

fMRI-measurable effects of Benzodiazepine on the cognitive brain: preliminary results on Placebo vs Blank

L.Nanetti^{1,2}, R. Renken¹, R. Kortekaas¹, I. Zijdwind^{1,4}, N. Meulman¹, A. Kuiper¹, I. den Daas⁵, P. de Boer⁶, G.J. ter Horst^{1,3}

1 University Medical Center Groningen, Neuro Imaging Center; 2 University Medical Center Groningen, Department of Neuroscience, Section Social Brain Lab; 3 University Medical Center Groningen, Department of Neuroscience, Section Anatomy; 4 University Medical Center Groningen, Department of Neuroscience, Section Medical Physiology; 5 Xendo Drug Development Groningen; 6 Johnson & Johnson Experimental Medicine Europe



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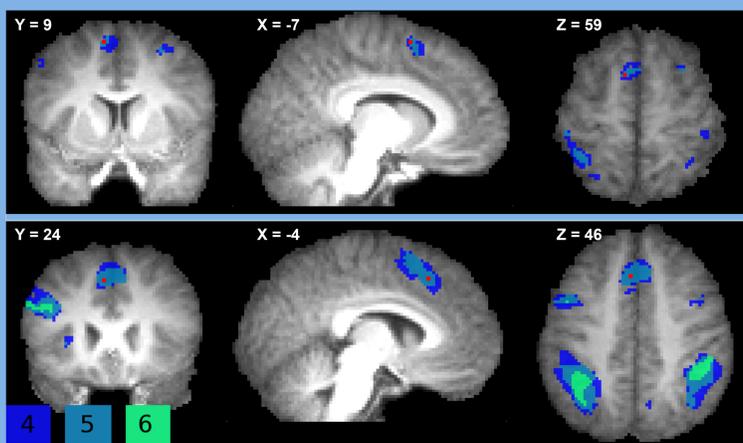
Introduction

The behavioral effects of drugs belonging to the family of benzodiazepines are well known, ranging from reduced attention to impaired ability to memorize, to increased sleepiness (1). However, it is not well known if and how there are (f)MRI measurable effects induced by these drugs. The Pharmacology-MRI project, founded by the European Union through the IAG2 project, aims to investigate this issue, and sees the collaboration of multiple entities: the Neuro Imaging Center Groningen (imaging, data analysis, protocol development), the RuG/University Medical Center Groningen (medical expertise), Xendo (drug/placebo management, protocol development), Johnson & Johnson (protocol development). The experimental protocol was designed to be suitable for investigating a wide class of CNS drugs. It includes a measurement of blood perfusion (ASL) and three different tasks: episodic memory (encoding/retrieval of pictures, modulated by the emotional content), working memory (n-back), and divided attention (different actions, to be performed sometimes simultaneously, reacting with one hand to a visual stimulus, and with the other to a oddball sound paradigm (2)). The subjects (20 healthy young males, age range 18-25) underwent a protocol consisting of 4 visits. Ingestion of drug and placebo was double-blinded. Here we present some relevant facts about the study as well as preliminary results concerning the contrast 2-back vs baseline (fixation cross) on a subsample of 12 participants.

Materials & Methods: n-back

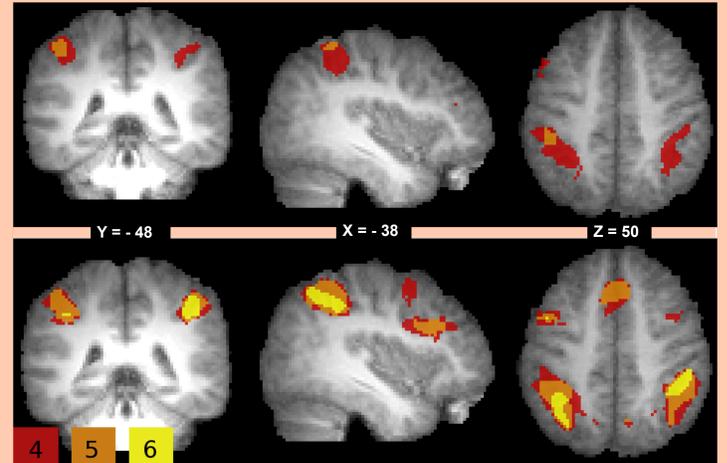
Subjects: 12 caucasian males, age range: 18-25, randomly divided in two subgroups of 6 participants each. The first subgroup did not ingest any substance, active drug nor placebo, whilst the second ingested placebo. The n-back task (letter-based) consisted in four levels: 0-, 1-, 2-, 3-back, presented in blocks of ~30 seconds. The levels' presentation order was such that each level was followed by all other levels twice (e.g., 2-back was followed twice by 0-back, twice by 1-back and twice by 3-back). To control for shape-based strategies, both upper- and lower-case letters were presented. To control for phonetic-based strategies, only dutch alveolar consonants were used. The analysis was performed using SPM8 on the High Power Computing Linux cluster at the Donald Smit Center for Information Technology, University of Groningen. The statistical maps resulting from the application of a threshold of 0.05 (FWE) were binarized and added, subgroup-wise, to build frequency maps of active areas. Each voxel gets then a maximum value of 6.

2-back: preSMA



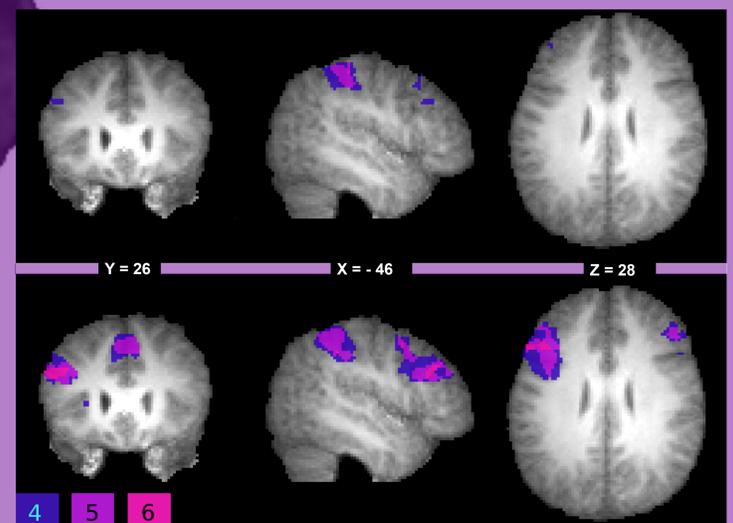
Frequency Maps of contrast 2-back vs baseline (FWE 0.05). Top: Blank; Bottom: Placebo. The Placebo group seems to activate a more anterior part of the preSMA than the Blank group, although the two areas overlap. The centers of the two regions where at least 5 subjects per group have suprathreshold activity are marked with red dots.

2-back: Intra Parietal Sulcus



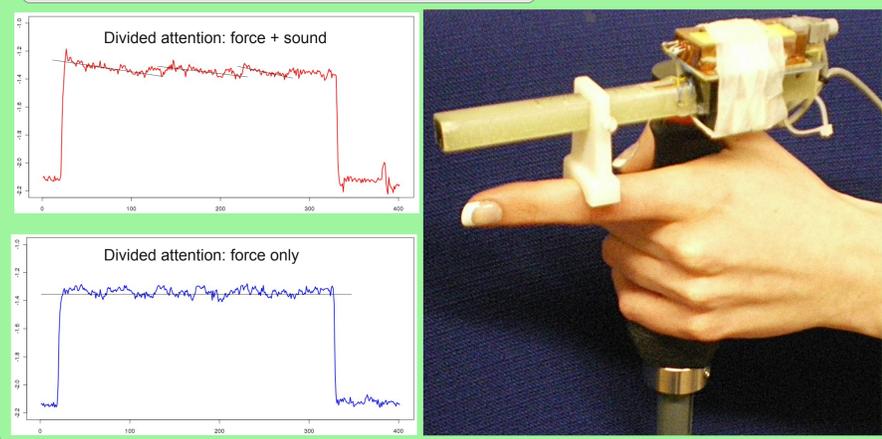
Frequency Maps of contrast 2-back vs baseline (FWE 0.05). Top: Blank; Bottom: Placebo. The bilateral activation of the putative IPS is common to both blanks (5 subjects out of 6) and placebos (up to 6 subjects out of 6). The spatial extent of the ROIs is however bigger for the Placebo subgroup (see also the preSMA panel).

2-back: Prefrontal Cortex



Frequency Maps of contrast 2-back vs baseline (FWE 0.05). Top: Blank; Bottom: Placebo. At this very conservative threshold, putative dorsolateral prefrontal cortex is only active in the Placebo group. At a frequency threshold < 4, patterns are similar.

A different task: divided attention



Discussion and Conclusions

A pattern common to both placebo and blank conditions emerged analyzing the contrast 2-back vs baseline (fixation cross). Bilateral parietal, bilateral premotor and bilateral prefrontal are common to both groups, although at different statistical thresholds: the effects in the Blank group sometimes appear at a more lenient threshold than the one used here (0.05 FWE). A difference seems, however, to consistently emerge about the preSMA, recruited more anteriorly in the Placebo case. Tentatively, the results shown here could fit in a framework where the perceived increased task difficulty due to the ingestion of what could have been the active drug consistently summoned a circuit more related, in a broad sense, to novelty. These preliminary results seem also to confirm the suitability of the protocol to (f)MRI investigation of CNS compounds, paving the way for further studies on differences in the effects induced by different drugs.

1) Mintzer, M.Z & Griffiths, R.R. A triazolam/amphetamine dose-effect interaction study: dissociation of effects on memory versus arousal. *Psychopharmacology* (2007) 192:425-440

2) Zijdwind, I., van Duinen, H., Zielman, R., Lorist, M.M., *Interaction between force production and cognitive performance in humans*, *Clinical Neurophysiology* 117 (2006) 660-667

