Successful fMRI of the hypothalamus at 3T

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Introduction:

The hypothalamus is a very small but extremely important part of the brain, located at the base of the brain, around the third ventricle, extending from a plane immediately anterior to the optic chiasma to posterior to the mammillary bodies. Laterally its borders are roughly the optic tract, the internal capsule, pes pedunculi, globus pallidus, and ansa penduncularis at various anteroposterior planes, while superiorly it does not extend above the level of the anterior commissure. Its weight in the adult human is less than five gram [1]. Although the role of the hypothalamus as a control unit for certain metabolic processes and other activities of the Autonomic Nervous System has been under investigation over the last decades, little is known as to the detailed mechanisms. The hypothalamus is linked to the endocrine system via the pituitary gland and controls the release of eight different hormones. It is also involved in the body temperature regulation, the control of food and water intake, the sexual behavior and reproduction, the control of daily cycles in physiological state and behavior and the mediation of emotional responses.

Hypothalamic activation due to an emotional state is of special interest considering the hypocretine (orexin) creation. Hypocretine 1 and Hypocretine 2 (also known as Orexin A and Orexin B) are neuropeptide hormones that are crucial to the regulation of sleep and wakefulness. These peptides activate wake-active monoaminergic and cholinergic neurons in the hypothalamus and the brain stem to maintain a long and consolidated awake period. Hypocretine dysregulation causes the sleep disorder narcolepsy [2]. A cardinal symptom of the disorder is excessive daytime sleepiness (i.e. an unavoidable urge to sleep), which manifests itself primarily as the subject is falling asleep at inappropriate times ('sleep attacks'). Nocturnal sleep is often disturbed by sleep fragmentation combined with the occurrence of hypnagogic hallucinations, vivid dreaming and sleep paralysis, which usually occur when patients fall asleep. Narcolepsy patients often suffer from a condition called 'cataplexy', which is characterized by a sudden weakening of muscle tone, ranging from jaw dropping and speech slurring to complete bilateral collapse of the postural muscles. Consciousness is preserved during cataplexy [2]. Importantly, often these attacks are triggered by sudden happy arousal. In this study we use high field functional magnetic resonance imaging (fMRI) at 3T to assess whether emotional stimuli may trigger activation in the hypothalamus in healthy subjects and if so, whether emotional valence is indeed modulating hypothalamic activation.

Materials & Methods:

The stimuli to manipulate the emotional state of the 12 healthy subjects comprise 60 different pictures, which can be divided in 5 subgroups regarding their effect on the emotional state: (1) very funny, (2) funny, (3) neutral, (4) sad and (5) very sad, respectively. Stimulus presentation order was randomized and each stimulus was shown for four seconds, with variable inter-stimulus interval ranging from 8 to 12 seconds. A white cross on black background was serving as baseline.

Functional imaging was performed on a SIEMENS Tim Trio Scanner at 3 Tesla using high-resolution gradient-recalled EPI, following the sequence parameter set recently presented by our group [3]. 20 axial slices were acquired centered at the hypothalamus, with a slice thickness of 1.9 mm, a slice gap of 0.9 mm and matrix size of 128 x 128. Parallel imaging was used with GRAPPA and a grappa factor of two (TE: 40 ms / TR: 2000 ms). Preprocessing including slice-timing correction, realignment, normalization to MNI-space and smoothing with a Gaussian kernel (FWHM=6mm) in SPM5. Realignment parameters were added as nuisance variables in the design matrix to reduce effects of residual motion artifacts. Random-effects analysis for significant activation differences between “very funny” and neutral stimuli was performed, and parameter estimates from the hypothalamic activation peak were extracted.

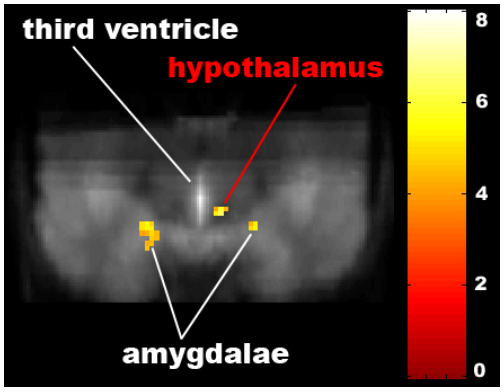

Fig. 1: Activation map:
Activation map overlaid on the mean of the reference scans of all twelve healthy subjects.

Results and Discussion:

Figure 1 displays regions with higher activation during “very funny” stimuli compared to neutral pictures ($p<0.001$, uncorrected) showing activation in the left hypothalamus and bilateral activation in the amygdalae. Parameter estimates in the hypothalamus (MNI-coordinates: 8, -8, -14) across the five stimulus categories are given in Fig. 2. It can clearly be seen that hypothalamus activation is strongly modulated by emotional valence (ANOVA $p<0.001$). Activation during “very funny” stimuli is significantly higher compared to all other stimulus categories confirming our hypothesis of specific hypothalamic activation for “very funny” stimuli. Interestingly, no activation while attending to “funny” stimuli was found. This could be due to the fact that only “very funny” stimuli actually caused happy arousal, while “funny” stimuli were just recognized as funny, but without consequences for the individual arousal status.

This is the first fMRI study that demonstrates valence-specific hypothalamic activation to emotional stimuli. In concordance with clinical evidence showing that sudden happy arousal may trigger narcolepsy attacks, our results support the theory that narcoleptic episodes are indeed initiated by hypothalamic activity.

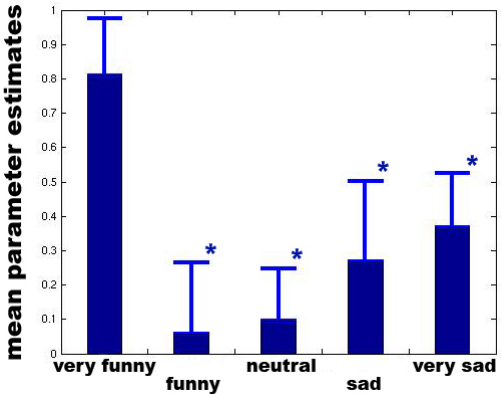

Fig. 2: Mean parameter estimates:
The mean of the parameter estimates over all subjects is plotted for all 5 stimulus subgroups.

References:

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