Differentiation of the effects of an AMPA potentiator on regional brain metabolism between working memory and control tasks: A functional PET (fPET) study.

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Background

Working memory is a core cognitive process that critically depends upon the integrity of prefrontal cortex. Altered prefrontal function in schizophrenia is associated with deficits in working memory which are an important indicant of outcome for patients.

We have previously reported that the noncompetitive NMDA antagonist ketamine produces profound impairments in spatial working memory in the nonhuman primate which can be significantly reversed by targeting critical sites in prefrontal circuitry. This reversal is associated with an attenuation of elevated regional glucose metabolism produced by ketamine in working memory related circuitry.

Agents targeted at these sites, including positive allosteric modulators of the AMPA receptor such as LY451646, also directly effect regional metabolism (rCMGlu) in the absence of ketamine, leaving open the potential that these effects may be an important biomarker for procognitive efficacy. In order to further understand the relevance of these effects to working memory function, we have now compared the action of LY451646 on rCMGlu under working memory versus control task conditions

We used high resolution PET-[^{18}F] fluorodeoxyglucose (FDG) to test the hypothesis that the beneficial effects of augmentation of AMPA receptor signaling for cognition should be better elucidated by the engagement of working memory circuitry

Processing and Analysis

MRIs: Images were acquired on a Siemens 3.0T Trio scanner, using an extremity coil. T1 weighted images were acquired in the coronal plane (matrix size = 0.5469 x0.5469 x0.5000 mm). Non-brain was removed and cropped to 176x176x176 pixels using PREPMR software before co-registration with PET images.

Template: A "standard" brain was chosen based on the size of the monkey, brain shape, and positioning and 6 of the remaining brains were each resliced into standard brain space using affine (12 parameter) normalized mutual information (NMI) registration with FLIRT (FMRIB's Linear Image Registration Tool) software. The 7 normalized images were averaged to create an NHP template image.

Registration: FDG PET images were acquired on a Siemens/CTI microPET Focus 220 scanner with a resolution of 1.5 – 2.0 mm. FLIRT software was used as an initialization step for the PET-MR registration, followed by 6-parameter NMI to obtain the first transform, T1, to map the PET data into MR space. The monkey's MR image was then registered to the template image using 12-parameter affine FLIRT NMI, and the transformation, called T2, was saved to Haven database. Multiplying the two transforms, T1xT2, takes the PET image into template space.

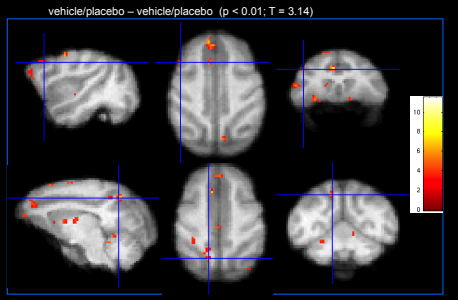
Analysis: Primary analysis was performed with statistical parametric mapping (SPM2, Wellcome Institute, UK) using the PET images normalized to the template and a multisubject/ condition/covariate design. For the data presented here we used global normalization and proportional scaling set to 50.

Testing the effects of LY451646 on rCMGlu in a control task

- In order to determine whether the nature of the behavioral task in which the animal is engaged has a significant influence on the magnitude, extent, and underlying circuitry affected by LY451646, we studied the effect of the low dose on rCMGlu in a simple control task
- In this task, a transparent screen was lowered for the same delays as the animal ordinarily experienced in the delayed response task. However, only one central well was baited and the food treat was not entirely covered on order to minimize the generation of any mnemonic representation. Otherwise all other environmental conditions were identical

- We used a standard dose of 5 instead of 3 mCi in order to ensure optimal signal to noise in the data
- We used the low dose of LY451646 as it appeared to interact with working memory circuitry in the previous study

Figure 6. Working Memory – Control Vehicle Conditions



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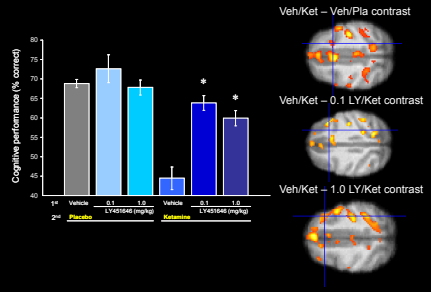

Figure 2. Elevation of rCMGlu by LY451646 in working memory

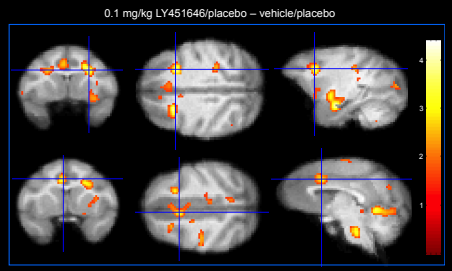

Figure 4. Moderate levels of activation were seen both frontal and posterior brain regions, including dlPFC, ACC, and LIP These were not significant at the cluster level

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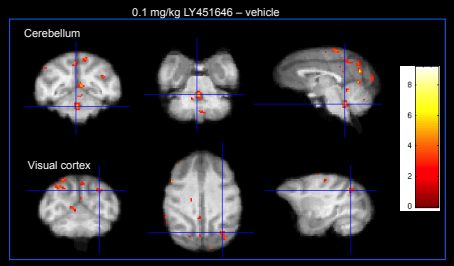
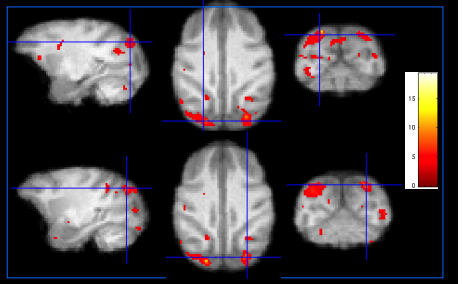


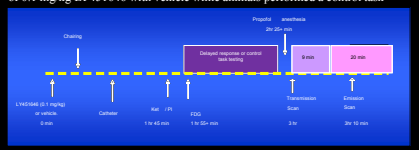
Figure 7. Control – Working Memory Vehicle Conditions



FDG-PET Methods

Preparation: The studies was performed on two overlapping groups of 8 young adult rhesus macaques that were pretrained to stable performance (mean 65 – 75% ± 2.5%) on a standard spatial delayed response task. Animals were required to work for 15 – 25 min, often using highly preferred treats

Experimental design: In the previous study, animals were tested under working memory conditions using a Latin squares design for LY451646 (0.1, and 1.0 mg/kg; SC) /vehicle pretreatments (2hr) vs. ketamine and placebo treatments (15 min)prior to FDG injection. In the second study we directly compared the effects of 0.1 mg/kg LY451646 with vehicle while animals performed a control task



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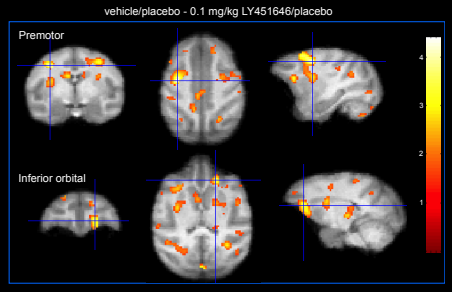

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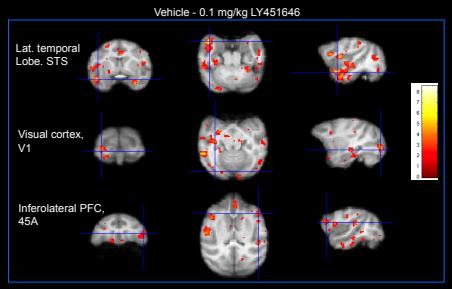

Significance of fPET for study of Procognitive agents

- We have shown that LY451646 reverses ketamine-induced cognitive deficits in association with a reduction in elevated metabolism in critical brain regions in nonhuman primates performing a working memory task. When we compared the ability of LY451646 to alter rCMGlu in a control task we saw substantial differences in its effects
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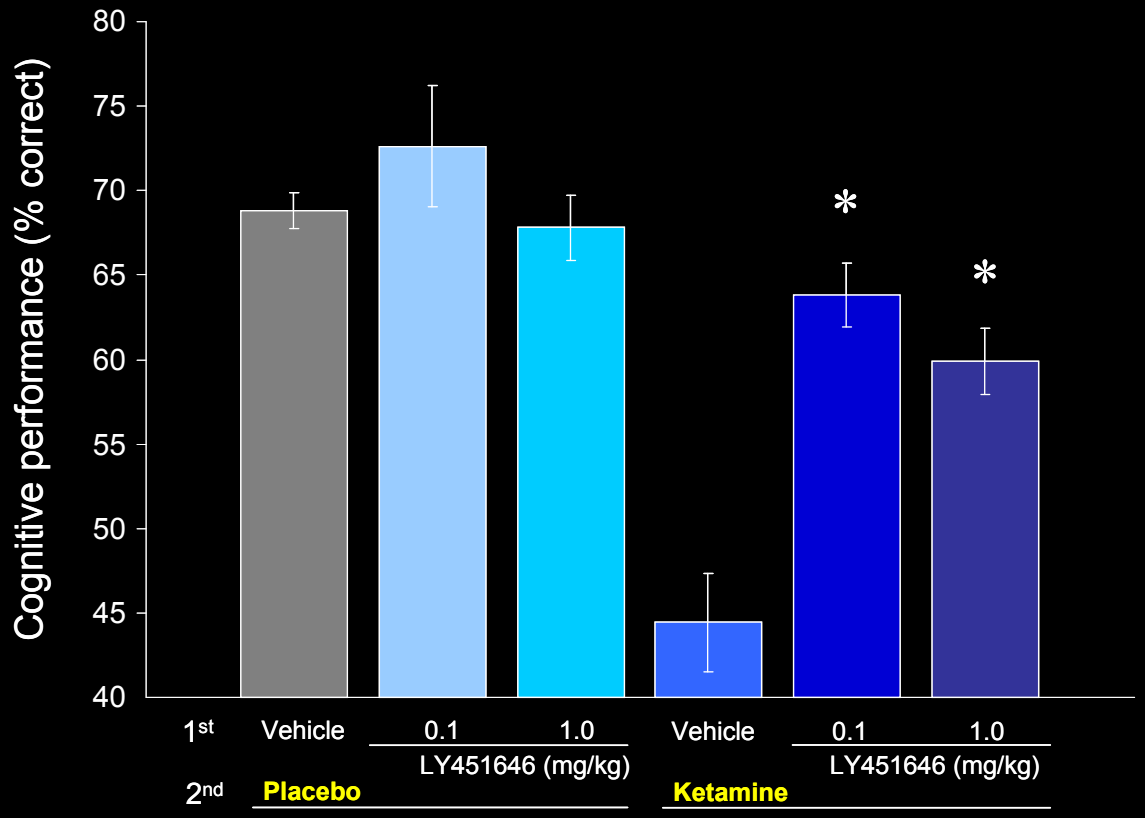

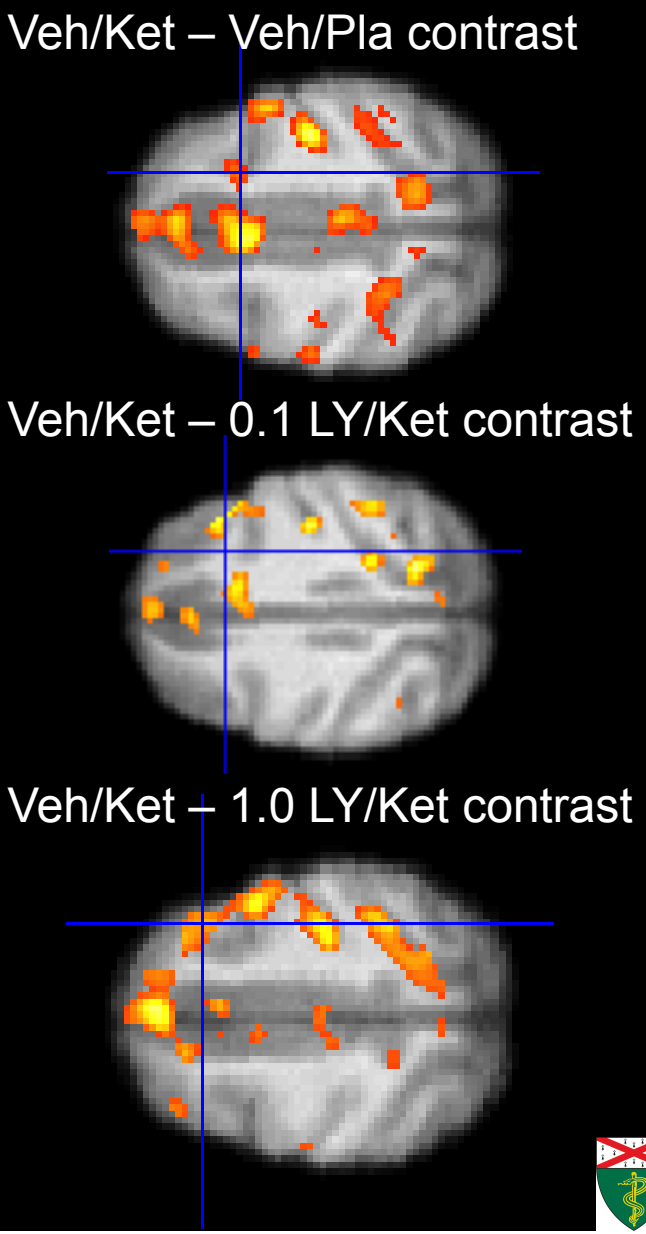

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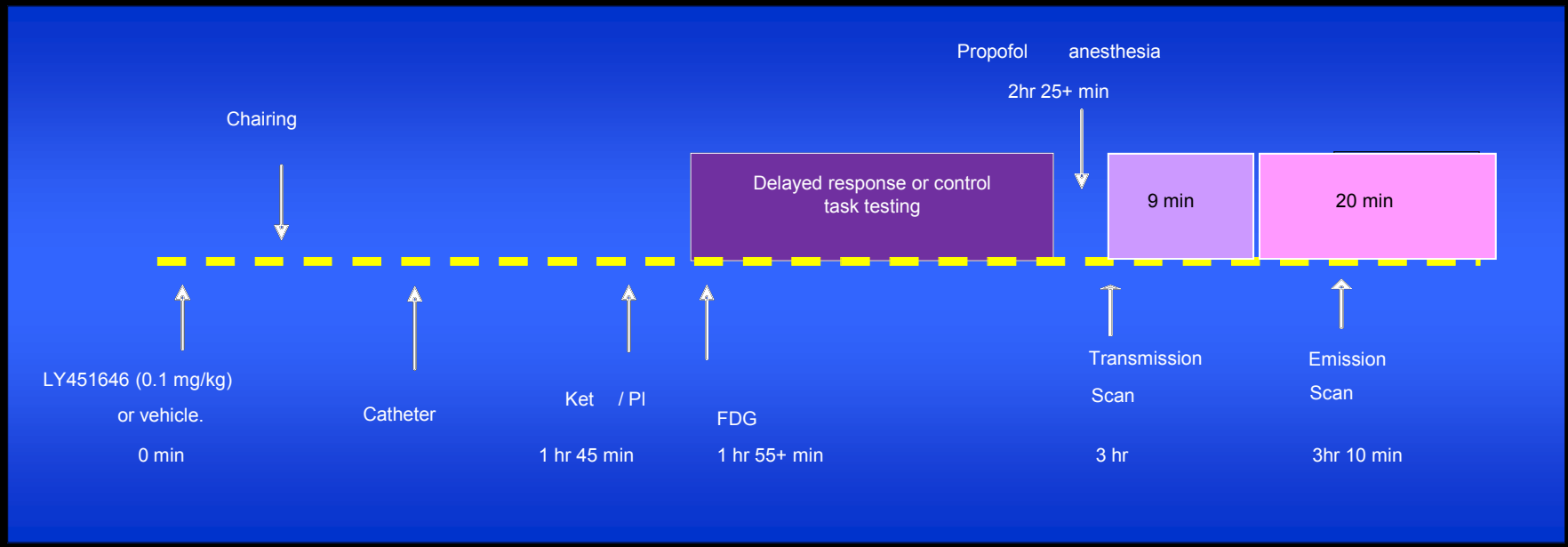

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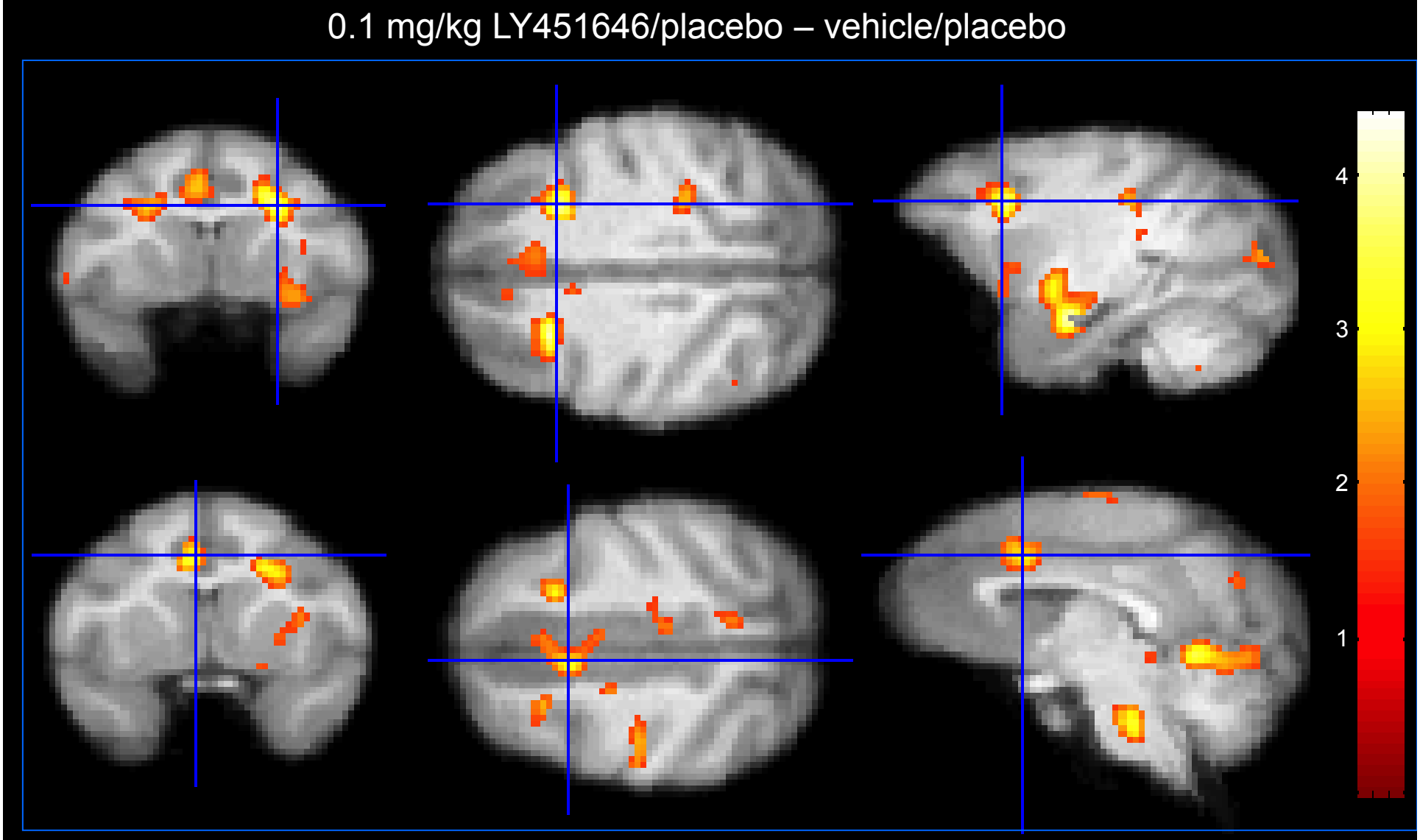

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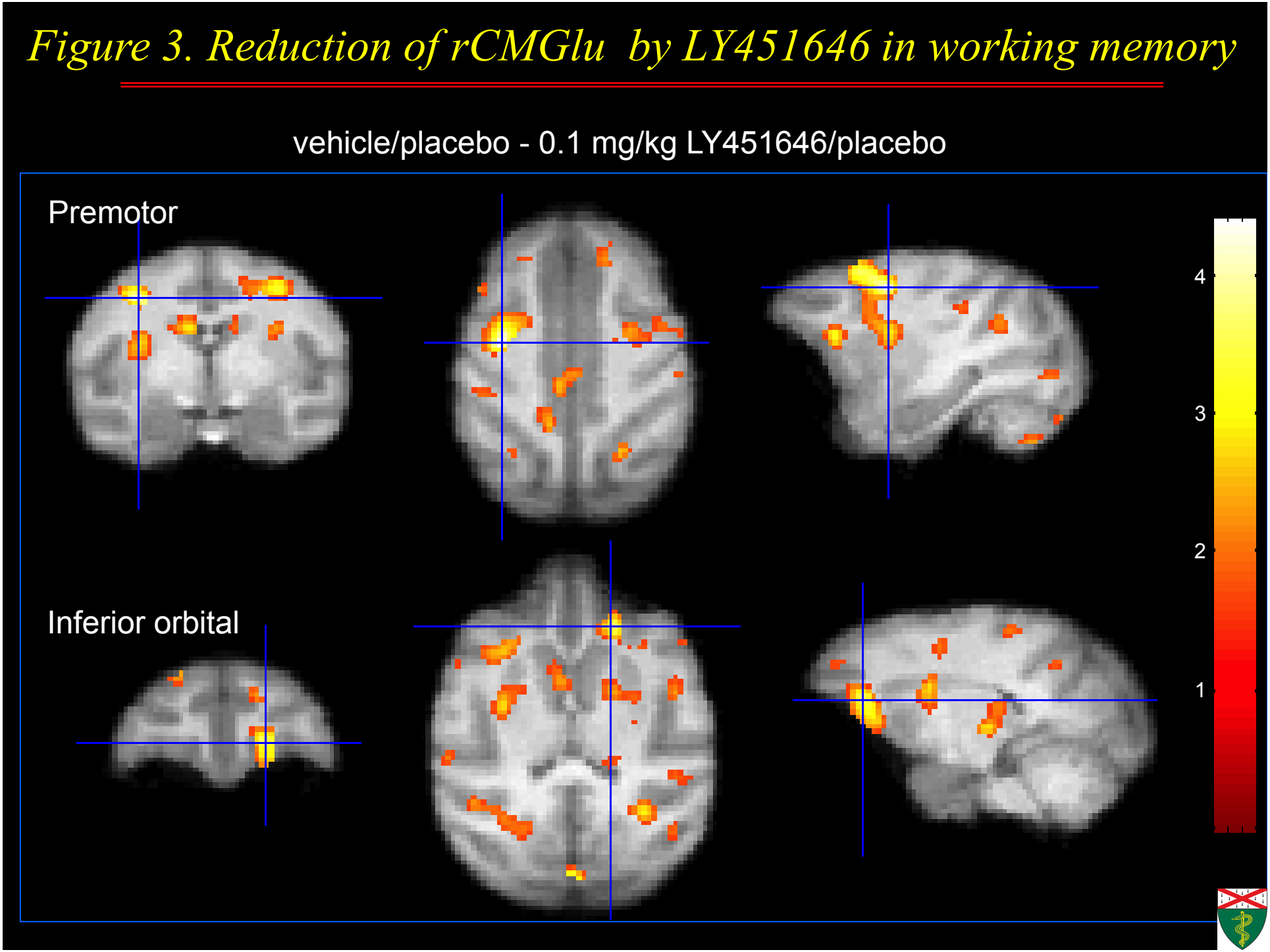

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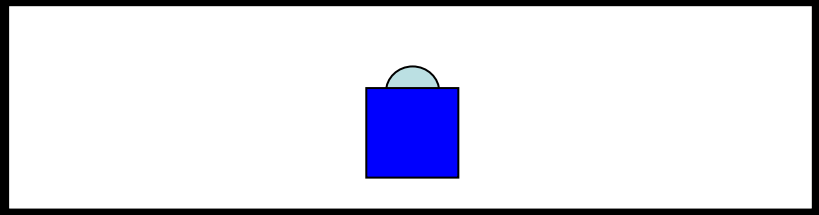

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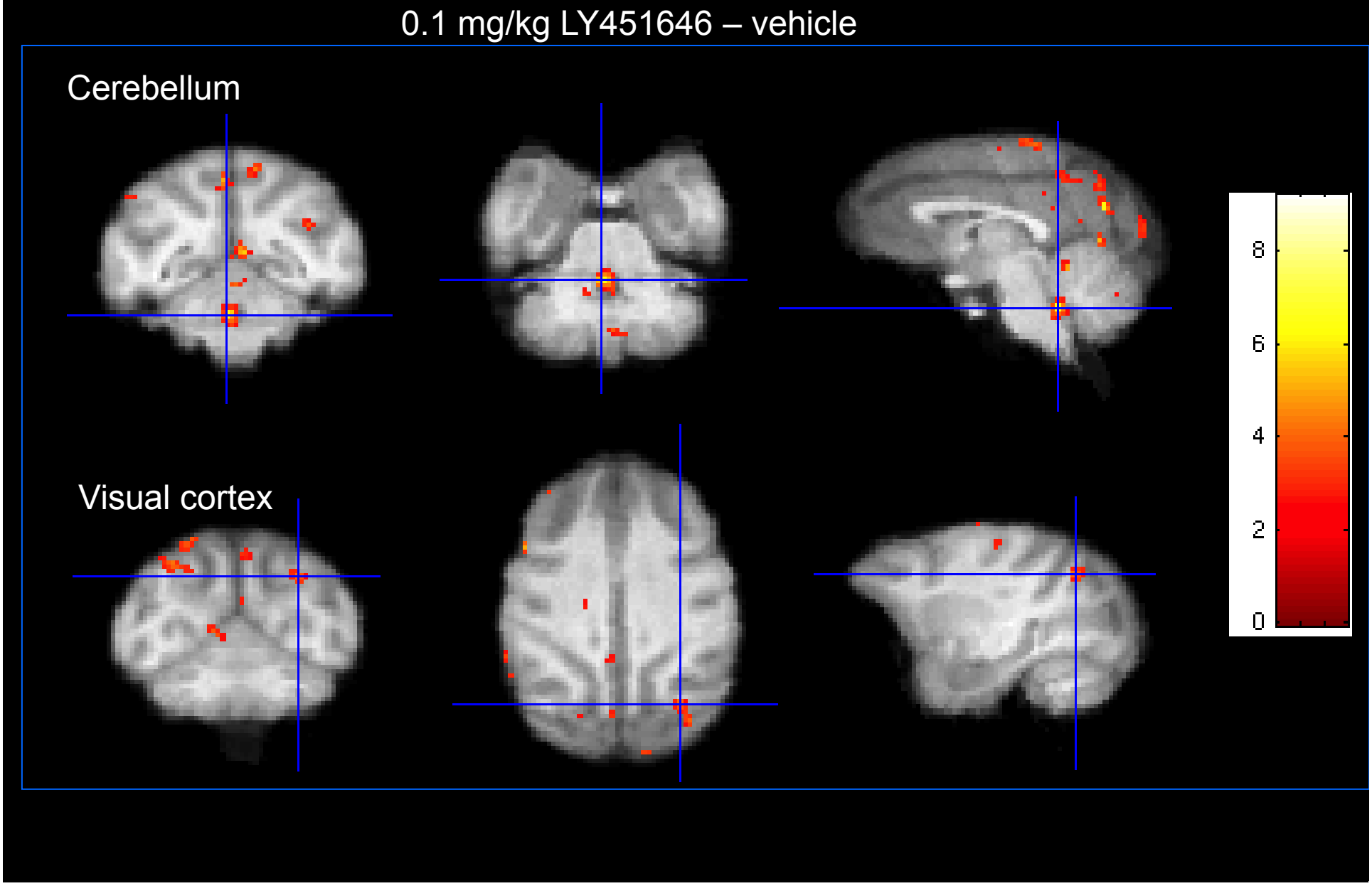

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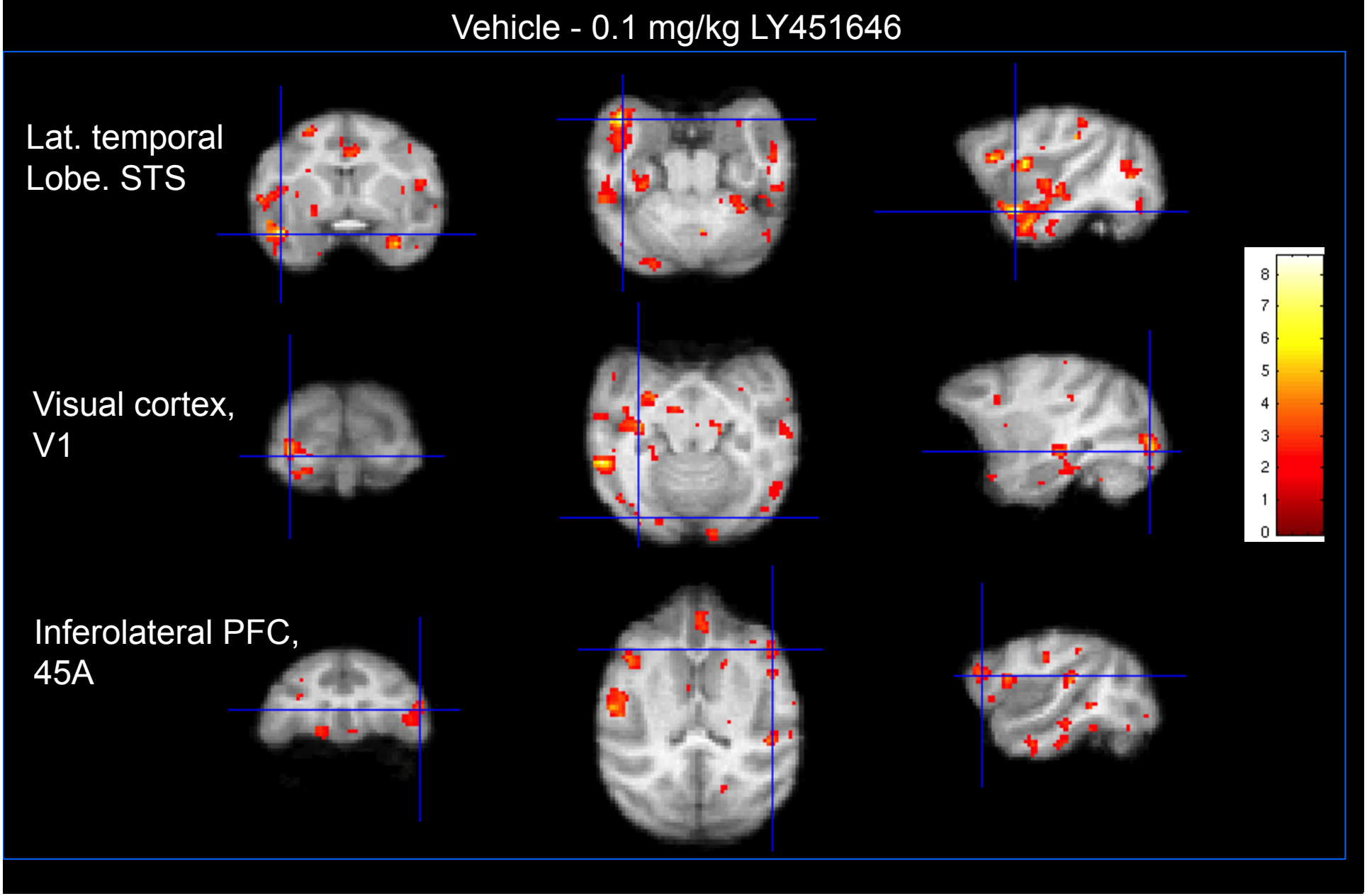

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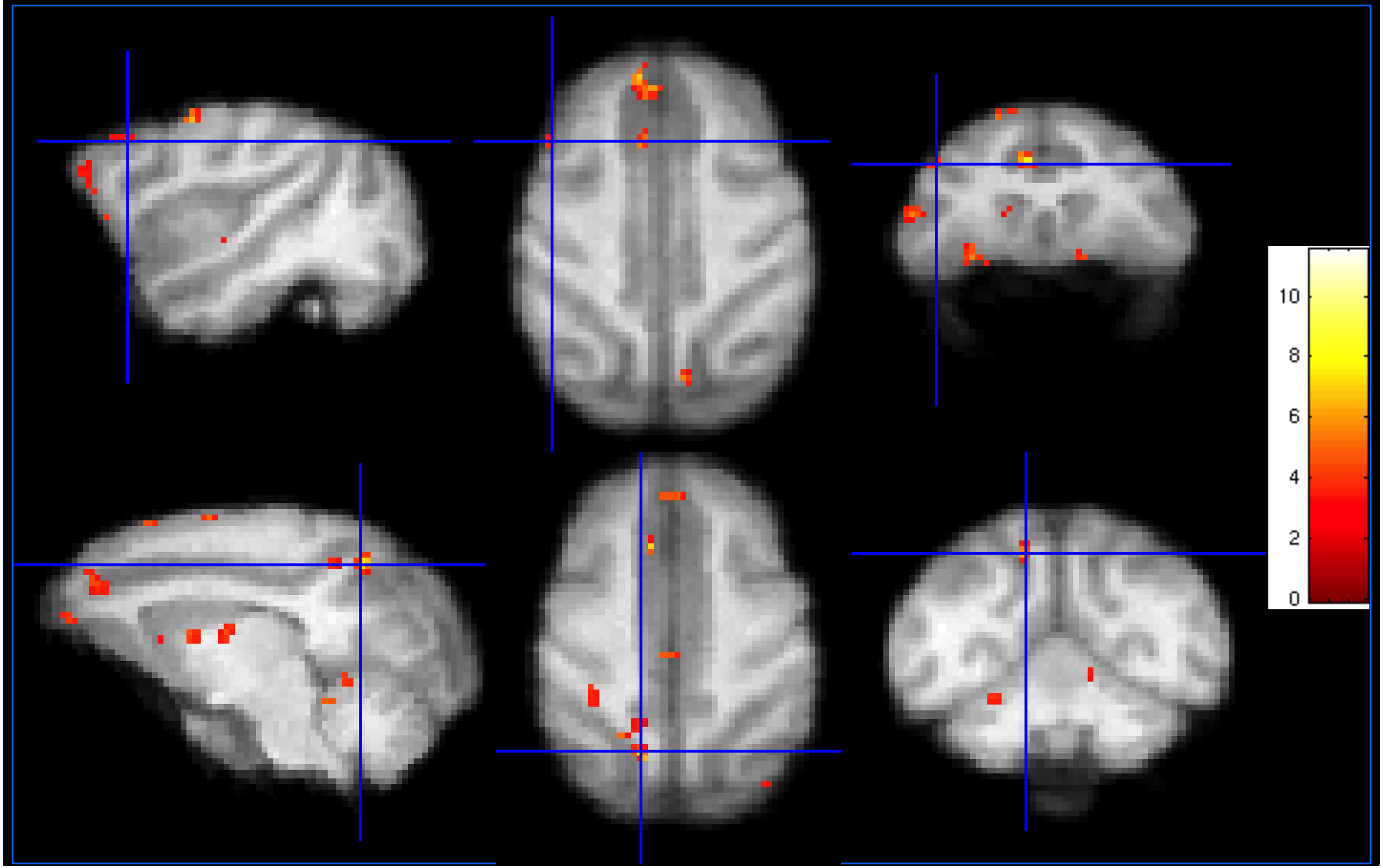
vehicle/placebo – vehicle/placebo (p < 0.01; T = 3.14)



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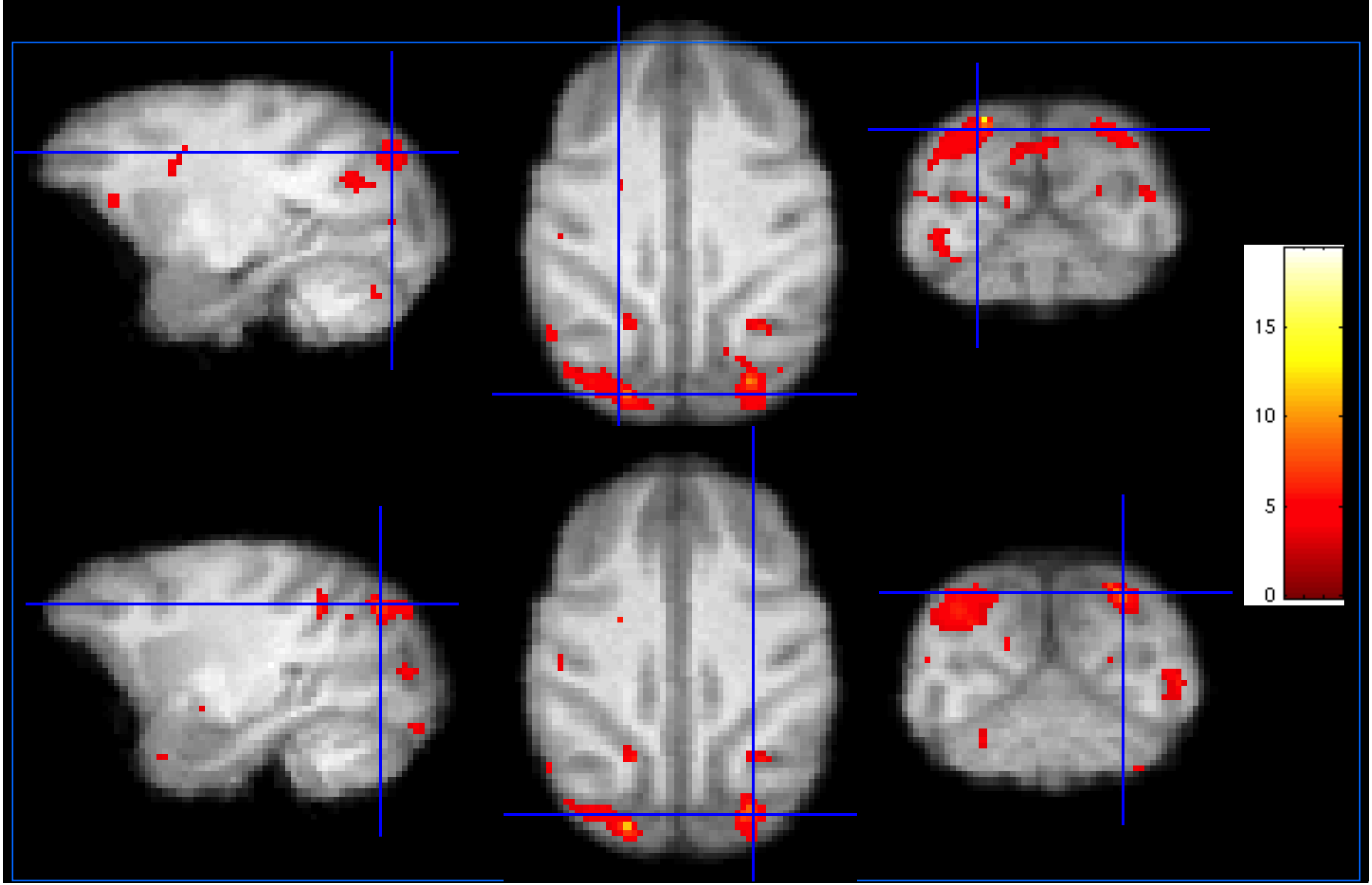

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