EXPLORING PSYCHOMOTOR SENSITIZATION IN HEALTHY VOLUNTEERS FOLLOWING REPEATED AMPHETAMINE EXPOSURE

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INTRODUCTION

- Repeated use of psychostimulants can alter dopaminergic neurotransmission, leading to behavioral and neurochemical 'sensitization' [1].
- Sensitization might serve as a biomarker to test the effects of novel compounds which have the potential to reverse dopaminergic hypersensitivity.
- The goal of this study was to explore the possibility of reliably eliciting and predicting amphetamine-induced behavioral changes following four doses of oral dexamphetamine.

METHODS

- 16 healthy male volunteers without previous amphetamine exposure (mean age 32 years, range 25-44 years).
- [^{11}C]raclopride PET at baseline and on Day 1, 60 minutes after first oral administration of 20 mg d-amphetamine.
- The NeuroCart performance test battery completed twice pre-dose and 1, 2, 3, 4 and 6 hours post-dose. Tests include: adaptive tracking, body sway, saccadic and smooth pursuit eye movements, finger tapping and the stop signal task (SST).
- Measures of subjective effects: Visual Analogue Scales, the Profile of Mood States and the amphetamine sub-scale of the Addiction Research Centre Inventory.
- Repeated measures task data were compared with a mixed model analysis of variance with fixed factors 'treatment', 'time' and 'treatment by time', and random factors 'subject', 'subject by treatment', 'subject by time' and the average pre-value per day. The average of all Day -1 test scores was included as a covariate.
- Dopamine D_2/D_3 receptor occupancy was calculated using a simplified reference tissue model with the cerebellum as reference.

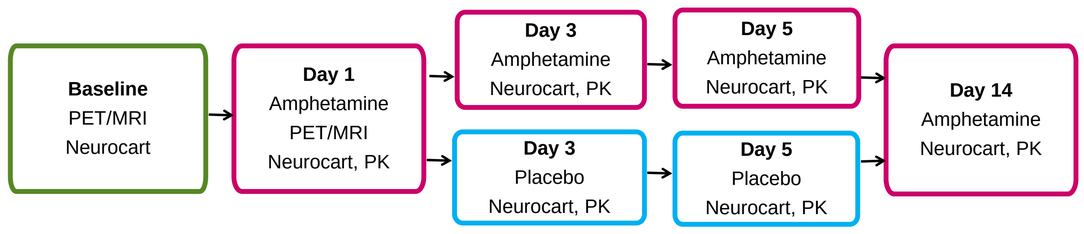


Figure 1: Overview of study design. All 16 subjects underwent a PET/MRI scan and Neurocart test day at baseline (separate days) and after the first dose of d-amphetamine. On days 3 and 5 10 subjects received d-amphetamine and 6 subjects received placebo. The test battery and PK blood sampling were performed twice pre-dose and 1, 2, 3, 4 and 6 hours post-dose.

RESULTS

- Post-amphetamine subjects showed significant improvement on all Neurocart performance tasks, and improvements on reaction time and accuracy on the SST.
- Although between-subject variability was large on all days, within-subject performance was highly consistent across post-amphetamine study days.
- There were no significant group differences (2 vs 4 doses) between Day 1 and Day 14 on any of the tasks.
- The subjective measures showed a similar pattern of within subject consistency across the study days.
- Statistically significant [^{11}C]raclopride dopamine receptor occupancy ($p<0.05$, single-sided paired T-test) was observed in the striatum following d-amphetamine when comparing pre- and post-dose group means.
- The number of missed Go-trials on the SST, measured after PET, correlated negatively with D2/D3 receptor occupancy in the caudate nucleus.

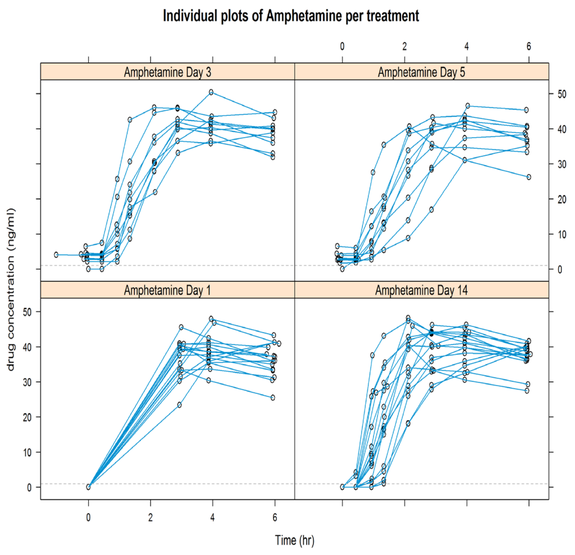


Figure 2: Individual plots of serum d-amphetamine levels (n=16 on Days 1 and 14, n=10 on Days 3 and 5)

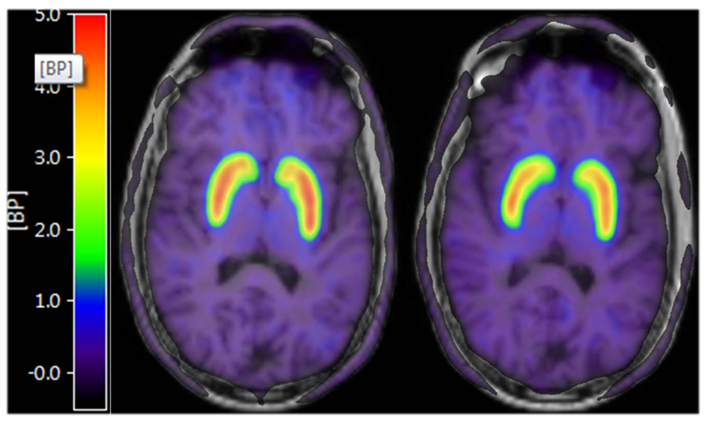
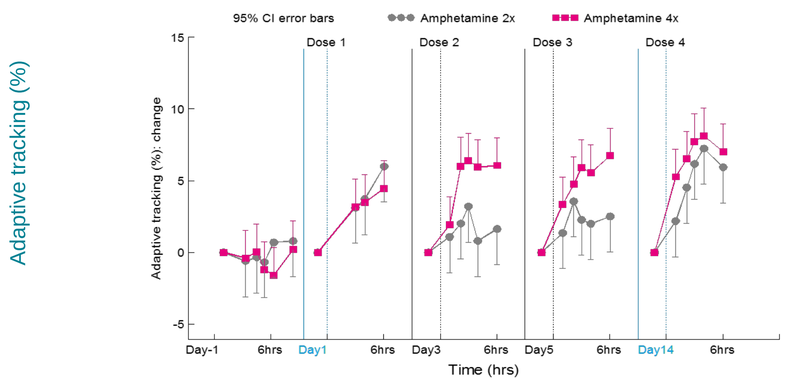
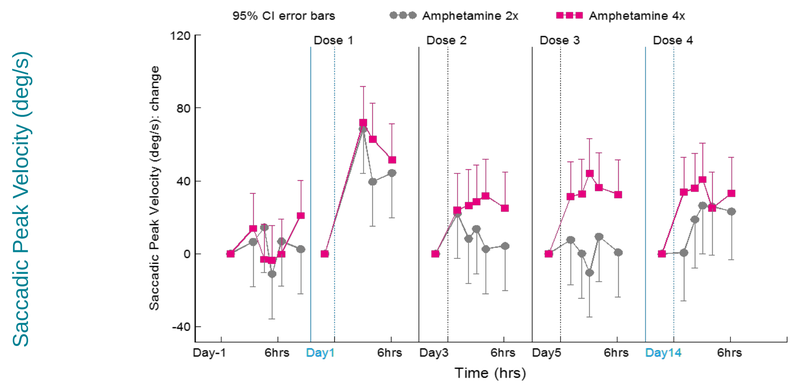


Figure 3: MRI anatomical image atop [^{11}C]raclopride pre-dose (left) and post-dose (right) BP_{ND} PET images for 1 subject





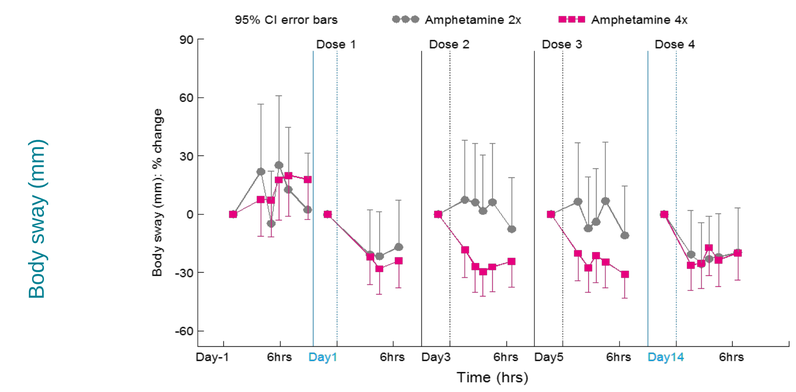


Figure 4: Summary graphs with 95% confidence intervals showing change from baseline least square means group results for adaptive tracking, saccadic peak velocity and body sway. The baseline value is the average of the two pre-dose measurements. The solid lines delineate the different study days, time of dosing in indicated with the thin line. On Day -1 no drug was given. On Days 1 and 14 (blue vertical lines), all subjects (n=16) received d-amphetamine; on Days 3 and 5 (grey vertical lines) 10 subjects received d-amphetamine (pink line) and 6 subjects received placebo (grey line).

DISCUSSION and CONCLUSIONS

- D-amphetamine consistently improved performance on the Neurocart performance tasks, but there were no signs of potentiation after repeated dosing.
- This study did not reproduce earlier findings suggestive of response sensitization.
- This study does, however, provide evidence of consistent and sustained amphetamine effects.
- There was a positive relationship between SST performance and amphetamine-induced elevated brain dopamine levels as measured by PET.

[1] Featherstone et al. "The Amphetamine-induced sensitized state as a model of schizophrenia"; Progress in Neuro-Psychopaharmacology & Biological Psychiatry 31 (2007) 1556-1571.

Acknowledgement

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Disclosure

HC van Gorsel, J van der Aart and JMA van Gerven were fully employed by the Centre for Human Drug Research (CHDR) at the time this study was carried out. P de Boer and M Timmers are fully employed by Janssen Research and Development.
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