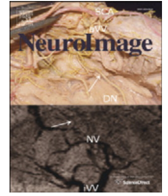
NeuroImage 74 (2013) 188–194

Contents lists available at SciVerse ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg



Real-time imaging of brain areas involved in the generation of spontaneous skin sympathetic nerve activity at rest

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ARTICLE INFO

Article history:
Accepted 15 February 2013
Available online 24 February 2013

Keywords:
fMRI
Microneurography
Skin sympathetic nerve activity

ABSTRACT

In thermoneutral conditions resting skin sympathetic nerve activity (SSNA) is related to the level of arousal and emotional state. The brain regions responsible for the generation of spontaneous SSNA are not known. In the present study we used concurrent recordings of SSNA and brain activity in awake humans to identify cortical and subcortical areas involved in the generation of spontaneous SSNA in 13 healthy subjects. Blood oxygen level dependent signal intensity increases covaried with SSNA in the left thalamus in the region of the ventromedial nucleus, the left posterior and right anterior insula, the right orbitofrontal cortex, the right frontal cortex, and bilaterally in the mid-cingulate cortex and precuneus. Functional connectivity analysis revealed a strong positive coupling between the right orbitofrontal cortex and the right anterior insula. Furthermore, signal intensity changes within the precuneus were temporally coupled to the left anterior and posterior insula, cerebellum, cingulate cortex and thalamus. It has been hypothesized that these brain regions monitor the internal state of the body and may regulate emotional state changes. Our results show that the activities within these regions are also correlated to spontaneous fluctuations in SSNA.

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Introduction

The sympathetic innervation of the skin in humans primarily subserves thermoregulation, by constricting or dilating cutaneous blood vessels and increasing or decreasing the release of sweat; while there is sympathetic innervation of the hairs, this is of less importance in humans. Both whole-body cooling and whole-body heating produce an increase in skin sympathetic nerve activity (SSNA), the former increasing cutaneous vasoconstrictor drive and the latter increasing sudomotor drive (Bini et al., 1980; Macefield and Wallin, 1996, 1999). In thermoneutral conditions resting SSNA is primarily composed of cutaneous vasoconstrictor activity (Bini et al., 1980), which is related to the level of arousal and emotional state (Hagbarth et al., 1972). We recently showed that viewing emotionally-charged images increases both cutaneous vasoconstrictor and sudomotor drive (Brown et al., 2012; Henderson et al., 2012b). Furthermore, using functional magnetic resonance imaging (fMRI), coupled with concurrent recordings of SSNA, we identified areas of the brain involved in generation of the increases in SSNA produced by emotionally-charged visual stimuli (Henderson et al., 2012b). However, what is not known is which areas of the brain are responsible for generating spontaneous SSNA in thermoneutral conditions, in the absence of external stimuli.

The aim of this study is to use concurrent recordings of SSNA and fMRI in awake human subjects to identify areas of the brain associated with the generation of spontaneous bursts of SSNA, using the approach we had developed earlier to identify discrete areas within the medulla – the human equivalents of the rostal and caudal ventrolateral medulla (RVLM & CVLM) and nucleus tractus solitarious (NTS) – in which blood-oxygen level dependent (BOLD) signal intensity covaried with spontaneous bursts of muscle sympathetic nerve activity (Macefield and Henderson, 2010). More recently, we published a study in this journal where we showed that muscle sympathetic nerve activity (MSNA) was positively correlated with BOLD signal intensity within the left mid-insula, bilateral dorsolateral prefrontal cortex, bilateral posterior cingulate cortex and bilateral precuneus, emphasizing the contributions of "higher centers" to human cardiovascular control (James et al., 2013). Furthermore, we also showed that MSNA covaried with signal intensity in the left dorsomedial hypothalamus and bilateral ventromedial hypothalamus (VMH), and used functional connectivity to establish coupling between the VMH and the insula, dorsolateral prefrontal cortex, precuneus, and RVLM (James et al., 2013). Like these earlier studies from our laboratory, in the current investigation spontaneous bursts of sympathetic nerve activity were recorded in the absence of any external stimuli.

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1053-8119/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neuroimage.2013.02.030

Materials and methods

Subjects

Experiments were performed on eleven male and six female subjects (mean age 24.2 ± 1.9 years, range 18–42 years) at Neuroscience Research Australia Imaging Facility (Achieva 3 T, Phillips Medical System, Netherlands). All participants were informed of the experimental protocol and supplied their written consent; subjects were told that they can withdraw from the study at any time. Procedures were approved by local Human Research Ethics Committees (University of New South Wales) and were conducted in accordance with the Declaration of Helsinki.

Nerve recording and MR imaging

Subjects lay supine on an MRI bed with their lower back and legs supported by a foam cushion to maintain comfort for the duration of the experiment. A small foam block was used to stabilize and support the knee. The common peroneal nerve was located by palpation and electrical stimuli delivered from a surface probe (1–10 mA, 0.2 ms, 1 Hz, Stimulus Isolator, ADInstruments, Sydney, Australia). An insulated tungsten microelectrode was manually guided into the nerve to locate cutaneous fasicles using weak electrical impulses (0.01–1 mA, 0.2 ms, 1 Hz). An uninsulated microelectrode was inserted into the skin subdermally (~1 cm from the nerve recording site) and served as a reference electrode.

An optimal recording site was confirmed by spontaneous skin sympathetic bursts occurring during arousal stimuli, such as an unexpected loud noise or a tap on the forehead. Furthermore, we were also able to map out the innervation territory of the cutaneous fascicle by stroking the skin on the dorsum of the foot or the lateral aspect of the leg activating cutaneous mechanoreceptors. Neural activity was amplified (gain 100, bandpass 0.1–5.0 kHz) using a MR compatible stainless steel isolated headstage (NeuroAmpEx, ADInstruments, Sydney, Australia) and further amplified, filtered (total gain 20,000; bandpass 0.3–5 kHz) and acquired (10 kHz sampling) on a computer-based data acquisition and analysis system (LabChart 7, PowerLab 30SP; ADInstruments, Sydney, Australia) within the MRI control room.

The subject's head was encased in an 8 channel SENSE head coil that was padded with foam to stabilize the head in the scanner and provide comfort for the subject. The subject was provided with headphones to facilitate communication in the scanner as well as to reduce scanner noise caused by imaging. Subjects were instructed to close their eyes during the scanning. Two hundred gradient echo, echo-planar images sensitive to Blood Oxygen Level Dependent (BOLD) contrast were collected continuously over a period of 27 min and encompassed the entire brain (46 axial slices, TR = 8 s, TE = 40 ms, flip angle = 90°, raw voxel size = 1.5 × 1.5 × 1.5 mm). Forty-six axial slices were collected in a caudal to rostral direction during the first 4 s of the 8 second TR. In each subject a 3D T1-weighted anatomical image set, covering the entire brain was also collected (turbo field echo; echo time = 2.5 ms, repetition time = 5600 ms, flip angle = 8º, voxel size = 0.8 × 0.8 × 0.8 mm).

SSNA analysis

SSNA burst frequency was measured manually from both the raw nerve signal and the RMS-nerve signal – with the assistance of an audio neural signal – during the 4 s inter-scan period. Manual measurement from both neural traces was done to increase overall sensitivity and ensure correct identification of skin sympathetic bursts. The 4 s inter-scan period was divided into 1 s increments and SSNA burst frequency was recorded for seconds 2, 3 and 4 only. In contrast with our previous study (James et al., 2013), where burst amplitude (mV) was used, we used burst frequency as an input model due to the nature of skin sympathetic nerve activity. It is known that, unlike the regular bursts of muscle sympathetic nerve activity (MSNA), bursts of SSNA occur irregularly, and can vary greatly in strength as well as duration between individuals (Delius et al., 1972; Hagbarth et al., 1972). Moreover, because we are not evoking bursts of SSNA by the use of maneuvers or task-related activities – we are simply measuring baseline sympathetic outflow at rest – the levels of activity will be highly unpredictable and will vary greatly across subjects. To eliminate inter-subject variability, burst frequency (the number of bursts per second) was an appropriate indicator of sympathetic activity across all subjects rather than burst amplitude.

MRI analysis

Using SPM8 (Friston et al., 1995), all functional images were motion corrected, intensity normalized, spatially normalized to the Montreal Neurological Institute (MNI) template and smoothed with a 5 mm full-width-at-half-maximum Gaussian filter. Changes in fMRI signal intensity were assessed during the subsequent 4 s period to take into account the ~5 s neurovascular coupling delay and the ~1 s required for conduction of the sympathetic bursts from the brain to the peripheral recording site, as described previously (Macefield and Henderson, 2010; Henderson et al., 2012a).

Since the brain images were collected from a caudal to rostral sequence, the brainstem images represented the 2nd second of the collection period, the diencephalon and surrounding cortex the 3rd second and the rostral cerebrum the 4th second of the collection period. Given this, we analyzed the 4 second recording period in 1 second epochs (excluding the 1st second since this included primarily spinal cord). Thus in each individual subject, SSNA burst frequencies for the 2nd, 3rd and 4th second periods were calculated. In each subject, SSNA burst frequency (bursts per second) during each of the 200 fMRI volumes was used as a model to search for significant signal intensity changes, that is, signal intensity changes which covaried with on-going SSNA. Motion artifacts were removed by adding the 6-parameter motion values as nuisance variables. The resulting contrast maps were then placed into a second level, random effects analysis and areas in which signal intensity increased or decreased during increases in SSNA were determined (uncorrected, $p < 0.001$, minimum cluster size 10 voxels).

In addition, signal intensity changes were extracted from each significantly activated region, percentage changes calculated (periods of SSNA increases compared with period of no SSNA change) and plotted. This was performed to show the degree of variance between individuals and to verify significance due to the initial uncorrected threshold. The results from the thirteen subjects were then collated and a mean signal intensity percentage change was calculated for all subjects. Finally, we performed a functional connectivity analysis on a select group of significantly activated regions (random effects, uncorrected, $p < 0.001$, min cluster size 10 voxels). We chose to explore connectivity of the orbitofrontal cortex and precuneus due to their strong coupling to SSNA and the potential role in an SSNA central command network.

Results

In 12 of the 17 subjects investigated, a stable spontaneous skin sympathetic nerve activity (SSNA) recording was obtained during the entire 200 volume fMRI scan (≈27 min) and as a result, the subsequent fMRI analysis was performed using 200 SSNA values. In one subject, the SSNA activity declined after 120 fMRI volumes, such that only the first 120 volumes were used for analysis. In the remaining 4 subjects, a stable level of SSNA was not maintained for over 100 volumes and so their data were excluded from further analysis. Recordings of spontaneous SSNA from two subjects are shown in Fig. 1. The subject illustrated in Fig. 1A was anxious during the recording: it

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