Effects of autonomic stimulation on the brain at rest and engaged by cognitive task: an fMRI investigation

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Introduction. Many physiological conditions, such as physical activity, mental stress and emotional stimuli, are associated with cardio-vascular modifications, detectable through carotid baroflex testing. Cardiovascular parameters such as heart rate, blood pressure and peripheral vascular resistances are continuously regulated by the sympathetic and parasympathetic branches of the autonomic nervous system (ANS), where afferent signals from peripheral sensors are processed at central level. So far, the anatomical location of autonomic receptors and the need of invasive procedures for physiological assessments, have made it difficult to study the central processing and control of ANS in humans. We recently developed a automated neck suction device, to induce a non-invasive, bilateral stimulation of the mechanoreceptors in the carotid sinus of humans. Such a device, used synchronously with functional Magnetic Resonance Imaging (fMRI), can be used to detect *in vivo* changes of brain activation as a function of the direct perturbation of ANS (1). In this study, for the first time, we perturbed the ANS (through parasympathetic stimulation) to assess changes in activation of the brain at rest (experiment 1), and while engaged in performing a cognitive task (experiment 2).

Methods. Fifteen right-handed healthy volunteers [all men; mean (SD) age=23.0 (3.4) years] underwent an fMRI investigation at 3T (Siemens Allegra system). An automated neck suction device, operated synchronously with fMRI acquisition, was used to induce bilateral stimulation of the mechanoreceptors in the carotid sinus. During fMRI experiments, the autonomic effect was controlled on a trial by trial basis by peripheral ECG recording. Efficacious and non efficacious stimuli were preliminary defined in a behavioral study, aimed at identifying the lowest suction pressure inducing peripheral autonomic response (-60 mmHg) and the highest pressure not inducing any autonomic response (-15 mmHg). Subjects were unable to differentiate between efficacious and non efficacious stimuli. Echo-planar (EPI) T2* sequence with BOLD contrast (TR=2080 ms, TE=30 ms, Matrix size=64 x 64,32 slices, thickness=2.5 mm) covering the whole brain was used for fMRI acquisitions. A Modified Driven Equilibrium Fourier Transform (MDEFT) scan (TR=1338 ms, TE=2.4 ms, Matrix = 256x 24, n. slices=176, thick. 1 mm) was also acquired and served as anatomical reference. In experiment 1, fMRI data were collected using an event-related design. Subjects were asked not to think of anything particular, and 50 efficacious and 30 non-efficacious neck suction stimuli (with a duration of 8 sec each) were randomly administered across the experiment (600 echo-planar imaging volumes, total duration= 16 min). Using SPM5, a within subjects ANOVA assessed differences in brain activation for the two experimental conditions.

In experiment 2, subjects were asked to perform a visuo-spatial attention task (with eight active target-condition blocks and eight control-blocks, each block including 28 stimuli (duration = 2 sec, each) for a total of 56 active and 56 control trials (500 echo-planar imaging volumes; duration= 17 min). Using SPM5, a within subjects ANOVA modelling the 4 conditions of the 2x2 design (ANS stimulation: ES/NES x Task: active/control) was employed to investigate the interaction between task performance and carotid stimulation. In all fMRI analyses, statistical thresholed was set to p values cluster level corrected<0.005)

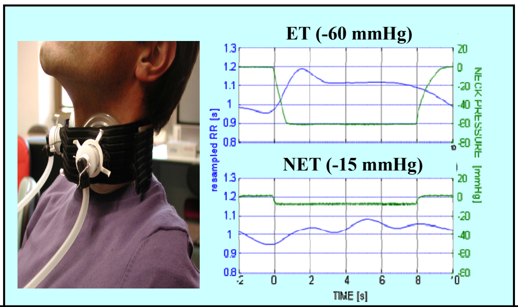

Fig. 1. Neck suction device (left); Efficacious (ES) and non- efficacious trials (NET) as assessed by continuous ECG recording (right).

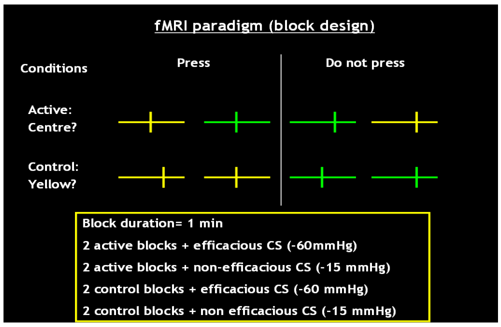

Fig 2. Paradigm: to press a button when the bisection of the horizontal line is symmetrical (active task), or the item is presented in yellow (control task)

Results

In experiment 1, efficacious versus non-efficacious stimuli induced an increased activation in the right superior temporal gyrus and the insula, and the left putamen, amygdala, parahippoccampal gyrus and caudate nucleus (Fig 3A). Non-efficacious stimuli did not produce any significant activation compared to the efficacious stimuli. In Experiment 2, the analysis of behavioural data revealed an increase of reaction times during efficacious carotid stimulation (mdn=506.3ms, mdn=382.6, respectively efficacious and non efficacious stimuli; Mann-Whitney U test, W(7) = 44, z=-2.5, p<0.01 two-tailed). As expected, the main effect of the task induced activation of the right parietal-frontal attention network (Fig.3B). Carotid stimulation induced an additional positive modulation of the activation of right inferior parietal lobule (Fig 3C), which is crucial for spatial-attention functions.

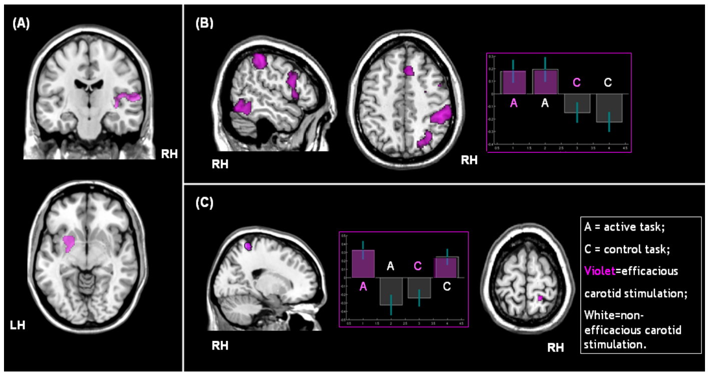

Fig 3. Exp.1: pattern of greater activation when efficacious are compared to non efficacious stimuli (A). Exp.2: main effect of task, irrespective of carotid stimulation (B); positive modulation of brain activation due to carotid stimulation when performing the task (C).

Discussion. In this study we demonstrate the feasibility of an *in vivo* investigation of brain activation by direct manipulation of the ANS, trough an appropriate neck collar device. Our results provide new evidence that autonomic perturbation of the parasympathetic system induces expected peripheral responses together with modulation of brain activity. Within the brain at rest (experiment 1), efficacious neck suction stimuli induced a positive modulation of activity in several brain regions. Some regions were previously associated with autonomic functions (insula) (2, 3), while other regions are involved in higher level functions (parahippoccampal gyrus; putamen amygda). This indicates that there is an overlapping between the neuronal networks controlling autonomic responses and higher level functions. When subjects were engaged in performing a cognitive task (experiment 2), efficacious stimulation of the carotid sinus induced an increase of RTs, indicating a reduced efficiency in task performance. Concomitantly, brain activation was positively modulated in one of the most crucial areas (right inferior parietal lobule) for visuo-spatial attention. These data suggest that a parasympathetic stimulation reduces the cognitive efficiency, and compensatory mechanisms (increased activation) are needed to maintain a satisfactory performance. The current study is relevant not only for neurophysiological speculations, but also to increase our pathophysiological understanding of many disorders (e.g., hypertension; Parkinson disease, stroke, etc) for which the implication of ANS seems to be crucial (4).

References

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