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Advances in functional magnetic resonance imaging of the human brainstem ☆

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ABSTRACT

The brainstem is of tremendous importance for our daily survival, and yet the functional relationships between various nuclei, their projection targets, and afferent regulatory areas remain poorly characterized. The main reason for this lies in the sub-optimal performance of standard neuroimaging methods in this area. In particular, fMRI signals are much harder to detect in the brainstem region compared to cortical areas. Here we describe and validate a new approach to measure activation of brainstem nuclei in humans using standard fMRI sequences and widely available tools for statistical image processing. By spatially restricting an independent component analysis to an anatomically defined brainstem mask, we excluded those areas from the analysis that were strongly affected by physiological noise. This allowed us to identify for the first time intrinsic connectivity networks in the human brainstem and to map brainstem–cortical connectivity purely based on functionally defined regions of interest.

Introduction

The brainstem is one of the most complicated anatomical entities of the human body. Despite its tremendous importance for our daily survival, the functional relationships between various brainstem nuclei, their projection targets, and afferent regulatory areas remain poorly characterized. The main reason for this lies in the sub-optimal performance of standard neuroimaging methods in this region, including functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). While the application of PET is limited by its spatial resolution, fMRI mainly suffers from an elevated level of physiological noise encountered in the brainstem (Beissner et al., 2011). This noise stems from pulsatile motion of large arteries in the direct vicinity of the brainstem as well as from the flow of cerebro-spinal fluid (CSF) (Harvey et al., 2008; Klose et al., 2000). Both cause strong motion artifacts, especially in the lower brainstem, which cannot be corrected by standard methods, such as realignment. Therefore, BOLD signals in the brainstem region are much harder to detect than those in cortical areas due to a greatly reduced signal-to-noise ratio. While there have been some successful attempts to measure the activity of single brainstem nuclei (D'Ardenne et al., 2008; Eippert et al., 2009; Thompson et al., 2006), the study of inter-nuclear or nucleo-cortical connectivity is still in its infancy. This is due to the fact that all attempts to apply independent component analysis (ICA) (McKeown et al., 1998), one of the standard methods for functional connectivity assessment, to the brainstem, have thus far been unsuccessful.

Here we describe and validate a fundamentally different approach to measure activation of brainstem nuclei as well as nucleo-cortical connectivity using a standard fMRI sequence and widely available tools for multivariate statistical image analysis. While most noise-suppression methods, like low-pass filtering and physiological noise regression (Figs. 1d+e), work in the temporal domain, our approach relies mainly on spatial characteristics of physiological noise. The fact that the major part of the noise stems from an area directly adjacent to the brainstem but not from the brainstem itself allows one to exclude those areas from the analysis that are subject to this influence. This is done by restricting the analysis to an anatomically-defined mask of the brainstem. A similar approach has been successfully applied to the cortex before (Formisano et al., 2004). Noise suppression by this masked ICA ("mICA") approach was followed by source localization by means of ICA, which can be used to detect intrinsic and extrinsic functional connectivity of the brainstem. Another reason to use a brainstem mask is that it prevents results from being driven by the much stronger signals of surrounding subcortical and cerebellar structures. Masked independent component analysis also offers a straightforward approach to measure functional connectivity between the brainstem and cortical areas, avoiding the usual problem of physiological noise interference.

To validate our novel approach, we study resting state connectivity networks in the brainstem and show that the majority of them are highly reproducible. Furthermore, we map brainstem–cortical connectivity to identify the brainstem components as neuronal or noise-related based on their projection targets. Our method significantly advances

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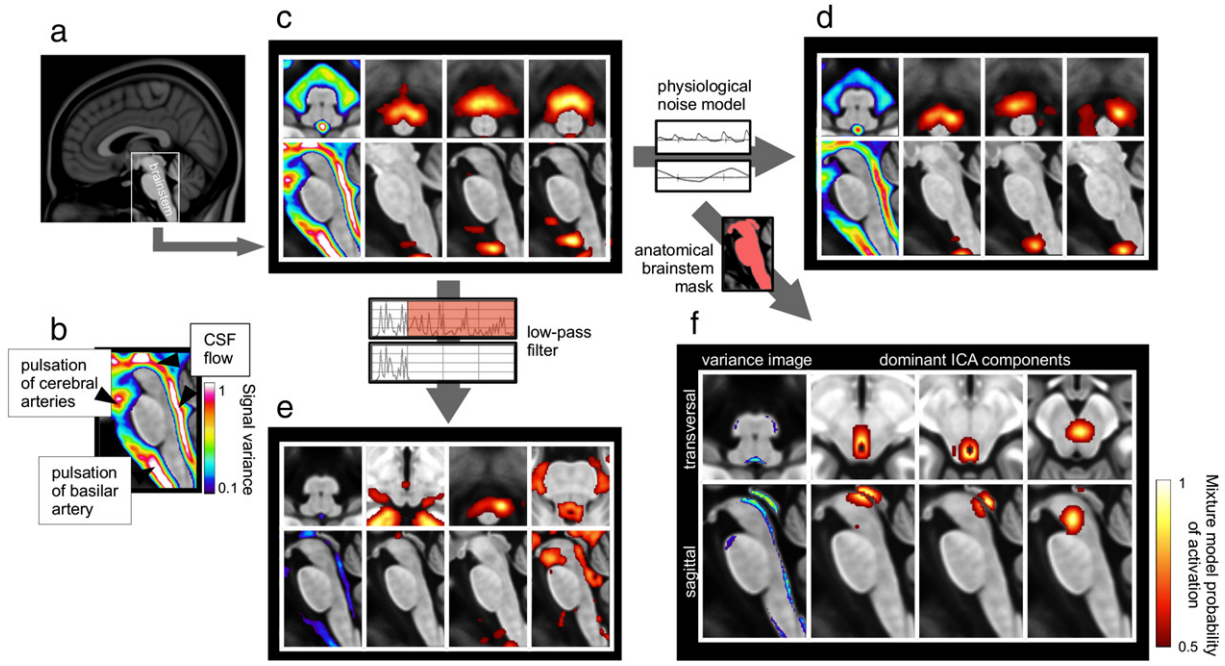

Fig. 1. Conceptual overview of the masked independent component analysis (mICA) approach and comparison of mICA results (f) to those obtained with state-of-the-art methods (d+e). For all analyses, a cuboid containing the brainstem was cut out of the whole-brain dataset (a). b shows the distribution and main sources of physiological noise in a sagittal slice of this cuboid. The results of applying standard ICA to the data without prior noise suppression (c) after regression of physiological signals (d), and after temporal low-pass filtering (e) are shown in the form of the three independent components with the highest uniquely explained variance. Due to their non-Gaussian structure, ICA mainly detected noise components, as can be seen by the peculiar shape of the activations (c–e) coinciding with areas of high physiological noise (b). In stark contrast, the application of an anatomical brainstem mask to exclude areas of high physiological noise leads to ICA results showing activations of individual brainstem nuclei and nuclear complexes (f).

the current capacity to understand the human brainstem and its interactions with other brain regions.

Materials and methods

Subjects

We recruited a sample of 143 healthy subjects (67 males) consisting of students of the local university as well as staff from the university hospital. 43 subjects had to be excluded (30 due to insufficient quality of ECG or respiratory recordings, 1 due to missing MRI data, and 12 due to excessive motion, i.e. >1 mm peak-to-peak, during the measurement).

The remaining 100 subjects (52 males) had a mean age of 25.2 ± 9.0 years (mean ± s.d.) and were of normal weight (BMI: 22.8 ± 2.5). None of the subjects had a history of trauma or any other interfering disease. The study was conducted according to the Declaration of Helsinki and all participants gave written informed consent following the guidelines of the local ethics committee who had approved the study.

For reproducibility analysis two sub-samples of n = 50 were formed that were matched by age, sex, handedness, body mass index and relative mean motion during the scan. In the following, we will refer to them as discovery and confirmation sample.

fMRI measurements

All measurements were taken on a 3 T whole body MR scanner (MAGNETOM Trio Tim, Siemens Medical Solutions, Erlangen, Germany) with a 12-channel head matrix coil. The whole measurement consisted of a resting state scan followed by a structural scan. Subjects were asked to keep their eyes closed during the whole measurement.

The sequence used for the functional run was gradient-echo echo-planar imaging (GRE-EPI) accelerated by parallel imaging using GRAPPA (Griswold et al., 2002). The parameters were: TE = 30 ms, TR = 2.52 s, GRAPPA factor = 2, PE direction = anterior–posterior, FOV = 220 × 210 mm^2, matrix size = 88 × 84, in-plane resolution = 2.5 × 2.5 mm^2, slice thickness = 2.5 mm, inter-slice gap = 0.625 mm, and slice tilt = 40°. 45 slices were acquired in ascending order for whole brain coverage including the lower brainstem. The measurement run consisted of 240 volumes with a total length of 10 min and 5 s.

The T1-weighted anatomical scan was an MPRAGE with the following parameters: TE = 3.03 ms, TR = 2.3 s, TI = 900 ms, partition thickness = 1 mm, matrix size = 256 × 256, FOV = 280 × 280 mm^2, 192 slices, and in-plane resolution = 1.09 × 1.09 mm^2.

Physiological recordings

Electrocardiogram (ECG) and respiration (RESP) were recorded during the MRI scans using an MR-compatible BIOPAC MP150 polygraph (BIOPAC Systems Inc., Goleta, CA, USA). ECG electrodes were arranged in a modified Einthoven's triangle. The sampling rate was 500 Hz for all channels. To remove MRI-related artifacts, ECG signals were band-pass filtered (cutoff: 0.05–35 Hz). The RESP signal was temporally smoothed over 100 samples followed by a simple detection of local maxima. R-waves were extracted after signal decomposition using Daubechies' wavelet of 14th order. Most rapid changes of the ECG signal were detected by thresholding excess of signal components at the highest decomposition level. Resulting inter-beat time series were post-processed by an adaptive filter algorithm described in detail by Wessel (2000). All results were checked off-line by visual inspection.

Data preprocessing

Software

All data processing was carried out using tools from SPM8 (Wellcome Department of Imaging Neuroscience, UCL, London, UK, available at http://www.fil.ion.ucl.ac.uk/spm), FSL5.0 (Oxford Centre for Functional MRI of the Brain, Oxford, UK, available at http://www.fmrib.ox.ac.uk/fsl/), as well as home-written scripts in MATLAB (MathWorks, Natick, MA, USA).