Response to Comment on “Homeostatic Sleep Pressure and Responses to Sustained Attention in the Suprachiasmatic Area”

Christina Schmidt,1 Philippe Peigneux,1,2* Pierre Maquet,1 Christophe Phillips1,3

Astafiev et al. question whether the blood oxygen level–dependent (BOLD) response that we reported in the brainstem was located in the locus coeruleus (LC). Using high-resolution T1-turbo spin echo images (T1-TSE) acquired in an independent group of subjects, we show that the reported task-related BOLD response in the brainstem is actually compatible with the anatomical location of the LC.

The commentary of Astafiev et al. (1) illustrates the fast pace at which neuroimaging techniques are currently progressing. Long-term studies requiring the recruitment of highly selective populations and complex, time-consuming designs constrained by the physiology of sleep/wake regulation are bound to be outdated by some of their technical aspects when they come to be published. However, this does not necessarily entail that their findings are invalidated. We used functional magnetic resonance imaging to study the effects of sleep/wake regulation on the cerebral mechanisms supporting cognition (2). We originally identified the localization of the blood oxygen level–dependent (BOLD) response using human brainstem atlases (3, 4). Statistical inferences were based on a priori coordinates from previous independent publications reporting responses in the LC [see methods described in the Supporting Online Material for (2)]. The potential anatomical inaccuracy of these approaches led us to cautiously label the reported activation as LC-compatible, a localization disputed by Astafiev et al.

Here, we confirm the localization of the reported activation in the LC in a follow-up investigation with an independent group of 20 healthy young subjects (mean age, 23.6 ± 2.35), using a magnetic resonance (MR) sequence sensitive to neuromelanin-related contrast. Three data sets were consecutively acquired using a 3 Tesla Allegri MR scanner (Siemens, Erlangen, Germany): (i) an echo planar imaging (EPI) temporal series voxel size, 3.4 × 3.4 × 3 mm3; matrix size, 256 × 224 × 176; TR, 7.92 ms; TE, 2.4 ms; TI, 910 ms; FA, 15°; and (iii) a high-resolution T1-turbo spin echo image (T1-TSE; voxel size, 0.43 × 0.43 × 3 mm3; matrix size, 400 × 512 × 10 voxels; TR, 600 ms; TE, 14 ms; FA, 90°).

Each individual data set was processed using the same procedure as in (2), allowing reliable comparisons with our published data set. The warped T1 and mLc images averaged across subjects reflected group-wise variability in overall brain, brainstem, and LC anatomy, as observed in (2). Figure 1B (left panel) shows the location of the peak activation reported as “LC compatible” in Schmidt et al. (1) on the mean T1 image, overlaid with the mean mLc image. The activation peak was located in the ventral and rostral part of the independently and anatomically identified LC, confirming our original claim that this activation was localized in an area compatible with this nuclear structure.

To make sure that this result was not induced by an inadequate warping of the brainstem, we further applied an optimized brainstem normalization procedure to the data (5). Warped T1 images were submitted to a second brainstem-specific normalization step (affine transform, brainstem-masked T1 template), and T1, T1-TSE, and mLc images were warped accordingly. The same procedure was applied to functional images. (Left panel) Peak activation overlaid on spatial transformations as in (2) (green dot; x = 4; y = −32; z = −18), displayed in coronal (top left image), sagittal (top right image), and transverse (bottom image) orientations. (Right panel) After optimized brainstem normalization (green dot; x = 6; y = −34; z = −14). (C) Average time course (PSTH) of task-related BOLD response associated with fast RTs (left panels) and intermediate RTs (right panels) during the evening session in the peak voxel located in the LC (x = 4; y = −32; z = −18, upper panels) and in the fourth ventricle (bottom panels), in morning (red) and evening (blue) types.

*To whom correspondence should be addressed. E-mail: Philippe.Peigneux@ulb.ac.be

References

1Cyclotron Research Centre, University of Liége, 4000 Liége, Belgium. 2Neuropsychology and Functional Neuroimaging Research Unit (UR2NF), Université Libre de Bruxelles, B-1050 Brussels, Belgium. 3Department of Electrical Engineering and Computer Science, University of Liége, 4000 Liége, Belgium.

1Cyclotron Research Centre, University of Liége, 4000 Liége, Belgium. 2Neuropsychology and Functional Neuroimaging Research Unit (UR2NF), Université Libre de Bruxelles, B-1050 Brussels, Belgium. 3Department of Electrical Engineering and Computer Science, University of Liége, 4000 Liége, Belgium.

Supporting Online Material for (1). We originally identified the localization of the reported LC, confirming our original claim that this activation was localized in an area compatible with this nuclear structure.

1Cyclotron Research Centre, University of Liége, 4000 Liége, Belgium. 2Neuropsychology and Functional Neuroimaging Research Unit (UR2NF), Université Libre de Bruxelles, B-1050 Brussels, Belgium. 3Department of Electrical Engineering and Computer Science, University of Liége, 4000 Liége, Belgium. 4To whom correspondence should be addressed. E-mail: Philippe.Peigneux@ulb.ac.be

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As illustrated in Fig. 1C, the LC response to a ventricle, in morning and evening type subjects. 

vigilance regulation) during the evening and intermediate RTs associated to the fastest reaction times (RTs) (optimal course of task-related BOLD responses asso-

ciation with LC location. We agree with Astafiev et al. that future research should refine the anatomical localization of brainstem responses.

Astafiev et al. (1) additionally question the biological validity of BOLD responses in the LC area. We further extracted the average time course of task-related BOLD responses associated to the fastest reaction times (RTs) (optimal vigilance regulation) and intermediate RTs (global vigilance regulation) during the evening session, both in the peak voxel located in the LC (x = 4, y = −32, z = −18) (2) and in the fourth ventricle, in morning and evening type subjects. As illustrated in Fig. 1C, the LC response to the fast RTs during the evening hours presented higher activity levels in evening as compared to morning types, and its time course followed the expected shape of the hemodynamic response function. In contrast, activity extracted in the fourth ventricle presented much larger inter-individual variability and did not follow any reproducible time course suggestive of consistent event-related hemodynamic response. Contrasting with the results of Astafiev et al. (1), these findings indicate the possibility to record consistent hemodynamic responses in the brainstem. Nevertheless, this discrepancy itself calls for caution when reporting BOLD responses in brainstem areas where a precise investigation of the BOLD time course requires the use of comprehensive models of hemodynamic response, using a complete set of basis functions, a finite impulse response model (7, 8), or a Bayesian estimation of the hemodynamic response (9, 10).

At the cellular level, the LC and its dendritic fields, which extend in the peri-LC area (11), receive a number of various afferents, not all of which have been chemically identified. Some of them originating from the frontal cortex and bulbular reticular formation are thought to be glutamatergic (11). Glutamate-immunoreactivity is present in a substantial proportion of synapses terminating on LC adrenergic cells (12). However, to add to the complexity of the system, glutamatergic afferents to the LC can sometimes result in decreased LC firing (13) through mGluR-related activity-dependent depression (14). Whether these effects concern the phasic or tonic mode of firing in the LC, and to what extent it influences the BOLD signal, remains also to be assessed.

References and Notes
10 July 2009; accepted 25 March 2010. 10.1126/science.1177949