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

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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.

**Key words**: fMRI, resting-state, brain networks, sensorimotor cortex, default mode network, head motion

## 1. 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. 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; Yan et al. 2013a; Satterthwaite et al. 2012, 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.

## 2. Methods

### 2.1. 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.

### 2.2. MRI acquisition

Each of the study populations underwent an identical imaging protocol at the same imaging facility. A 1.5 Tesla 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, 90º) within a field of view of 24 cm, with a 64 x 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.

### 2.3. 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.

### 2.4. 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-minute scan (Van Dijk et al. 2012; Power et al. 2012; Satterthwaite 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).

### 2.5. 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 each voxel with all other voxels as the sum of correlations above a given Pearson correlation coefficient threshold (Sepulcre et al. 2010).

As applied here, connectivity degree maps were generated for each subject using the preprocessed EPI time-series, resliced to a voxel dimension of 6.3 x 7.6 x 6.8 mm to increase signal-to-noise ratio and to optimize computational efficiency. Volume means of white matter, CSF, and global brain signal time courses were regressed from each voxel's time series and a high pass filter set at 128 sec was used to remove low frequency drifts. Each voxel's resulting time series was then correlated with that of every other voxel, to generate a Pearson correlation coefficient r-matrix. The analysis was restricted to gray matter, which allowed us to define a total amount of 4,097 voxels or brain “nodes”. From the correlation matrix data, connectivity degree of each voxel was computed by summing the number of correlations that a given voxel had above a threshold $r > 0.35$, which may be considered a moderately high connectivity threshold (Buckner et al. 2009; Cole et al. 2010). Connectivity degree was finally expressed in relative values as the ratio of total supra-threshold connections over all possible connections. Global (whole-brain gray matter) and

"regional" connectivity degree maps were estimated. Regional maps were defined by 30 mm-radial spheres.

### 2.6. Head motion effect analysis

First-level (individual) connectivity degree images were subsequently included in second-level (group) analyses in SPM8 to generate "connectivity-motion" correlation maps using the motion estimated for each individual as a regressor. The results allowed us to quantify both the severity and spatial distribution of the effects of motion on functional connectivity measurements. Separate analyses were conducted using both global and regional connectivity degree maps. Data will be reported only for the regional approach as both global and regional approaches demonstrated a similar pattern of results, albeit more robustly for regional connectivity. This latter observation is consistent with the notion that motion effects are most relevant on short-distance functional connectivity (Power et al., 2012, 2014; Satterthwaite et al. 2012, 2013a; Van Dijk et al. 2012). Results were considered significant with clusters of 1.3 ml (4 voxels) at a height threshold of $p< 0.005$, which satisfied the family-wise error (FWE) rate correction of $P_{FWE} < 0.05$ according to recent Monte Carlo simulations (Pujol et al. 2013).

## 3. Results

### 3.1. Young adults

Figure 1 shows boxplots of motion estimates for each study population. Young healthy adults demonstrated a small mean level of motion and narrow range. In this group, the effect of motion on connectivity measurements showed a notably local pattern. Positive correlations (greater motion predicting greater connectivity) involved the sensorimotor cortex at the body and feet level and the visual cortex bilaterally (Figure 2). Negative correlations indicating more connectivity in subjects with less motion involved core regions of the default mode network, namely the posterior cingulate cortex, medial frontal cortex and inferior parietal cortex (Figure 2). It is relevant to note that this latter finding corresponds to a *negative correlation* with regional functional connectivity, whereas in prior studies the influence of motion on such measurements has been described only in terms of positive correlations (Satterthwaite et al. 2012).

To examine whether the positive correlation between motion and functional connectivity was biased towards regions demonstrating stronger initial levels of functional connectivity degree, we compared those regions demonstrating a positive correlation with motion (i e., sensorimotor and visual cortex) with those regions demonstrating the most robust connections in our whole-brain mapping. Minimal anatomical overlap was observed between these effects as illustrated in Supplementary Figure 1.

To emphasize the anatomical specificity of the findings for both positive and negative correlation maps, common resting-state functional networks were identified using a data-driven Independent Component Analysis (ICA) and were spatially compared with the

brain areas related to motion. Figure 2 shows the clear overlap between motion/connectivity correlation results and core regions of the ICA-identified functional networks. The ICA methodology is described in the Supplementary Material.

The motion-connectivity analysis was repeated after including the whole-brain average of connectivity degree for each individual as a covariate. That is, we performed a secondary analysis controlling for a global variable that is sensitive to the general voxel-wise effect of motion on connectivity measurements. This analysis reproduced the anatomy of the correlations described above with a tendency for the correlations to be more robust (Supplementary Figure 2). These results therefore indicate that the initial findings in young adults likely do not reflect the general effect of motion on brain connectivity measurements.

Mean inter-frame motion is a composite measurement of three translations and three rotations across the x, y and z axes. We further tested whether the effect of motion on connectivity was preferentially related to a specific head motion direction. In these separate analyses, sensorimotor cortex connectivity was preferentially correlated with head rotations and specifically with the combination of rotations about the x (pitch) and z (yaw) axes. Figure 3 shows a highly selective correlation between head rotation measurements and connectivity in the sensorimotor strip from the feet to the neck and upper face cortical representation bilaterally.

The primary analyses above determined the nature of correlations between head motion and whole-brain connectivity degree. Changes in connectivity degree reflect changes in the functional synchrony of implicated voxels or nodes with *other* brain regions, but do not inform about the anatomy of these *other* regions. Therefore, in order to characterize

these results more comprehensively, a post hoc region-of-interest (seed-based) functional connectivity analysis was performed on the previously identified region showing the largest magnitude correlation with head motion (left motor body representation; MNI coordinates x= -25, y= -18, z= 68 mm). The corresponding results indicated a positive correlation between head motion and the functional connectivity of this region with bilateral areas of the sensorimotor network specifically (Supplementary Figure 3). This analysis is described in full in the Supplementary Material.

To briefly summarize, young adults showed relatively low amounts of head motion that correlated with connectivity measurements showing a neural system-specific anatomy. This observation does not appear to represent the general distorting effect of motion on connectivity measurements, but rather appears to indicate subtle connectivity changes related to genuine neural activity in sensorimotor, visual and default mode networks.

A further analysis was conducted to specifically assess the relationship between the temporal evolution of motion and the fMRI signal time course within the selected motor cortex region in each individual. We observed minimal temporal correlation between these two variables, which had an across-subject mean Pearson value of r= 0.05, SD= 0.11 (range r= -0.20 to r= 0.35). There were additionally no significant differences when comparing the strength of the correlation (using z-transformed parameters) between individuals with high (n= 40) and low (n= 40) motion. Inspection of individual data instead suggested: *(i)* only an occasional coupling between periods of relevant motion and periods of signal increase; *(ii)* no systematic overlap in the duration and magnitude between periods of signal increase and motion; and *(iii)* that motion periods were more probable at the end of periods of signal increase (Supplementary Figure 4). Overall, these results are consistent with the notion of

poor temporal coincidence between fMRI signal changes and changes in head motion, but do not argue against an association between sensorimotor cortex activity and motion across subjects. Despite the fact that the temporal correlation was not significant in most individuals, the subtle but systematic tendency across individuals was highly significant at the group level. This effect was demonstrated with a one-sample t-test of the z-transformed individual correlations between fMRI signal time-course and motion time-course ($t= 4.2$; $p= 0.00006$; mean $z= 0.48$; $SD= 1.02$).

The above temporal analysis was then expanded with a "cross-correlation" analysis to investigate the correlation between the temporal evolution of motion (inter-frame motion at each time point) and fMRI signal at different temporal delays. A conventional cross-correlation approach (normalized sliding dot product) was used in which the correlation between motion and fMRI signal time courses was repeated by successively applying (forward and backward) time-lags of 2 s (1 frame) to the motion time course. The cross-correlation was performed at the individual level and group-averaged results are presented in Figure 4. This analysis revealed two key results further suggesting the association of motion with neural activity. Firstly, motion correlated positively with fMRI in the sensorimotor cortex of young adults, whereas the effect expected of an artifactual correlation should be characterized by decreasing signal coinciding with motion (see the "children" example in Figure 4). Secondly, the positive correlation was also significant after moving forward the motion time course up to 4 s (2 frames), which approaches the expected hemodynamic delay of the fMRI signal with respect to neural activation in the sensorimotor cortex (Handwerker et al. 2012).

### 3.2. Children and older adults

In reference to Figure 1, motion was characterized by a wide range of values in children, whereas it was more homogenous and large as a group in older adults (Figure 1). In children, head motion was positively correlated with a notably diffuse connectivity degree pattern involving large brain areas (Figure 5). In the older adults, the correlation with motion was also highly distributed (but less prominent) and involved similar brain regions (Figure 5).

After controlling for whole-brain average connectivity degree, the effect of motion on connectivity was dramatically attenuated in children whereby only a few clusters remained significant, including part of the sensorimotor cortex (Supplementary Figure 5). In older adults, a similar observation was made with the remaining significant correlations also involving part of the sensorimotor cortex (Supplementary Figure 5).

Thus, unlike the anatomical specificity of the findings in young adults, children and older adults showed larger head motion that was associated with widespread and non-specific changes in functional connectivity.

### 3.3. Genetic disorders

The three genetic disorder groups showed a relatively wide range of motion, which was largest for Williams syndrome patients (Figure 1). The correlation of head motion with connectivity degree measurements in Down syndrome demonstrated a major involvement of the anterior and dorsal aspect of the brain (Figure 6). This finding was almost entirely

reproduced using the x axis (pitch) head rotation measurement as a regressor (Supplementary Figure 6). In Prader-Willi syndrome patients, significant effects were mostly located in basal (frontal and temporal) brain regions, although significant correlations were also identified along the dorsal anterior cingulate cortex (Figure 6). In Williams syndrome patients, significant correlations between motion and connectivity extended broadly throughout gray matter voxels (Figure 6).

The effect of controlling for whole-brain average connectivity degree was also distinct across these populations. In Down syndrome, the covariate analysis led to a partial reduction of the anterior dorsal changes; in Prader-Willi syndrome, a smaller decrease in the magnitude and extent of correlations was observed; whereas in Williams syndrome a dramatic reduction in motion-connectivity correlations was apparent (Supplementary Figure 7).

Overall, our analyses of the three clinical populations indicate that large levels of motion may be correlated with connectivity measures in clearly distinct ways. This refers both to the magnitude and anatomical distribution of the observed correlation patterns, as well as their association with the general confounding effects of motion.

### 3.4.Group-level removal of motion effects

Two further analyses were preformed to illustrate the outcome of removing the effect of head motion on functional connectivity measurements across subjects. The child sample was split into separate subgroups of higher (n= 35) versus lower (n=36) motion and compared with respect to brain connectivity degree. As expected, the subgroup of children

with relatively higher motion showed a widespread increase in connectivity degree (Figure 7) with a similar pattern to the overall group correlation results shown in Figure 5. A further analysis including motion measurements as a covariate removed almost all of the observed subgroup differences (Figure 7).

Similarly, the young adult sample was split into higher (n= 40) versus lower (n=40) head motion cases and compared with regards to brain connectivity degree. The analysis of group differences showed increased connectivity in default mode network areas in the group with lower motion (Figure 7) similar to the findings obtained in the overall group correlation analysis (Figure 2). We performed this contrast (lower motion > higher motion), as these group differences in regional connectivity degree most likely do not represent motion artifact. The inclusion of motion measurements as a covariate in further analysis removed all subgroup differences in default mode network areas.

These two analyses indicate that group-level regression with a summary motion measurement efficiently removes potential motion-related artifacts, but may additionally remove changes potentially related to neural activity.

## 4. Discussion

We have mapped the association between head motion and functional connectivity in six different populations expressing a range of motion during resting-state fMRI. Our results indicate notably distinct patterns across groups with regard to the magnitude and spatial distribution of correlations. In highly compliant young adults, the correlation of head motion with connectivity degree estimates corresponded to system-specific anatomy involving the sensorimotor cortex, visual areas and key default mode network regions. These correlations were not explained by a general distorting effect of motion on regional functional connectivity measurements. In the populations with largest head motion, motion-connectivity correlations were generally more pervasive, but also demonstrated population-specific features. Importantly, group-level regression of motion estimates led to the efficient removal of both general changes and putative system-specific changes.

It is difficult to consider that our findings in healthy young adults are the sole consequence of head motion artifact. This notion becomes apparent when considering: *(i)* the exquisite anatomical specificity of the observed correlations; *(ii*) the lack of association between these correlations and a representative global measurement of functional connectivity; *(iii)* that the correlation between motion and fMRI signal is more evident when adjusting for the hemodynamic delay; and *(iv)* the fact that head motion does not appropriately explain the observed increases in regional functional connectivity in default mode network regions in subjects with low motion (i.e., the opposite effect should be expected [Power et al. 2012, 2014; Satterthwaite et al. 2012]). These findings appear to suggest that, in the lower range of head motion, there are relevant motion-related functional connectivity changes that express genuine variations of neural activity within implicated

regions. This hypothesis was originally proposed by Yan et al. (2013a,b) when analyzing the impact of motion on the fMRI signal. Positive motion-fMRI signal correlations were detected in motor areas particularly in subjects with low motion (Yan et al. 2013a). By contrast, motion-related signal changes were not generally consistent with neural activity in the studies by Power et al. (2012, 2014), who included samples with relatively large degrees of motion.

Our dynamic analysis of individual time-series revealed a weak coupling between the temporal evolution of resting signal fluctuations in the motor cortex and the temporal evolution of head motion at the individual level, as in the studies by Power et al. (2012, 2014). Nonetheless, we also observed that a weak but systematic association between fMRI signal and motion at the individual level may be significant across subjects as in the results of Yan et al. (2013a). Importantly, our cross-correlation analysis suggests contrasting temporal dynamics for changes putatively reflecting artifacts versus genuine neural activity. In the case of suspected artifact, motion temporally coincided with fMRI signal decrease, whereas in the case of suspected genuine activity, motion predicted increasing (delay-adjusted) signal (Figure 4). Considered together, these previous observations (Power et al. 2012, 2014; Yan et al. 2013a) and our current results are consistent with the notion that changes potentially related to genuine neural activity are subtle but significant, and evident mainly at low-motion range (i.e., less detectable in the presence of large motion artifact).

It is unclear why motion is significantly associated with changes in functional connectivity of the visual cortex. Some positive associations between primary sensorimotor and visual cortex connectivity have been previously reported (Doucet et al. 2011), as was also shown in our region-of-interest analysis (Supplementary Figure 3). Nevertheless, the

motor and visual coupling in the context of head motion is not obvious. Yan et al. (2013a) provided the argument that dorsomedial visual areas are implicated in analyzing self-motion in relation to the environment. Unlike their findings, primary visual cortices were largely implicated in our results. Future studies may test whether this association may additionally reflect, for instance, occasional eye opening during scanning.

A more intriguing finding was the correlation between head motion and connectivity measurements in the default mode network. Subjects lying more still during scanning demonstrated more functional connectivity among these regions. In line with current ideas about the default mode network (Buckner et al. 2008; Harrison et al. 2008a; Pujol et al. 2013), this result may represent a putative correlate of greater self-referential mental activity. Other previous studies also suggest some level of functional competition or antagonism between the default mode network and other brain systems including sensorimotor cortex (Doucet et al. 2011; Fox et al. 2005; Kelly et al. 2007; Pujol et al. 2013), as well as the attentional modulation of their mutual interaction (Harrison et al. 2011; Harrison et al. 2008b; Pagnoni, 2012). Based on our current findings, it may therefore be suggested there is a relative bias to greater default mode network-related activity in subjects with low levels of motion. Overall, the results in young adult participants further reinforce the notion that functional connectivity measured during resting state conditions does not only reflect “intrinsic” signal fluctuations among metabolically coupled brain regions, but also superimposed neural activity changes related to spontaneous mental processes (Sonuga-Bark and Castellanos 2007; Mason et al. 2007; Harrison et al. 2008b).

The populations with largest head motion exhibited the most pronounced motion-connectivity correlations, with the most dramatic changes observed in the groups with the

greatest range of motion (i.e., children and Williams syndrome). However, the spatial distribution of the correlations was notably different for each group. In Down syndrome, motion was related to changes in dorsal anterior brain regions, which was mostly explained by pitch rotations about the x axis. This is a relevant finding as head rotation stereotypies are common in this disorder (Capone et al. 2005; Ji et al. 2011; Carter et al. 2008). The pattern of connectivity-motion correlations in Prader-Willi syndrome patients was also unique. These correlations showed little modification after adjusting for a measurement of global connectivity and, interestingly, involved areas expected to show relevant functional alterations in this genetic disorder, including the hypothalamus (Goldstone 2004). The specificity of these results reinforces the idea the motion effects should be carefully characterized before attempts are made to statistically remove them at the group level.

Group-level removal of motion-related changes in functional connectivity using summary motion measurements is considered among the efficient motion correction strategies (Yan et al. 2013a). We have shown that both the magnitude and distribution of motion-correlated functional connectivity changes may vary notably across different study populations and, consequently, the removal of these effects will also be distinct. Characterization of the impact of motion using correlation maps may be useful for anticipating the outcome of removal strategies, which as highlighted by our findings, may involve both artifacts and potential genuine changes related to neural activity.

**Conclusions**. Overall, the current study endorses a relatively simple approach for mapping distinct effects of head motion on functional connectivity measurements at the group level as well as feasibility in removing these effects when subsequently adjusting for mean inter-frame motion. Importantly, our characterization of results in highly compliant (i.e., low

motion) subjects supports the intriguing hypothesis that a relevant component of motion-connectivity correlations may reflect genuine system-specific neural activity.

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**Conflicts of interest**

The authors declare no conflict of interest.

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**Figure legends**

**Figure1**. Box-plots of head motion for the six study populations (after excluding group outliers). Group differences are apparent both with regard to the magnitude and range of motion. Mean and variance values for young adults (defined as the reference population) were significantly different from each of the other samples with p values < 0.005.

**Figure 2**. Voxel-wise maps representing significant correlations between head motion and functional connectivity degree in young adults. Positive correlations involved the sensorimotor and visual cortices bilaterally. Negative correlations involved core areas of the default mode network including the posterior cingulate and medial frontal cortices. Color bars correspond to t values. An Independent Component Analysis (ICA) was used to identify the implicated resting-state functional networks (bottom panel). Note the clear overlap between motion/connectivity correlation results and core regions of the ICA-estimated functional networks.

**Figure 3**. Voxel-wise maps representing significant correlations between head rotation (combined x axis and z axis rotations) and functional connectivity degree in young adults. Note the precise involvement of the sensorimotor strip – extending from the feet to the neck and upper face cortical representation. Color bars correspond to t values.

**Figure 4**. Group results from the cross-correlation analysis. The temporal evolution of inter-frame head motion was correlated with the fMRI signal time course (group mean cross-correlation r values with ± standard error of mean in axis y). The correlation was repeated after applying 1 frame (2 s) time-lags to the motion time course both forward (positive

values in axis x) and backward (negative x values). In children's dorsal frontal cortex (MNI -12, 38, 44), the largest negative correlation at zero delay (i.e., signal decrease temporally coinciding with motion) suggests an artifactual effect. In young adults, by contrast, motion was positively correlated with fMRI signal of the motor cortex (MNI -25, -18, 68) at zero time-lag and also when applying motion time course delays up to 2 frames (4 s). This pattern suggests a coupling of motion with hemodynamically delayed fMRI signal increase related to neural activity.

**Figure 5.** Voxel-wise maps representing significant correlations between head motion and functional connectivity degree in children and older adults. Significant correlations involved widespread areas in both groups, although children showed the most pronounced effects. Color bars correspond to t values.

**Figure 6**. Voxel-wise maps representing significant correlations between head motion and functional connectivity degree in patients with Down syndrome, Prader-Willi syndrome and Williams syndrome. Note the distinct distribution of correlations across these populations. Color bars correspond to t values.

**Figure 7.** Group-level removal of motion effects: Connectivity degree differences between the subgroup of children with higher (n= 35) > lower (n= 36) motion involved widespread brain areas. Including motion measurements as a covariate removed almost all of the observed subgroup differences. Similarly, connectivity degree differences between the subgroup of adults with lower (n= 40) > higher (n= 40) motion were mostly removed when applying this covariate. Color bars correspond to t values.

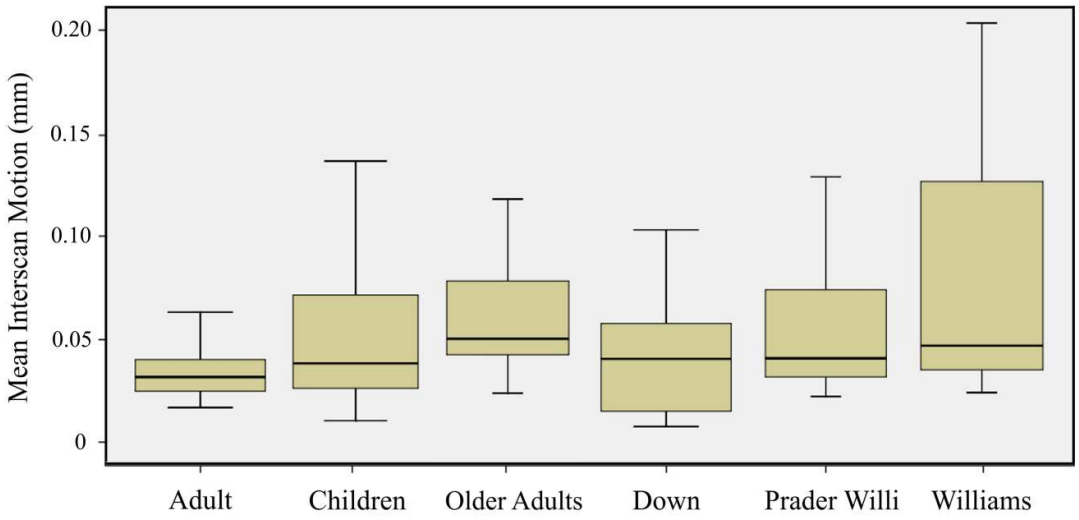


**Figure 1**

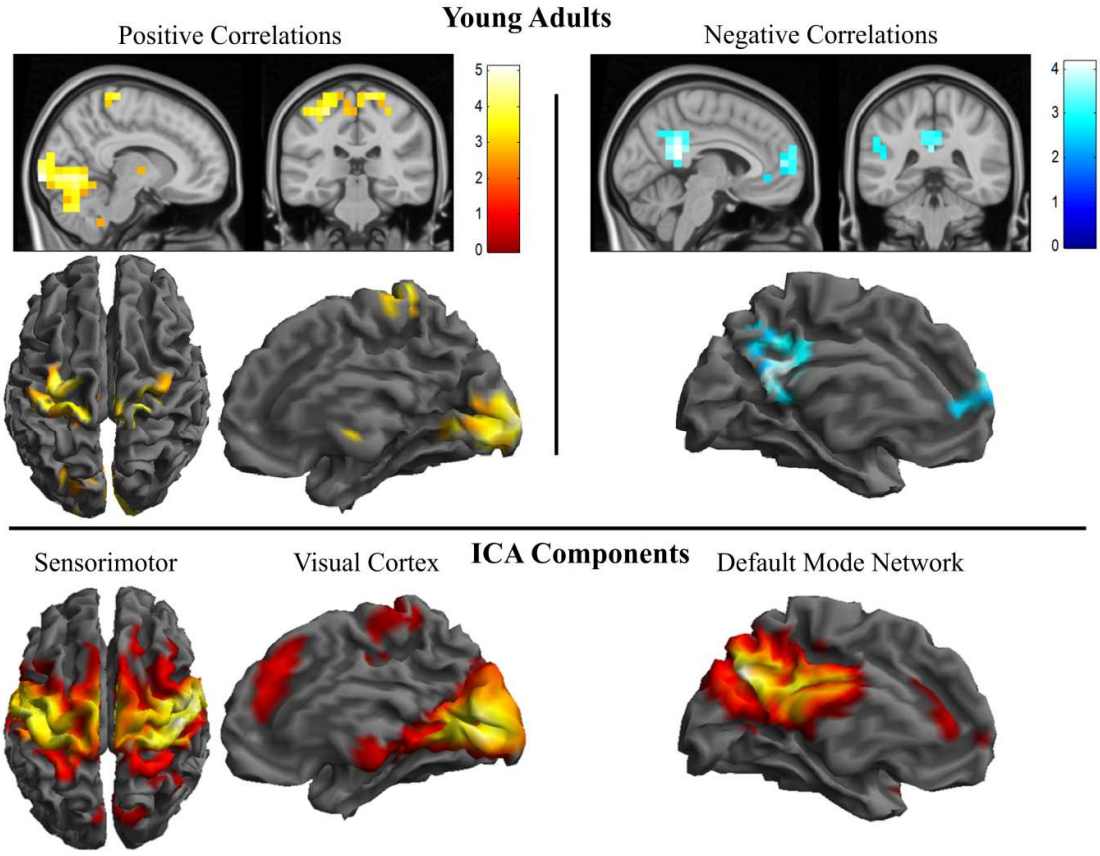


**Figure 2**

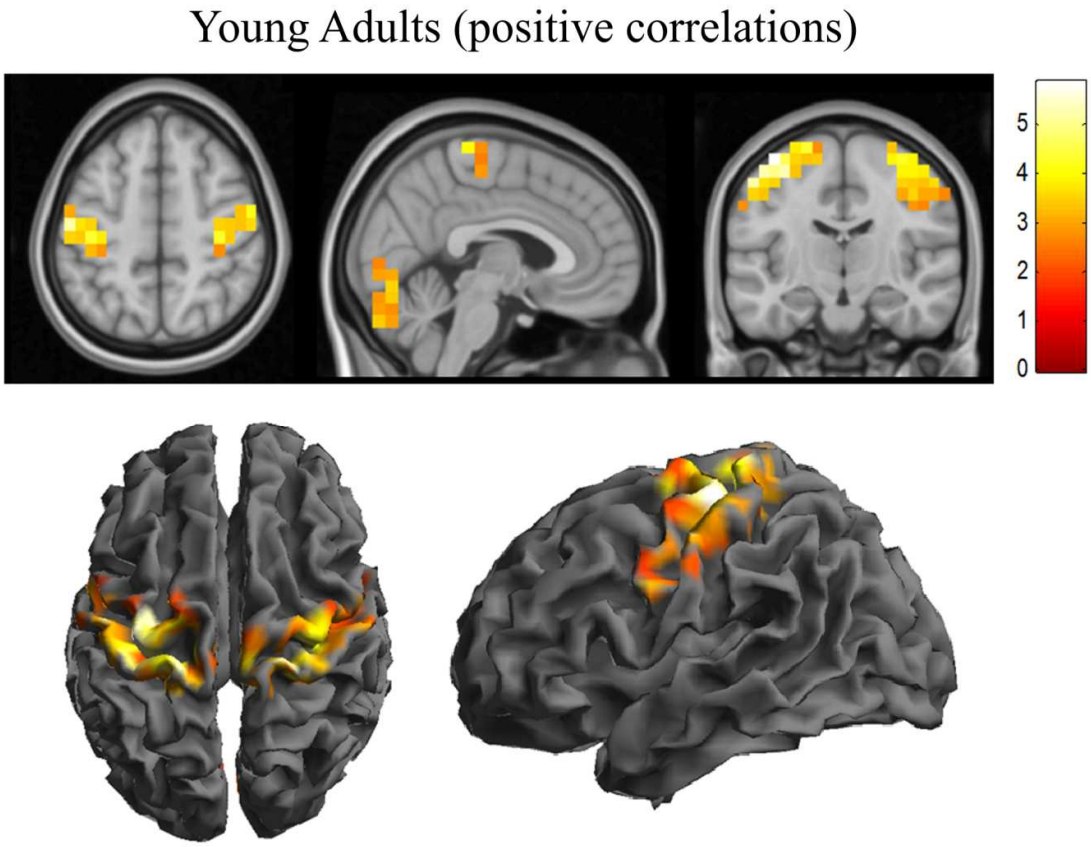


**Figure 3**

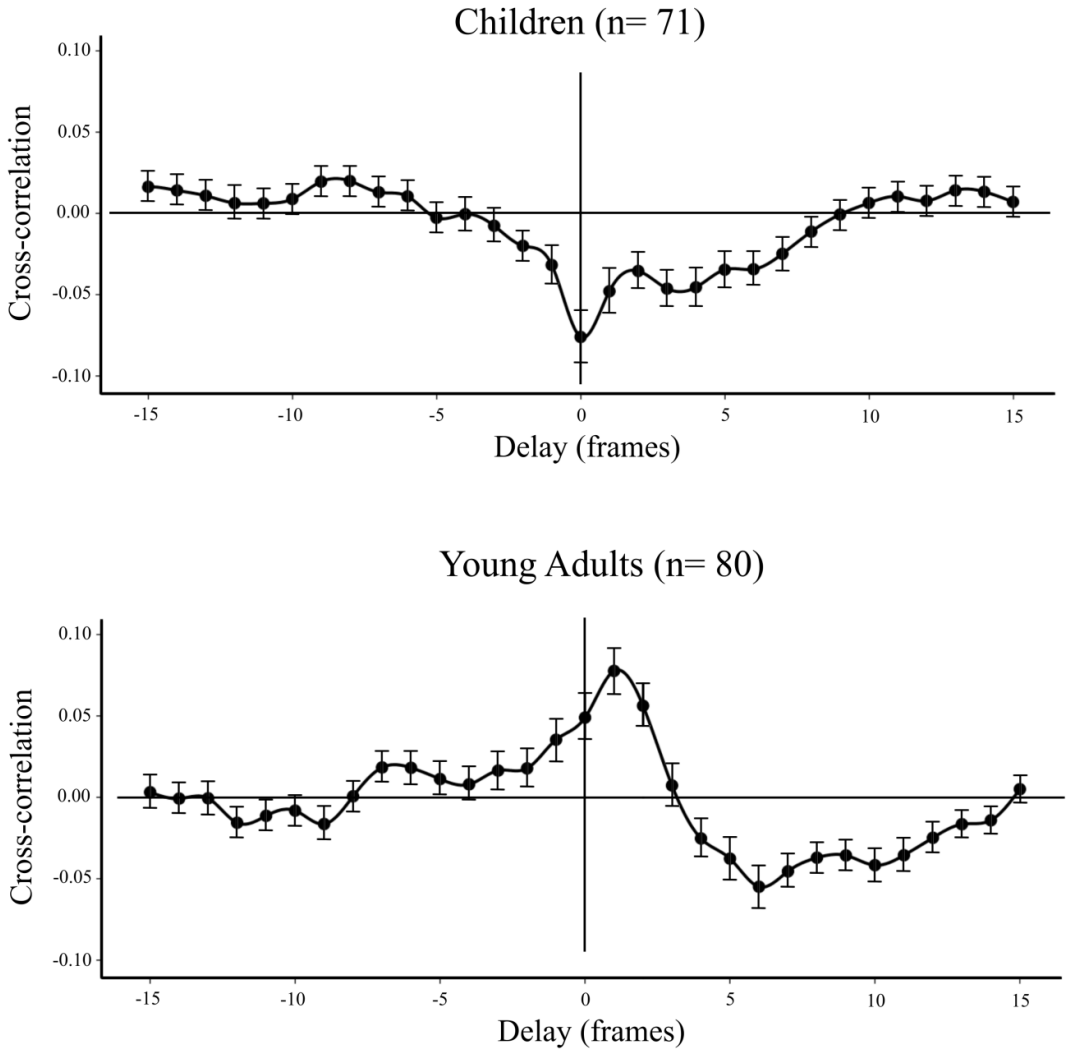


**Figure 4**

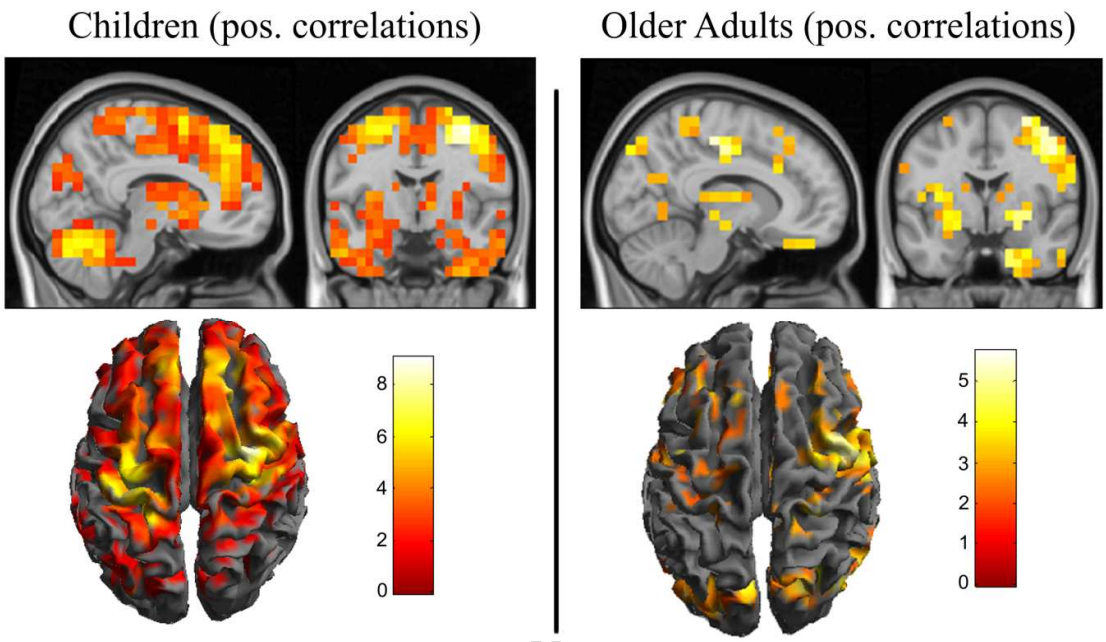


**Figure 5**

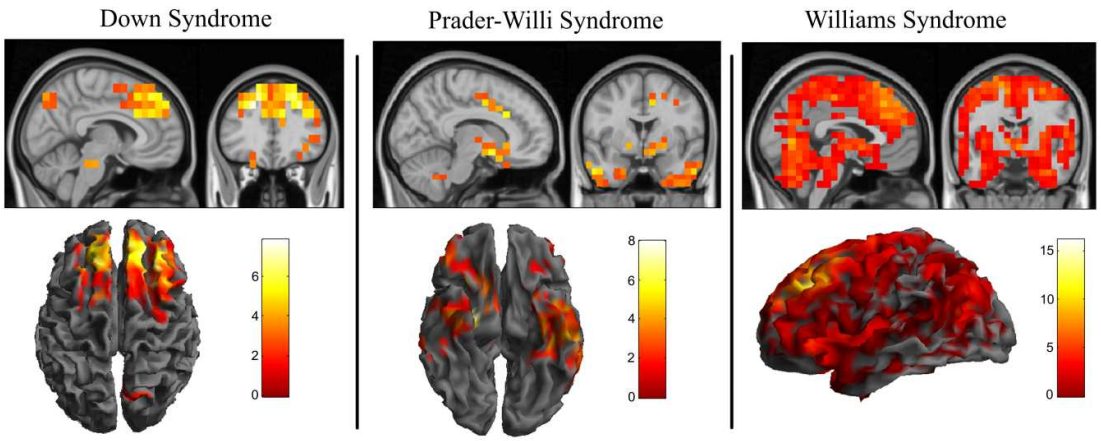


**Figure 6**

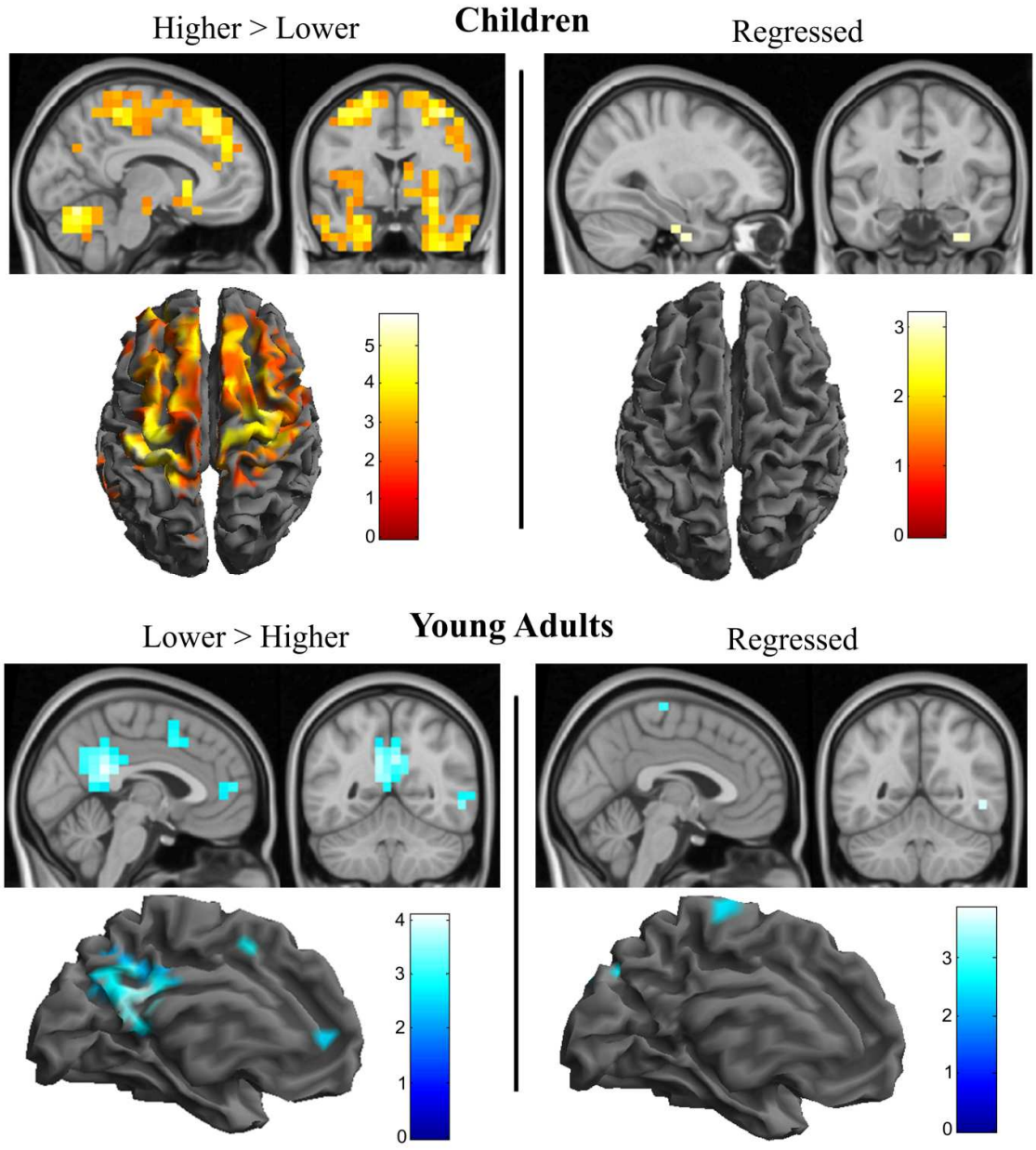


**Figure 7**

## Highlights

Head motion distinctively affects functional connectivity in different populations
Motion-related connectivity changes partially reflect genuine neural activity
Mapping population-specific motion effects may help connectivity data interpretation

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