Effect of NMDA-receptor inhibition on relative cerebral blood flow to the hippocampus and medial prefrontal cortex: a placebo controlled repeated measures study of Ketamine in healthy young men

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Purpose: The fronto-hippocampal network plays a critical role in memory and learning (Chan, et al. 2001) and in regulating adaptive behaviors that can influence brain's healthy function across the lifespan (McEwen 2007). The excitatory N Methyl D-Aspartate (NMDA) receptor system in the hippocampus plays a critical role in neuronal plasticity that underlies adaptive learning (Morgado-Bernal 2011) and is therefore a prime candidate for investigating the neurochemical substrates of maladaptive aging and psychiatric disorders (Rotaru, et al. 2012). Therefore, developing objective biomarkers for translational examination of the functional integrity of this system is desirable. In recent years, Ketamine, a potent (NMDA) receptor blocker that plays a key role in excitatory glutamatergic neurotransmission, has come to the fore of psychiatric, aging and pain studies. Our study aimed to examine the impact of Ketamine on central nervous system signals measured by pseudocontinuous arterial spin labeling (PCASL).

Methods: Twelve healthy male volunteers (age 19-36; body mass index: 21-27 kg/m^2) without any neurological or psychiatric contra-indications were studied in a single-blind repeated measures placebo-controlled study. Subjects received S(+)-ketamine (Ketanest-S, Pfizer BV, Capelle a/d IJssel, The Netherlands) on one occasion and placebo (NaCl 0.9%) on the other. The timing of the experiment is set with respect to the start of infusion time, t = 0. Subjects received a low dose of ketamine (20 mg/70 kg/h) for the first 60 minutes, followed by a high dose (40 mg/70kg/h) for another 60 minutes. The MRI sessions were performed using a 3-Tesla Achieva Scanner (Philips Medical System, Best, The Netherlands) and consisted of 5 scanning episodes. The delays between scans are illustrated in the Figure 1. The imaging data used in this report include one 3D-T_1 anatomical scan (TR/TE=9.7/6.5 ms; α=8°, 2mm isotropic); and 5 pCASL perfusion scans (30-pair tag/control; SS-EPI, 19 slices of 7 mm with an in-plane resolution of 3x3 mm^2, SENSE factor 2.5, TE=13.9 ms at a delay of 1525 ms, slice time 35 ms, labeling duration 1650 ms, background inversion pulses at 1680 ms and 2760 ms after start of labeling). After computing the average subtraction images, the CBF was quantified voxelwise by the approach outlined in (van Osch, et al. 2009) using MATLAB 2009a (Mathworks, Inc.). The CBF maps were subsequently registered to standard space and blurred with a 5 mm kernel. The quantitative CBF maps were tested with a mixed-effect generalized linear model (GLM) to identify which brain regions were most significantly affected by the drug-by-time interactions. We used fixed factors drug and time, and random factors subject and global average CBF. Particularly, we tested the difference between ketamine-placebo, while accounting for the variance across time (four post-injection time points vs. the first preinfusion). Statistical maps were thresholded at FEW corrected $p < 0.05$.

Results: Significant reduction of relative CBF was observed in the right hippocampus, cerebellum, sensorimotor and the primary visual areas, concomitant with an increase in relative CBF in the prefrontal and inferior frontal regions. Effects in the hippocampus are especially noteworthy, as the reduction appears to be dose-related. The absolute CBF values in the hippocampus, putamen and the cerebellum were stable, but they significantly increased in the medical prefrontal regions. Both the absolute and the relative CBF in the placebo session were stable over time.

Discussion and conclusions: These results clearly demonstrate that pCASL is an effective technique for measuring regional changes in cerebral function in response to receptor targeting drugs. The stability of absolute cerebral blood flow in the hippocampus, despite the significance of its relative change, might hint at the critical role of this structure in sustaining states of alertness. Significant alteration in the prefrontal perfusion, together with relative reduction of CBF in the hippocampus is consistent with the expected relation between NMDA receptor function and brain areas that constitute the memory system. Our previous observation of an increased connection between the right hippocampus and a resting-state brain network involved in somatosensation and physiological regulation (Niesters, et al. 2012) provides further support for this interpretation. Future work needs to examine the underlying mechanisms that govern the dynamics of blood flow in the hippocampus and its effective functional connectivity to the rest of the brain.

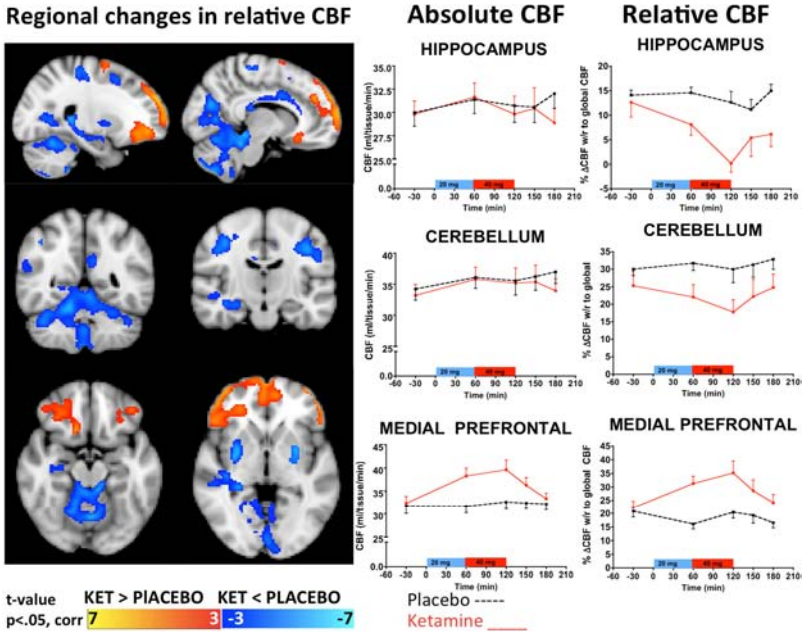

Figure 1: Effect of Ketamine over time compared to placebo

References

Chan KH, Morell JR, et al. 2001. *Behavioural brain research* 119(2):111-30; McEwen BS. 2007. *Physiological reviews* 87(3):873-904. Morgado-Bernal I. 2011. *Neuroscience* 176:12-9; Niesters M, Khalili-Mahani N, et al. S.2012. *Anesthesiology* 117(4):868-877; Rotaru DC, Lewis DA, Gonzalez-Burgos G. 2012. *Reviews in the neurosciences* 23(1):97-109. van Osch MJ, Teeuwisse WM, et al 2009. *MRM* 62(1):165-73.