

FMRI study of Memantine and Donepezil effect on cerebral activation in WM task and sleep deprivation.

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INTRODUCTION

This study aimed at using the fMRI to assess the cerebral activation induced by the 15-days administration of donepezil and memantine in young healthy people when submitted to a working memory (WM) task before and after a single night of sleep deprivation. Memantine is an NMDA receptor antagonist whereas donepezil is a non-competitive and reversible effective acetylcholinesterase Inhibitor. Both are used to reduce cognitive deficits in start-to-moderate Alzheimer Disease (1,2). We compared both drugs to Placebo

SUBJECTS / METHODS

Ten right-handed, healthy young adult males (mean age: 33, sd=5.6) were included
WM task : N-back (N=2 or 3) with letters. Control condition, click when letter X is seen.

Double-blind cross-over design:

Phase A: At random Donepezil (5 mg tablet, one per day) or Placebo

Phase B: at random Memantine (10 mg, tablet one per day) or Placebo.

Sessions were separated by about 1 month to ensure complete washout of the drug before the next session. The order of treatments was balanced across subjects. After 15 days of drug or placebo administration, the subjects were scanned.

For each session (Donepezil, Memantine or Placebo), the subject had 2 scans, the first one after normal sleep and the second after sleep deprivation. For each scan we recorded 218 images (3x16 control, 3x16 2-Back, 3x16 3-Back separated by fixation periods). Data were acquired on a 3-Tesla scanners, TR was set to 2.55s.

We used SPM12 (Institute of Neurology, London) to realign, to normalize (in MNI template) and smooth the images. For each condition sleep or deprivation, we compared Donepezil and Memantine to placebo in group studies. Statistical map were threshold at $p < 0.05$, FWE corrected, spatial extent set to 30.

Main results:

a) (2Back-Control) in normal sleep:
no pixel survive the threshold in Donepezil vs Placebo nor in Memantine vs placebo

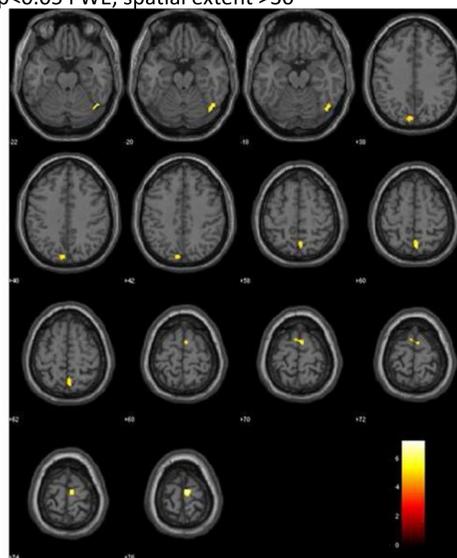
b) (2Back-Control) in sleep deprivation :
Donepezil vs Placebo, no pixel
Memantine vs placebo, we found activation in the right parietal (MNI coordinates: 36 -66 48, spatial extent: 55)

c) (3Back-Control) in normal sleep:
Donepezil vs Placebo and Memantine vs placebo no voxel

d) (3Back-Control) in sleep deprivation :
- Donepezil vs Placebo: many areas mainly in right and left Supplementary Motor area, Cerebellum, right Precuneus, left Cuneus and left Occipital gyrus (see Fig. 1).
- Memantine vs Placebo: 14 activated areas were found, see Fig. 2 and Table 1

RESULTS

Fig.1 Donepezil vs Placebo in 3back-Control comparison after sleep deprivation
 $p < 0.05$ FWE, spatial extent > 30



Location of maxima	Cluster size	Areas
32 -76 40	284	BA 7, 39 19
-6 -50 46	378	Left precuneus
56 28 4	58	Right BA 45
-16 -68 60	144	Left Parietal Sup. (BA 45)
60 -54 8	83	Right Temporal mid (BA 21, 37)
-48 -42 4	168	Left Temporal mid
56 -42 28	48	Right Supramarginal
-44 4 28	284	BA 44, 6
-38 -54 36	225	BA 40, 7
-20 -60 18	104	Left calcarine (BA 17, 18)
46 0 46	50	Right precentral (BA 6, 4)
-8 -80 38	38	Left Cuneus Occipital Sup. (BA 18, 19)
4 -64 62	30	Right Precuneus (BA 7)
46 -50 50	43	Right Parietal Inf (BA 40)

Table 1 Memantine vs Placebo in 3back-Control comparison after sleep deprivation
 $p < 0.05$ FWE, spatial extent > 30

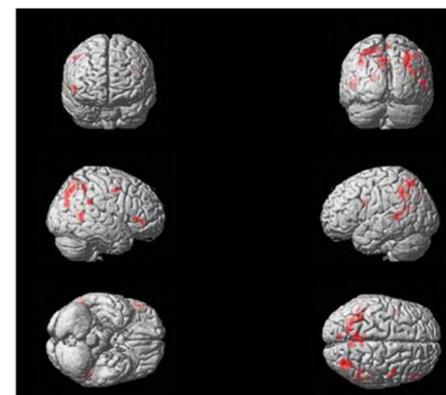


Fig.2 Memantine vs Placebo in 3back-Control comparison after sleep deprivation
 $p < 0.05$ FWE, spatial extent > 30

DISCUSSION / CONCLUSION

The effect of Memantine on the cerebral activity seems more pronounced than the effect of Donepezil. This is particularly seen in case where the subjects were sleep deprived and when the N-back task is more difficult (N=3). Many of the areas found are known to be related to working memory (4)

- REFERENCES :**
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 - (4) Owen A.M. "N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies" *Hum Brain Mapp.* 2005 May;25(1):46-59.