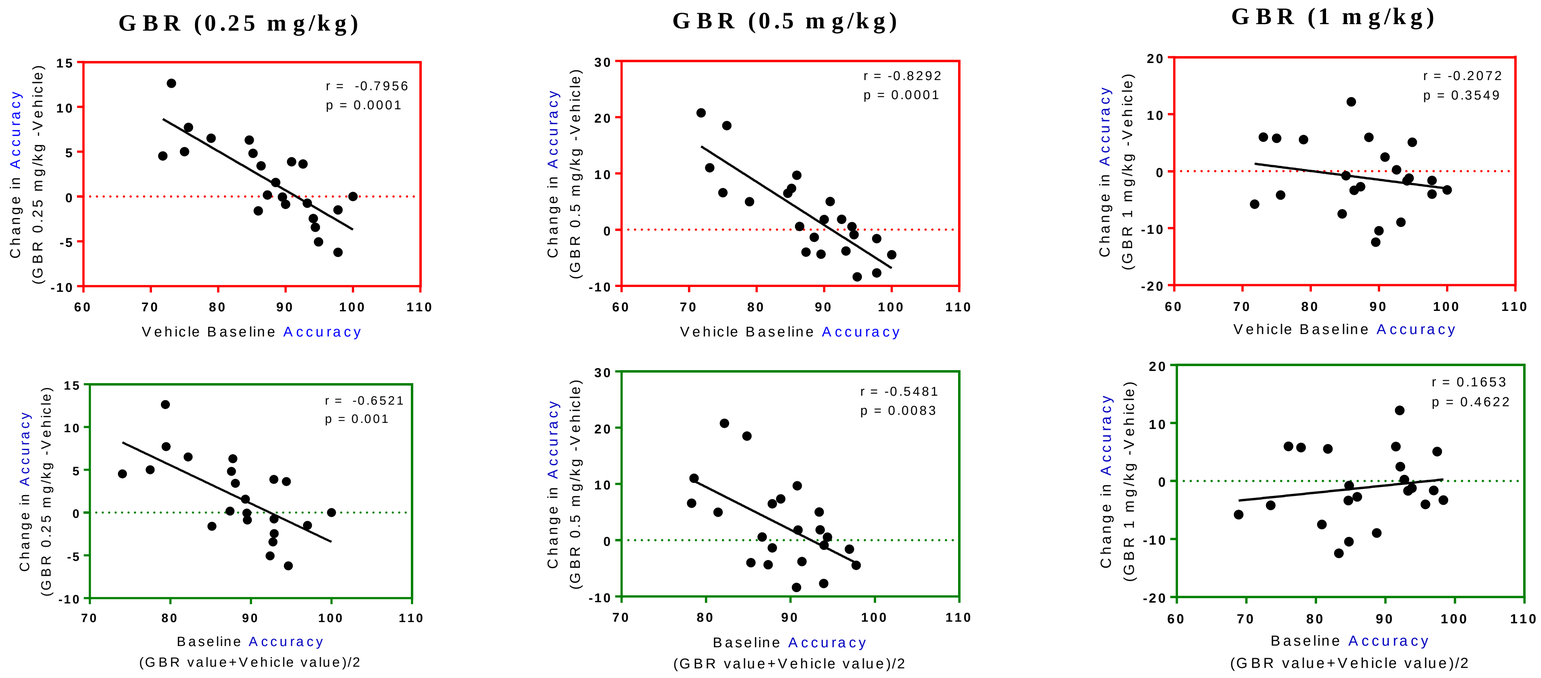

Figure 3. Effect of GBR on accuracy. 0.25 and 0.5 mg/kg GBR12909 had a classical rate dependent effect on accuracy.

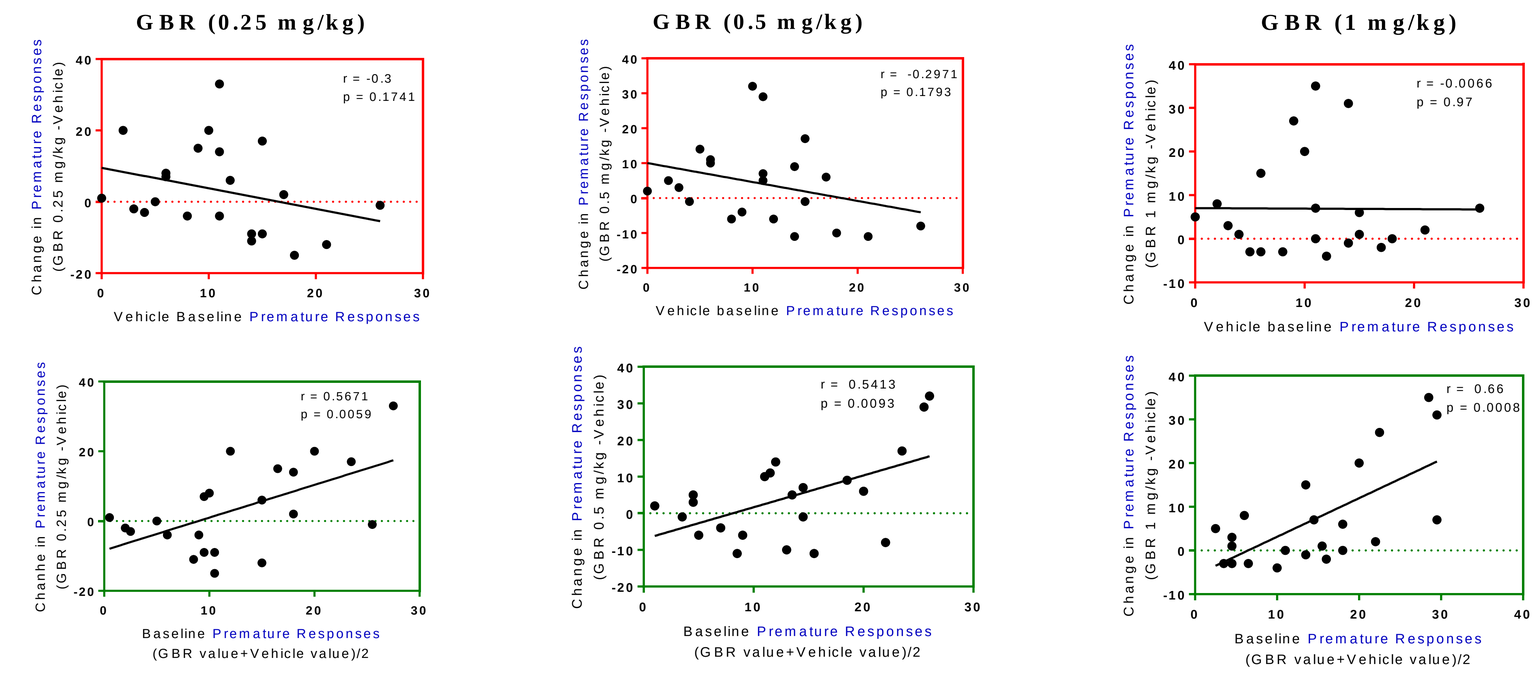

Figure 4. Effect of GBR on impulsivity. Oldham's method showed a positive correlation between baseline impulsivity and the change.

Conclusions

1. We show a rate-dependent relationship between baseline 5C-CPT performance and the response to Atomoxetine or GBR12909.
2. As expected, atomoxetine improved sustained attention in low-attentive rats and reduced impulsivity in high-impulsive rats.
3. GBR12909 improved selective attention in low-attentive rats and increased impulsivity in high-impulsive rats
4. A correlative analysis (e.g., Oldham's method) may be particularly effective in revealing drug effects on behaviour.