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Does motion-related brain functional connectivity reflect both artifacts and genuine neural activity?

Jesus Pujol [a,b,*], Dídac Macià [a], Laura Blanco-Hinojo [a,c], Gerard Martínez-Vilavella [a], Jordi Sunyer [d,e], Rafael de la Torre [c,f], Assumpta Caixàs [g], Rocío Martín-Santos [h], Joan Deus [a,i], Ben J. Harrison [j]

[a] MRI Research Unit, CRC Mar, Hospital del Mar, Barcelona, Spain
[b] Centro Investigación Biomédica en Red de Salud Mental, CIBERSAM G21, Barcelona, Spain
[c] Human Pharmacology and Clinical Neurosciences, Hospital del Mar Medical Research Institute, Barcelona, Spain
[d] Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain
[e] Universitat Pompeu Fabra (UFP), Barcelona, Spain
[f] CIBER-Fisiopatología de la Obesidad y Nutrición (CIBEROBN), S. de Compostela, Spain
[g] Diabetes Endocrinology and Nutrition Department, Hospital de Sabadell, Institut Universitari Parc Taulí, Universitat Autònoma de Barcelona, Barcelona, Spain
[h] Department of Psychiatry and Clinical Psychobiology, Clinical Institute of Neuroscience, Hospital Clínic, CIBERSAM, University of Barcelona, Barcelona, Spain
[i] Department of Clinical and Health Psychology, Autonomous University of Barcelona, Barcelona, Spain
[j] Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne, Melbourne, Australia

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ABSTRACT

Imaging research on functional connectivity is uniquely contributing to characterize the functional organization of the human brain. Functional connectivity measurements, however, may be significantly influenced by head motion that occurs during image acquisition. The identification of how motion influences such measurements is therefore highly relevant to the interpretation of a study's results. We have mapped the effect of head motion on functional connectivity in six different populations representing a wide range of potential influences of motion on functional connectivity. Group-level voxel-wise maps of the correlation between a summary head motion measurement and functional connectivity degree were estimated in 80 young adults, 71 children, 53 older adults, 20 patients with Down syndrome, 24 with Prader–Willi syndrome and 20 with Williams syndrome. In highly compliant young adults, motion correlated with functional connectivity measurements showing a system-specific anatomy involving the sensorimotor cortex, visual areas and default mode network. Further characterization was strongly indicative of these changes expressing genuine neural activity related to motion, as opposed to pure motion artifact. In the populations with larger head motion, results were more indicative of widespread artifacts, but showing notably distinct spatial distribution patterns. Group-level regression of motion effects was efficient in removing both generalized changes and changes putatively related to neural activity. Overall, this study endorses a relatively simple approach for mapping distinct effects of head motion on functional connectivity. Importantly, our findings support the intriguing hypothesis that a component of motion-related changes may reflect system-specific neural activity.

Introduction

Imaging research on neural connections is making a unique contribution to our understanding of the functional organization of the human brain. Functional MRI (fMRI) of spontaneous brain activity permits the characterization of relevant functional networks on the basis of region synchronization – typically defined as "functional connectivity" (Buckner et al., 2013). Despite the broad appeal of the approach, it has become increasingly recognized that connectivity measurements are influenced by common head motion that occurs during image acquisition. This artifact appears to have a general distorting effect of increasing short-distance connectivity measurements and may reduce long-distance measurements (Power et al., 2012, 2014; Satterthwaite et al., 2012, 2013a; Van Dijk et al., 2012). Recognition of these effects has generated much concern as incorrect estimations of connectivity may lead to erroneous conclusions in studies comparing groups with different levels of head motion (Deen and Pelphrey, 2012), as in autism where anomalous functional connectivity is considered a key pathophysiological factor (Just et al., 2012). In response to this concern, several analysis strategies have been developed to mitigate the influence of head motion on connectivity measurements (see Yan et al., 2013a for a review) and have been applied in challenging populations, such as children with autism (Supekar et al., 2013) as well as normally developing children and adolescents (Satterthwaite et al.,

* Corresponding author at: Department of Magnetic Resonance, CRC-Mar, Hospital del Mar, Passeig Marítim 25-29, 08003 Barcelona, Spain. Fax: +34 93 221 21 81.
E-mail address: jpujol@crccorp.es (J. Pujol).

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2013b). It nevertheless remains unclear which strategy may be most optimal in a given study context.

Functional connectivity-based assessments could potentially be more accurate if the actual impact of head motion on such measurements could be predicted specifically for the population of interest. Samples with the largest motion will presumably show the most dramatic effects, but we anticipate that the "anatomy" or spatial distribution of these effects may also vary as a function of the study population. In addition, there exists the intriguing possibility that genuine neural activity related to motion may also contribute to motion-induced connectivity changes, as proposed recently by Yan et al. (2013a,b). The identification of how head motion influences functional connectivity is important both for understanding how motion may influence a given study's results and what should be expected from the subsequent removal of motion effects with post-acquisition analyses.

In this study we sought to map the influence of head motion on functional connectivity measurements in different populations. Previous studies have comprehensively assessed the magnitude of motion effects on brain fMRI measurements using a variety of analysis (Power et al., 2014; Satterthwaite et al., 2012, 2013a; Yan et al., 2013a; Zuo et al., 2013). We aimed to complement this research by mapping the anatomical distribution of these effects in six samples representing a wide range of potential influences of head motion on functional connectivity. To generate the maps, a representative motion measurement was obtained for each individual and regressed against whole-brain functional connectivity measurements at the group level. The average inter-frame head position variation across each resting-state acquisition was used as an optimal summary of the individual's head motion (Power et al., 2012; Satterthwaite et al., 2012; Van Dijk et al., 2012) and maps of "connectivity degree" served to summarize whole-brain functional connectivity (Buckner et al., 2009; Cole et al., 2010; Tomasi and Volkow, 2011). Our study populations included highly collaborative healthy young adults, normally developing children, neurologically preserved older adults and three clinical reference populations: Down syndrome, Prader–Willi syndrome and Williams syndrome.

Methods

Study populations

Three healthy subject populations with distinct age ranges and anticipated differences in spontaneous head motion were recruited. We also included three genetic disorder populations with comparable levels of cognitive impairment but notably different clinical syndrome profiles. Prior to exclusions (see further) the groups originally comprised 82 young adults, 80 children, 58 older adults, 26 Down syndrome patients, 30 Prader–Willi syndrome patients and 20 Williams syndrome patients. In the healthy groups, primary exclusion criteria included the presence of any relevant medical disorders, substance abuse, psychiatric illness or current medical treatments. All participants in the clinical populations had a genotype-confirmed disorder and estimated intelligence quotients (IQ) for the final samples were 45.8 ± 7.1 (range 40–66) in Down syndrome, 67.6 ± 12.1 (range 40–92) in Prader–Willi syndrome and 63.7 ± 7.0 (range 57–82) in Williams syndrome. Each participant was capable of understanding the MRI assessment and demonstrated a willingness to participate in the study.

This study was conducted according to the principles expressed in the Declaration of Helsinki and was approved by the Clinical Research Ethical Committee of the Parc de Salut Mar of Barcelona and the Corporació Sanitària Parc Taulí of Sabadell. Written informed consent for fMRI assessment and subsequent analyses was obtained from the participants and parents of the patients with genetic disorders.

MRI acquisition

Each of the study populations underwent an identical imaging protocol at the same imaging facility. A 1.5 T Signa Excite system (General Electric, Milwaukee, WI, USA) equipped with an eight-channel phased-array head coil and single-shot echoplanar imaging (EPI) software was used. The functional sequence consisted of gradient recalled acquisition in the steady state (time of repetition [TR], 2000 ms; time of echo [TE], 50 ms; pulse angle, 90°) within a field of view of 24 cm, with a 64 × 64-pixel matrix, and with a slice thickness of 4 mm (inter-slice gap, 1.5 mm). Twenty-two interleaved slices were prescribed parallel to the anterior–posterior commissure line covering the whole-brain. A 6-min continuous resting-state scan was acquired for each participant and was always the first acquisition sequence after the initial localizer. Participants received identical instructions to relax, stay awake and to lie still without moving, while keeping their eyes closed throughout. This sequence generated 180 whole-brain EPI volumes. The first four (additional) images in each run were discarded to allow magnetization to reach equilibrium.

Image preprocessing

Imaging data were processed using MATLAB version 2011b (The MathWorks Inc, Natick, Mass) and Statistical Parametric Mapping software (SPM8; The Wellcome Department of Imaging Neuroscience, London). Preprocessing involved conventional realignment procedures, spatial normalization and smoothing using a Gaussian filter (full-width half-maximum, 8 mm). Data were normalized to the standard SPM-EPI template and resliced to 2 mm isotropic resolution in Montreal Neurological Institute (MNI) space. All image sequences were inspected for potential acquisition and normalization artifacts.

Head motion measurements

Motion was quantified using realignment parameters obtained during image preprocessing, which included 3 translation and 3 rotation estimates. Average inter-frame motion measurements (head position variations of each volume as compared to the previous volume) were used to capture head motion across the 6-min scan (Power et al., 2012; Satterthwaite et al., 2012; Van Dijk et al., 2012). A motion summary measurement that combined translations and rotations was computed in mm by adapting the formula of Van Dijk et al. (2012). Motion was also considered separately for each translation (in mm) and rotation (in angular degrees) index in the correlation analyses conducted for each group. Results from this separate analysis are reported when preferential correlations were obtained. A full description of the estimation of motion measurements is reported in the Supplementary Material.

To optimize the homogeneity of the samples and better characterize group effects, outliers (and extremes) within each group with regard to mean motion were excluded using conventional boxplot criteria (cases beyond the quartile Q3 by one-and-a-half Q3-Q1 interquartile range [SPSS 15.0; SPSS Inc., Chicago IL]). The number of excluded outliers was 2 for the young adult sample (final $n = 80$; mean ± SD age = 26.4 ± 7.5 years; 35 females), 9 for the child sample (final $n = 71$; 9.6 ± 0.9 years; 41 females), 5 for the aged sample (final $n = 53$; 67.4 ± 7.2 years; 29 females), 6 for Down syndrome patients (final $n = 20$; 24.5 ± 4.1 years; 10 females), 6 for Prader–Willi syndrome patients (final $n = 24$; 26.3 ± 6.9 years; 12 females), and none for Williams syndrome patients ($n = 20$; 25.2 ± 4.2 years; 9 females).

Connectivity degree mapping

Whole-brain maps of the degree of functional connectivity were generated on a voxel-wise basis (Buckner et al., 2009; Cole et al., 2010; Tomasi and Volkow, 2011). We adopted the data-driven method described by Sepulcre et al. (2010), but applied study-specific parameters. Overall, this approach measures the degree of connectivity of