Noradrenergic modulation of stopping impulsivity in Cocaine Use Disorder

P.203

R. Rodrigues[1], C. Meng[1], S. Morein-Zamir[1,2,5], H. Ziauddeen[1,3], E. Fernandez-Egea[1,3], R. Regenthal[4], B.J. Sahakian[1,5], E.T. Bullmore[1,3,5,6], T.W. Robbins[1,5], K.D. Ersche[1,5]

[1] University of Cambridge, Departments of Psychiatry and Psychology, Cambridge, UK
[2] Anglia Ruskin University, Department of Psychology, Cambridge, UK
[3] Cambridgeshire and Peterborough Foundation Trust, Cambridge, UK
[4] Leipzig University, Division of Clinical Pharmacology, Rudolf-Boehm-Institute of Pharmacology and Toxicology, Leipzig, Germany
[5] University of Cambridge, Behavioural and Clinical Neuroscience Institute, Cambridge, UK
[6] GlaxoSmithKline, Immuno-Inflammation Therapeutic Area Unit, Stevenage UK

Introduction

High levels of motor impulsivity are a potential marker of addiction vulnerability[1] that predict treatment dropout in individuals with Cocaine Use Disorder (CUD)[2]. Stopping impulsivity is one facet of motor impulsivity characterised by greater difficulties in inhibiting dominant motor responses. Poorer response inhibition in the Stop-Signal Task accompanied by hypoactivity in noradrenaline-rich prefrontal areas, such as the right inferior frontal gyrus (IFG), has been observed in CUD patients[3].

Developing pharmacological interventions that target self-control could help to improve recovery prospects for individuals with CUD. Evidence shows that the cognitive enhancer atomoxetine (Strattera™) improves response inhibition by increasing activity within the right IFG[4]. We, therefore, investigated whether atomoxetine improves response inhibition, as measured by the Stop-Signal Task, in patients with a current DSM-IV diagnosis of CUD and healthy, non-drug using controls.

We hypothesised that atomoxetine would improve response inhibition and associated cognitive functions in patients with CUD and healthy controls. We also predicted that these effects would depend on individual differences in the ability to successfully inhibit a response at baseline, and on atomoxetine plasma levels.

Method

We investigated the effect of a single 40mg dose of atomoxetine on stopping performance in patients with CUD (N=28) and healthy controls (N=28), using a stop-signal functional MRI paradigm (Figure 1) within a placebo-controlled, double-blind, crossover design. Participants were excluded from the analyses if their task performance did not meet the assumptions of the race model used to estimate stop-signal reaction time (eight CUD participants), or due to poor imaging quality (two CUD participants).

Behavioural Analysis: The effect of atomoxetine on each group's response inhibition (stop-signal reaction time, SSRT) and related cognitive functions (response time on go trials, Go RT; variability in go response times, Go SD) were analysed using mixed analysis of variance (ANOVA) models. To explore the effect of atomoxetine while accounting for heterogeneity within our samples, the change in SSRT between placebo and atomoxetine sessions (Δ SSRT) was correlated with baseline stopping performance and atomoxetine plasma levels.

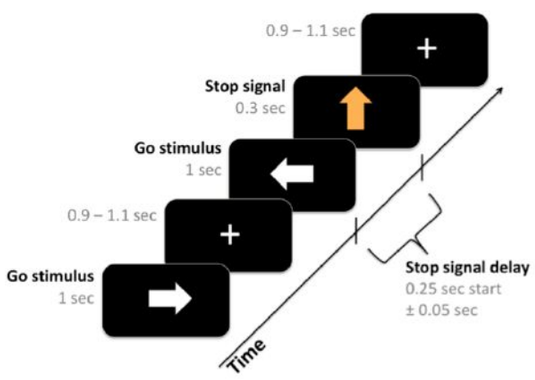

Figure 1. MRI adapted stop-signal paradigm

Neuroimaging Analysis: Functional activity during successful stopping was determined by contrasting successful stop trials against a baseline of successful go trials. Group effects in the whole brain and in an anterior insula/ frontal operculum ROI were analysed using mixed ANOVA models, and the change in activity between placebo and atomoxetine sessions (Δ Activity) was correlated with Δ SSRT (SPM12, voxel p=0.001 uncorrected, cluster p<0.05 FWE corrected).

Behavioural Results

Mixed ANOVA models showed no significant difference in SSRT between the CUD group and control group ($F(1,46)<0.1$, $p>0.99$). The CUD group did, however, show a trend towards slower Go RTs, with significantly greater variability in Go RTs, relative to controls (Go RT: $F(1,46)=3.73$, $p=0.059$, $d=-0.56$; Go SD: $F(1,46)=10.45$, $p=0.002$, $d=0.94$). There was no significant effect of atomoxetine on SSRT ($F(1,46)=0.40$, $p=0.528$), although it significantly speeded Go RT and had a trend towards reducing the variability of Go RTs across all participants (Go RT: $F(1,46)=6.75$, $p=0.013$, $d=0.28$; Go SD: $F(1,46)=3.40$, $p=0.071$, $d=0.20$).

Individual differences associated with improved response inhibition on atomoxetine

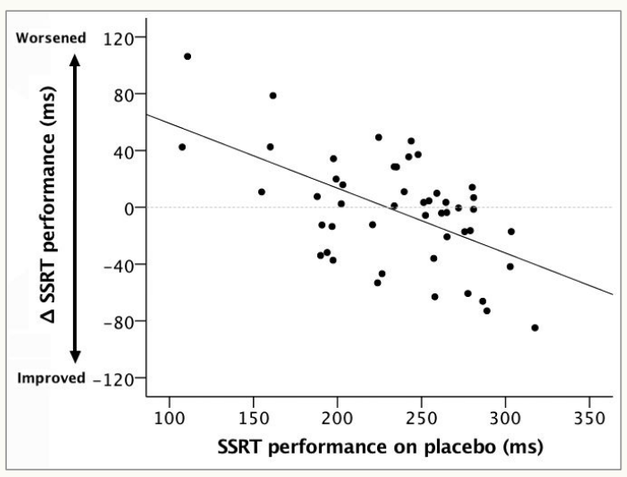

Figure 2 A. Correlation between SSRT on placebo and Δ SSRT. CUD and control participants (N=48) with poorer SSRT performance at baseline showed greater improvements in response inhibition on atomoxetine (r=-0.56, p<0.001).

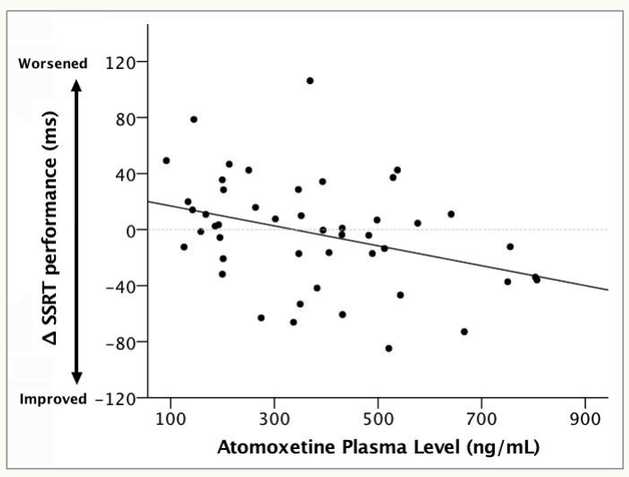

Figure 2 B. Partial correlation between atomoxetine plasma levels and Δ SSRT, controlling SSRT placebo. Higher plasma levels of atomoxetine were associated with greater improvements in response inhibition on atomoxetine in CUD and control participants (N=48) (r=-0.36, p=0.013).

Neuroimaging Results

The effect of atomoxetine on brain activity during successful stopping

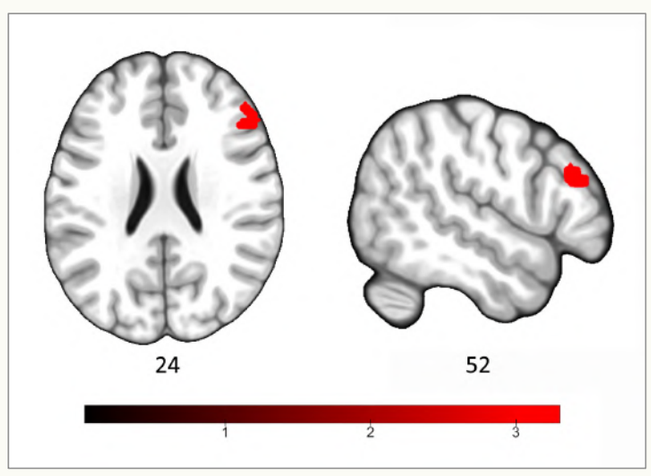

Figure 3 A. Δ Activity in one cluster, which included the right inferior frontal gyrus pars triangularis and right middle frontal gyrus, negatively correlated with Δ SSRT performance in CUD and control participants (N=46), covarying atomoxetine plasma levels (anterior insula / frontal operculum small volume correction, MNI= 52, 30, 24, p=0.015).

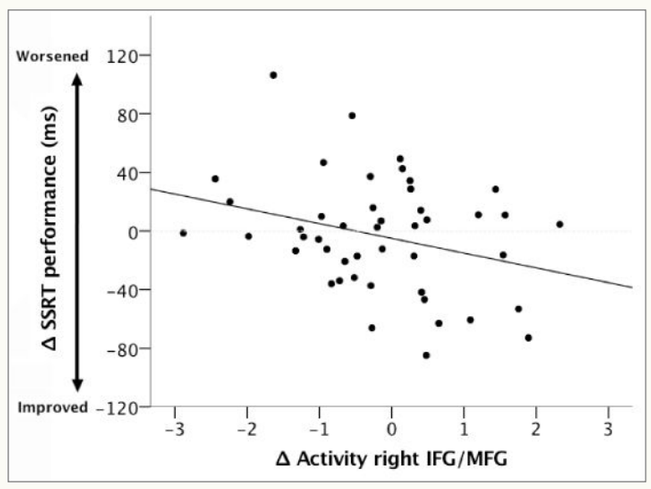

Figure 3 B. CUD and control participants (N=46) with greater task activation in this cluster (right inferior frontal gyrus, IFG; right middle frontal gyrus, MFG) showed greater improvements in response inhibition on atomoxetine.

References

[1] Belin, D., Mar, A. C., Dalley, J. W., Robbins, T. W., & Everitt, B. J., 2008. High impulsivity predicts the switch to compulsive cocaine-taking. Science, 320(5881), 1352-1355.
[2] Moeller, F. G., Dougherty, D. M., Barratt, E. S., Schmitz, J. M., Swann, A. C., & Grabowski, J., 2001. The impact of impulsivity on cocaine use and retention in treatment. Journal of substance abuse treatment, 21(4), 193-198.
[3] Morein-Zamir, S., Jones, P. S., Bullmore, E. T., Robbins, T. W., & Ersche, K. D. 2013. Prefrontal hypoactivity associated with impaired inhibition in stimulant-dependent individuals but evidence for hyperactivation in their unaffected siblings. Neuropsychopharmacology, 38(10), 1945.
[4] Chamberlain, S. R., Hampshire, A., Müller, U., Rubia, K., Del Campo, N., Craig, K., ... & Bullmore, E. T. 2009. Atomoxetine modulates right inferior frontal activation during inhibitory control: a pharmacological functional magnetic resonance imaging study. Biological psychiatry, 65(7), 550-555.
[5] Hiemke, C., Bergemann, N., Clement, H. W., Conca, A., Deckert, J., Domschke, K., Eckermann, G., Egberts, K., Gerlach, M., Greiner, C. & Gründer, G., 2017. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. Pharmacopsychiatry.

Conclusions

Stop-signal response inhibition improved when atomoxetine enhanced activation in the inhibitory motor control network. This replicates prior work showing that atomoxetine exerts its beneficial effects during successful stopping by modulating activity within the right IFG[4].

As participants with slower SSRT performance on placebo showed the greatest improvement on atomoxetine, patients with CUD who exhibit poorer self-regulatory ability at baseline may benefit more from treatment with atomoxetine.

Future studies should include a range of doses to account for differences in atomoxetine metabolism, which may achieve optimal atomoxetine plasma concentrations of 200 – 1000 ng/mL[5] across all participants.

Acknowledgements

This research was funded by a Medical Research Council (MRC) grant (MR/J012084/1) to TWR, KDE, ETB, and BJS and conducted within the Behavioural and Clinical Neuroscience Institute at the University of Cambridge, which is jointly funded by the Medical Research Council and the Wellcome Trust. This study was jointly sponsored by the Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge. TWR consults for Cambridge Cognition, Lundbeck, and Mundipharma and holds a research grant from Shionogi. ETB is employed part-time by GlaxoSmithKline and part-time by the University of Cambridge and serves as the Head of Research and Development at the Cambridgeshire and Peterborough National Health Service Foundation Trust. BS reports receiving consulting fees and lecture honoraria from Lundbeck, lecture honorarium from Servier, consulting fees from Cambridge Cognition, and a grant from Janssen/Johnson & Johnson. All other authors report no biomedical financial interests or potential conflicts of interest.

Contact

Rachel Rodrigues **rr554@cam.ac.uk**