Normative dataset description

Subjects. Fifty healthy adult subjects (25 females, mean age: 33.6y, age range 21-67y, standard deviation 10.5y) with no prior history of neurological or psychiatric disorder, cranial surgery or pulmonary diseases were included in this study. To eliminate potential effects of caffeine on BOLD signal and CVR, we asked the participants to avoid caffeine during the 4 hours preceding scanning.

MRI acquisition. All MRI data acquisitions were performed on a research-dedicated hybrid 3T SIGNA PET-MR scanner (GE Healthcare, Milwaukee, Wisconsin, USA) using a 24-channel head and neck coil. Subjects were comfortably placed in the supine position on the PET-MR bed. Their head was immobilized using soft padding. Earplugs and headphones were used to minimize the noise associated with MRI data acquisition.

Functional data were acquired by using single-shot Gradient-Echo EPI T2*-weighted images, covering the whole brain (time of repetition (TR)/time of echo (TE)/flip angle (α): 3000 msec/34 msec/90°; field of view: 28 cm; acquired matrix: 96 × 96; slice thickness: 3 mm; in-plane resolution: 2.9 × 2.9 mm; 40 slices; 120 volumes). Four dummy scans (total duration: 12 seconds) were obtained prior to each session to allow the MR signal to reach a steady state, and were subsequently automatically discarded by the scanner.

A 3D T1-weighted BRAVO sequence covering the whole brain was acquired to coregister the functional data on morphological data (TR/TE/α: 8.3 msec /3.1 msec/12°; isotropic voxels of 1 mm).

Gas delivery and recordings. Gas type and delivery was done following the guidelines given in [1]. More specifically, we used carbogen (5% of CO_2, 21% of O2 and 74% of N2) placed in a 200L Douglas bag. The bag was connected to a three-way valve that can be manually operated to allow room air or carbogen to flow in the breathing circuit. An operator stayed inside the scanner room to switch the valve according to the experimental paradigm. From the three-way valve, the system was connected through a gas delivery tube to a T-shaped two-way non-rebreathing valve (Hans Rudolf, 2700 series, Kansas, USA) to prevent exhaled air from being sent back into the Douglas bag. A sampling line for CO_2 recording was then connected to the mouth piece through a disposable bacteria and virus filter (AirLife uni-filter by CareFusion, Vermon Hills, IL, USA). An extra pair of tubes where also connected for raw flow estimation through differential pressure measurements.

Outside the scanning room, the CO_2 sampling line was connected to a Nomoline sampling tube and eventually to a sidestream CO_2 sensor (Masimo Corporation, Irvine CA, USA). The CO_2 and raw flow data were acquired using a SmartLab Data Acquisition System (Hans Rudolf, Kansas, USA) connected to a computer. The length of the raw flow dual tubes and the CO_2 sampling lines was 6 meters; both were recorded with a sampling frequency of 100 Hz. Recordings started in synchronization with the first valid fMRI volumes (after the dummy scans) and was stopped about 30 seconds after the end of the fMRI acquisition to allow the complete wash-out of the CO_2 sampling line.

Experimental paradigm. We opted for a 60-second block design, starting with hypercapnia, to allow for the recording of the CO_2 bolus wash-out during the last minute of acquisition. The data are therefore composed of 20 volumes of hypercapnia, followed by 20 volumes of normocapnia; the cycle being repeated three times for a total duration of 6 minutes. The participants were asked to breathe normally through their mouth without any other specific instructions. When possible or required by the subject, a nose clip was used to ensure correct mouth breathing. The raw flow live readings were used to ensure that the subjects continuously used they mouth to breathe during acquisition. In a similar fashion, the CO_2 has been monitored to ensure correct carbogen delivery.
Methodological Compliance. All methods used in this study are performed in accordance with the guidelines provided by the of the CUB Hôpital Erasme Ethics Committee as well as the regulations of the CUB Hôpital Erasme hospital.

fMRIPrep methods

Results included in this manuscript come from preprocessing performed using *fMRIPrep* 21.0.4 (Esteban et al. [2]; Esteban et al. [3]; RRID:SCR_016216), which is based on *Nipype* 1.6.1 (Gorgolewski et al. [4]; Gorgolewski et al. [5]; RRID:SCR_002502).

Anatomical data preprocessing A total of 1 T1-weighted (T1w) images were found within the input BIDS dataset.The T1-weighted (T1w) image was corrected for intensity non-uniformity (INU) with `N4BiasFieldCorrection` [6], distributed with ANTs 2.3.3 [7, RRID:SCR_004757], and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped with a *Nipype* implementation of the `antsBrainExtraction.sh` workflow (from ANTs), using OASIS30ANTs as target template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using `fast` [FSL 6.0.5.1:57b01774, RRID:SCR_002823, 8]. Brain surfaces were reconstructed using `recon-all` [FreeSurfer 6.0.1, RRID:SCR_001847, 9], and the brain mask estimated previously was refined with a custom variation of the method to reconcile ANTs-derived and FreeSurfer-derived segmentations of the cortical gray-matter of Mindboggle [RRID:SCR_002438, 10]. Volume-based spatial normalization to two standard spaces (MNI152NLin2009cAsym, MNI152NLin6Asym) was performed through nonlinear registration with `antsRegistration` (ANTs 2.3.3), using brain-extracted versions of both T1w reference and the T1w template. The following templates were selected for spatial normalization: *ICBM 152 Nonlinear Asymmetrical template version 2009c* [Fonov et al. [11], RRID:SCR_008796; TemplateFlow ID: MNI152NLin2009cAsym], *FSL's MNI ICBM 152 non-linear 6th Generation Asymmetric Average Brain Stereotaxic Registration Model* [Evans et al. [12], RRID:SCR_002823; TemplateFlow ID: MNI152NLin6Asym].

Functional data preprocessing For each of the 1 BOLD runs found per subject (across all tasks and sessions), the following preprocessing was performed. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) are estimated before any spatiotemporal filtering using `mcflirt` [FSL 6.0.5.1:57b01774, 13]. BOLD runs were slice-time corrected to 1.46s (0.5 of slice acquisition range 0s-2.92s) using `3dTshift` from AFNI [14, RRID:SCR_005927]. The BOLD time-series (including slice-timing correction when applied) were resampled onto their original, native space by applying the transforms to correct for head-motion. These resampled BOLD time-series will be referred to as *preprocessed BOLD in original space*, or just *preprocessed BOLD*. The BOLD reference was then co-registered to the T1w reference using `bbregister` (FreeSurfer) which implements boundary-based registration [15]. Co-registration was configured with six degrees of freedom. Several confounding time-series were calculated based on the *preprocessed BOLD*: framewise displacement (FD), DVARS and three region-wise global signals. FD was computed using two formulations following Power (absolute sum of relative motions, Power et al. [16]) and Jenkinson (relative root mean square displacement between affines, Jenkinson et al. [13]). FD and DVARS are calculated for each functional run, both using their implementations in *Nipype* [following the definitions by 16]. The three global signals are extracted within the CSF, the WM, and the whole-brain masks. Additionally, a set of physiological regressors were extracted to allow for component-based noise correction [*CompCor*, 17]. Principal components are estimated after high-pass filtering the *preprocessed BOLD* time-series (using a discrete cosine filter with 128s cut-off) for the two *CompCor* variants: temporal (tCompCor) and anatomical (aCompCor). tCompCor components are then calculated from the top 2% variable voxels within the brain mask. For aCompCor, three probabilistic masks (CSF, WM and combined CSF+WM) are generated in anatomical space. The implementation differs from that of Behzadi et al. in that instead of eroding the masks by 2 pixels on BOLD space, the aCompCor masks are subtracted a mask of pixels that likely contain a volume fraction of GM. This mask is obtained by dilating a GM mask extracted from the FreeSurfer's *aseg* segmentation, and it ensures components are not extracted from voxels containing a minimal fraction of GM. Finally, these masks are resampled into BOLD space and binarized by thresholding at 0.99 (as in the original implementation). Components are also calculated separately within the WM and CSF masks. For each CompCor decomposition, the k components with the largest singular values are retained, such that the retained components' time series are sufficient to explain 50 percent of variance across the nuisance mask (CSF, WM, combined, or temporal). The remaining components are dropped from consideration. The head-motion estimates calculated in the correction step were also placed within the corresponding confounds file. The confound time series derived from head motion estimates and global signals were expanded with the inclusion of temporal derivatives and quadratic terms for each [18]. Frames that exceeded a threshold of 0.5 mm FD or 1.5 standardised DVARS were annotated as motion outliers. The BOLD time-series were resampled into standard space, generating a *preprocessed BOLD run in MNI152NLin2009cAsym space*. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. Automatic removal of motion artifacts using independent component analysis [ICA-AROMA, 19] was performed on the *preprocessed BOLD on MNI space* time-series after removal of non-steady state volumes and spatial smoothing with an isotropic, Gaussian kernel of 6mm FWHM (full-width half-maximum). Corresponding "non-aggresively" denoised runs were produced after such smoothing. Additionally, the "aggressive" noise-regressors were collected and placed in the corresponding confounds file. All resamplings can be performed with *a single interpolation step* by composing all the pertinent transformations (i.e. head-motion transform matrices, susceptibility distortion correction when available, and co-registrations to anatomical and output spaces). Gridded (volumetric) resamplings were performed using `antsApplyTransforms` (ANTs), configured with Lanczos interpolation to minimize the smoothing effects of other kernels [20]. Non-gridded (surface) resamplings were performed using `mri_vol2surf` (FreeSurfer).

Many internal operations of *fMRIPrep* use *Nilearn* 0.8.1 [21, RRID:SCR_001362], mostly within the functional processing workflow. For more details of the pipeline, see the section corresponding to workflows in *fMRIPrep*'s documentation.

Copyright Waiver

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