Benzodiazepine-induced fMRI measurable effects on the working memory circuit: the 2-back task

L. Nanetti[1,2], R. Renken[1,2], R. Kortekaas[1,2], N. Meulman[1], I. Zijdewind[1,2], A. J. Kuiper[1,2], P. de Boer[3], I. den Daas[4], J. Wemer[4], G.J. ter Horst[1,2]

1 University Medical Center Groningen, Neuroimaging Center; 2 University Medical Center Groningen, Department of Neuroscience; 3 Johnson & Johnson Experimental Medicine Europe; 4 Xendo Drug Development Groningen

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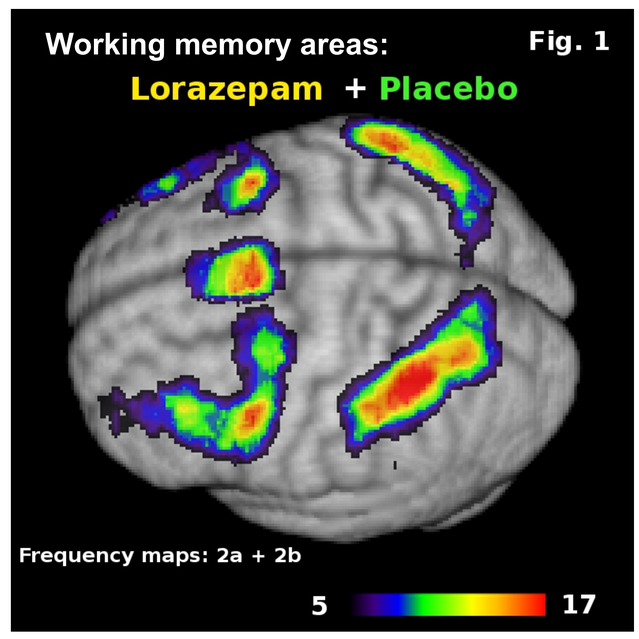
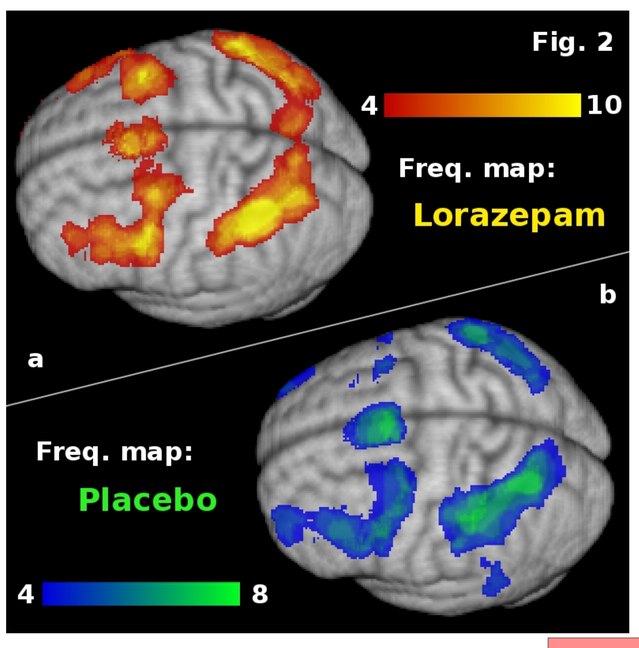
Introduction

The behavioral effects of benzodiazepines are well known, including reduced attention, impaired ability to memorize, and increased sleepiness [1,2]. However, only few studies explored (f)MRI measurable effects induced by these drugs (see e.g. [3]). The aim of the present study was to investigate the expected modulation induced by either a benzodiazepine or a placebo on brain activity during a cognitive effort. The experimental protocol tests various circuits (working and episodic memory, divided attention, resting state) as well as blood perfusion. Here we present results about a classic 2-back task [4].

Materials & Methods: n-back

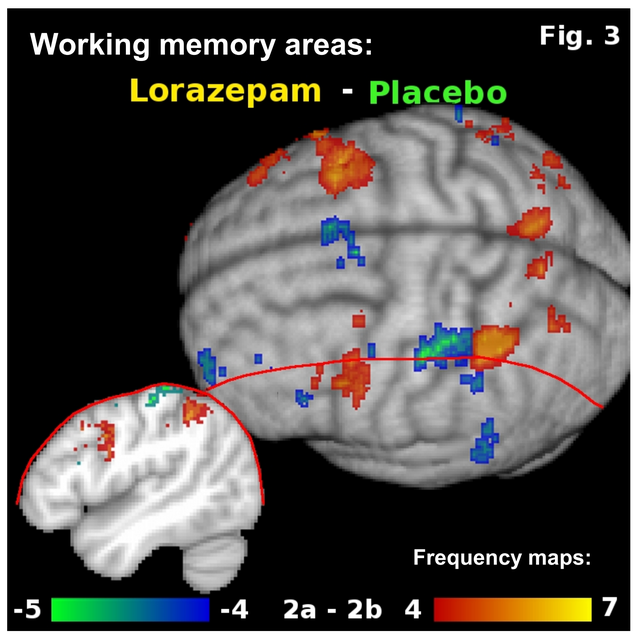
Subjects: 20 Caucasian males, right-handed, age range: 18-25, randomly divided in two treatment groups (2 mg Lorazepam/placebo, administered orally) of 10 participants each. fMRI parameters: Scanner Philips Intera 3T, vox. dim. = 3.5 x. 3.5 x 3.5, 39 slices, TR 2.11 sec. Subjects were measured 4 times (1 week interval) The n-back task (letter-based) consisted of four levels: 0-, 1-, 2-, 3-back, presented in balanced, pseudo-randomized blocks of ~ 30s each, followed by a fixation cross (baseline, ~ 30 s). Every letter was shown for 0.5s, followed by 3 s of blank screen (answer time window). 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 Performance Computing Linux cluster at the Donald Smits Center for Information Technology, University of Groningen.
The first level (single-subject) statistical maps resulting from the application of a threshold of 0.05 (FWE) to the result of the contrast 2-back – fixation cross were binarized, and used to build frequency maps relative to: the main effect of the 2-back task (sum of all 20 maps, see **Fig. 1**), the effect of the 2-back task on the two treatment groups (**Fig. 2**), and the differential effect of the two treatments Lorazepam – Placebo on the corresponding groups (**Fig. 3**). The possibly different effects of the two treatments were also checked with a t-test on the contrast 2-back vs baseline (**Fig. 4**).





Results

- Regardless of the treatment, at least half of the subjects activated (Fig. 1) **right dorsolateral prefrontal dortex (DLPFC), bilateral supramarginal gyrus (SMG), left premotor area (probable hand area), bilateral supplementary motor area (preSMA)**.
- **Drug-treated subjects**: more task related activations (Fig. 2a, 3, 4) in **posterodorsal SMG, globus pallidus, left premotor cortex, right DLPFC**.
- **Placebo-treated subjects** more task related activations (Fig. 2b, 3, 4) in **anterodorsal SMG, posterior superior temporal sulcus (STS), preSMA, left parietal operculum, primary visual cortex, right Inferior Parietal Lobule (IPL)**.

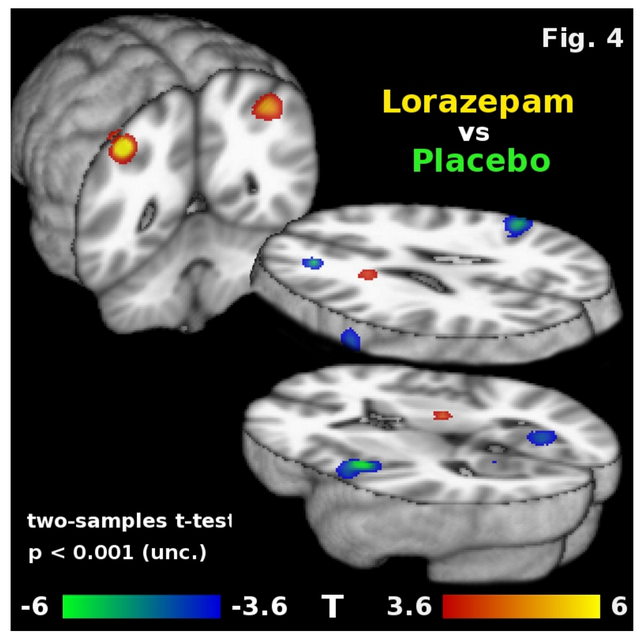


Conclusions

- The results of this study are in general good agreement with what is known about the effects of benzodiazepines on the n-back task from behavioral [1,2], PET [5] and fMRI [3] studies, especially concerning the circuit pertinent to the task.
- Differently from [3], we found significant differences between drug/placebo treatments, most evident on the parietal cortex. This discrepancy might be explained by the allotted answering time, twice longer in our study (3 s). Subjects treated with benzodiazepines are likely to need a longer time for decisional processes involving the retrieval of sequences of items and the matching with current targets .
- Finally, these results suggest that:

a) this study's experimental protocol is suitable for investigating a broad range of CNS drugs, and

b) fMRI is a valuable tool as part of early phase proof-of-principle in the drug development pipeline.



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Contacts: l.nanetti@med.umcg.nl, r.j.renken@med.umcg.nl, r.kortekaas@med.umcg.nl, g.j.ter.horst@med.umcg.nl

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[1] Donald Smits Center for Information Technology, University of Groningen
[2] Neuroimagingcenter, University Medical Center Groningen
[2] Dept. of Neuroscience, Sect. Medical Physiology, University Medical Center Groningen