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Neuroimaging biomarkers in genetic frontotemporal dementia : towards a timely diagnosis

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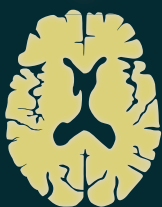
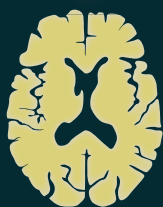
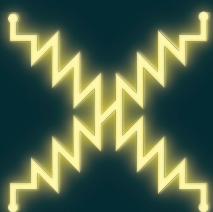
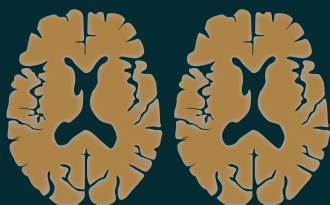


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Chapter 5

Methods: multicentre data harmonisation through artefact removal in resting-state functional MRI

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ICA-based artifact removal diminishes scan site differences in multi-center resting-state fMRI

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Abstract

Resting-state functional magnetic resonance imaging (rs-fMRI) has shown considerable promise in providing potential biomarkers for diagnosis, prognosis, and drug response across a range of diseases. Incorporating rs-fMRI into multicentre studies is becoming increasingly popular, imposing technical challenges on data acquisition and analysis, as fMRI data is particularly sensitive to structured noise resulting from hardware, software, and environmental differences.

Here, we investigated whether a novel clean-up tool for structured noise was capable of reducing centre-related rs-fMRI differences between healthy subjects. We analysed 3 T rs-fMRI data from 72 subjects, half of whom were scanned with eyes closed in a Philips Achieva system in The Netherlands, and half of whom were scanned with eyes open in a Siemens Trio system in the UK. After prestatistical processing and individual independent component analysis (ICA), FMRIB's ICA-based X-noiseifier (FIX) was used to remove noise components from the data. Group-level ICA and dual regression were run, and non-parametric statistics were used to compare spatial maps between groups before and after applying FIX.

Large significant differences were found in all resting-state networks between study sites before using FIX, most of which were reduced to non-significant after applying FIX. The between-centre difference in the medial/primary visual network, presumably reflecting a between-centre difference in protocol, remained statistically significant.

FIX helps facilitate multicentre rs-fMRI research by diminishing structured noise from rs-fMRI data. In doing so, it improves combination of existing data from different centres in new settings and comparison of rare diseases and risk genes for which adequate sample size remains a challenge.

Keywords: resting-state functional MRI, multicentre analysis, independent component analysis, dual regression, structured noise reduction

Introduction

Resting-state functional magnetic resonance imaging (rs-fMRI) has become an important tool in neuroimaging research to examine resting-state networks (RSNs) in normal brains, during the ageing process, and in various neurological disorders (Greicius et al., 2003; Fox et al., 2005; De Luca et al., 2006; Fox & Raichle, 2007; Littow, 2010). One of the techniques used for this purpose is independent component analysis (ICA)—a data-driven technique that facilitates comparison of functional networks in the brain without requiring a priori selected seed regions (Beckmann & Smith, 2004).

(Rs-)fMRI research has certain challenges, such as problems regarding sample size in clinical and at-risk populations. Multicentre analysis may help to solve these limitations, but has been shown to be difficult to perform for (rs-)fMRI. Specifically, differences between groups may not always be attributable to the feature of interest, such as disease or gene mutation carrier status, but may also be secondary to scanner hardware differences (manufacturer, head coil), software differences (filters, k-space acquisition method, scan parameters) and environmental differences (radio-frequency noise; Casey et al., 1998; Zivadinov & Cox, 2008). Confounding centre effects also manifest as noise in multicentre analysis, reducing power.

Whilst several studies have investigated and provided guidelines and recommendations for these difficulties for fMRI (Zou et al., 2005; Costafreda et al., 2007; L. Friedman et al., 2008; Wegner et al., 2008; Zivadinov & Cox, 2008; Glover et al., 2012), multicentre research using rs-fMRI is still an underdeveloped field. Long et al. (2008) were able to cross-validate the default mode network in a multicentre study even though scanner parameters were not controlled. Biswal et al. (2010) demonstrated that functional connectivity has a universal architecture in an extensive study with 1,414 subjects. However, they also found many differences due to centre-related variability. As data sharing becomes more important in imaging research, e.g., the Genetic Frontotemporal dementia Initiative (GENFI; Rohrer et al., 2013); 1,000 Functional Connectome Project (Biswal et al., 2010); ADHD 200 Consortium data set (The ADHD-200 Consortium, 2012); and Autism Brain Imaging Data Exchange (ABIDE; Di Martino et al., 2014), methods for reducing scan site differences must be developed.

In the current study, a novel tool for the clean-up of structured noise-components from ICA was used to study whether rs-fMRI data from different scan sites become more comparable in a multicentre analysis. The Functional Magnetic Resonance Imaging of the Brain Centre's (FMRIB's) ICA-based X-noiseifier (FIX) is a plug-in to FMRIB Software Library (FSL) that is able to automatically classify and remove structured noise-components (e.g., motion-effects, scanner artefacts, [non-neuronal] physiological noise, etc.) from rs-fMRI data, once it has been trained through hand-classifications (Griffanti et al., 2014; Salimi-Khorshidi et al., 2014). FIX has been used before to clean up structured noise in order to heighten the quality of rs-fMRI data (Salimi-Khorshidi et al., 2014), but this is the first time FIX is used to diminish scanner differences in a multicentre study.

Methods

Participants

In this study, MRI data was included from subjects scanned at the Leiden University Medical Centre (LUMC) and from subjects scanned at the Oxford Centre for Clinical Magnetic Resonance Research (OCMR). The LUMC data (referred to here as the ‘Dutch sample’) consisted of 36 subjects from the control group of an earlier rs-fMRI study investigating the effect of microtubule-associated protein tau (*MAPT*) and progranulin (*GRN*), risk genes for Frontotemporal Dementia (FTD), on the brain (Dopper et al., 2014). The OCMR data (referred to here as the ‘English sample’) consisted of 36 subjects from control groups of earlier rs-fMRI studies investigating the effect of apolipoprotein E ϵ 4 (*APOE4*), a risk gene for Alzheimer’s Disease (AD), on the brain (Filippini et al., 2009, 2011; Heise et al., 2011; Trachtenberg et al., 2012a, 2012b).

The English subjects were selected from a larger cohort in order to match the Dutch subjects in age, sex and sample size.

For a detailed description of the recruitment protocols, see Dopper et al. (2014) for the Dutch data, and Filippini et al. (2009, 2011) and Trachtenberg et al. (2012a) for the English data. In short, 36 *MAPT* and *GRN* non-carriers were selected from a pool of 160 healthy first-degree relatives of FTD patients with either an *MAPT* or *GRN* mutation. It is assumed that non-carriers from these families have the same risk for dementia as the general population. Thirty-six *APOE4* non-carriers, scanned at the OCMR, were selected from the general population and the data from most (30/36) were reported in previous studies (Filippini et al., 2009, 2011; Trachtenberg et al., 2012a).

Pre-scan exclusion criteria included MRI contraindications, history of drug abuse, and current or past neurologic or psychiatric disorders for the Dutch sample, and head injury, substance abuse (including alcohol), corticosteroid therapy, youth diabetes therapy, memory complaints, and current or past neurologic or psychiatric disorders for the English sample.

All participants provided written informed consent, and ethical approval for data acquisition was obtained from National Research Ethics Service Committee South Central—Oxford C (Oxford data), and the Medical Ethical Committees in Rotterdam and Leiden (Leiden data).

Image acquisition

LUMC scans were acquired using a Philips 3 T Achieva MRI scanner with an 8-channel SENSE head coil. OCMR scans were acquired using a Siemens 3 T Trio scanner with a 12-channel head coil. Participants were instructed to keep their eyes closed (LUMC) or open (OCMR), to think of nothing in particular (OCMR), and to remain awake. The scan parameters used for the high-resolution 3-dimensional anatomical T_1 -weighted and for the rs-fMRI T_2^* -weighted images are shown in Table 5.1.

Image analysis

FSL (<http://www.fmrib.ox.ac.uk/fsl>) tools were used for all data analyses (Smith et al., 2004; Woolrich et al., 2009; Jenkinson et al., 2012).

Prestatistical processing

Individual preprocessing included motion correction (Jenkinson et al., 2002), brain extraction (Smith, 2002), spatial smoothing using a Gaussian kernel of 6 mm full width at half maximum,

4D grand-mean scaling, and high-pass temporal filtering corresponding to a period of 150 s (~ 0.007 Hz). fMRI volumes were registered to MNI152 standard space (Montreal Neurologic Institute average T_1 -weighted image created from 152 normal subjects' T_1 scans). Boundary-based registration (Jenkinson & Smith, 2001; Jenkinson et al., 2002; Greve & Fischl, 2009) was used to register each individual's echo-planar imaging volumes onto their respective high-resolution T_1 -weighted structural images. T_1 -weighted structural scans were aligned to MNI152 standard space using nonlinear image registration (Anderson et al., 2007; Jenkinson et al., 2012). The resulting registration matrices were then used to register the echo-planar imaging volumes onto MNI152 standard space. Individual ICA was carried out and voxel-by-voxel intensity normalisation was performed manually, dividing each voxel by its mean value across time and multiplying by 10,000.

Table 5.1 Structural and functional scan parameters per scan site

Parameters	Structural		Resting-state	
	LUMC	OCMR ^a	LUMC	OCMR
Slices, n	140	192	38	34
TR, ms	9.8	2,040	2,200	2,000
TE, ms	4.6	4.7	30	28
Flip angle, °	8	8	80	89
Volumes, n	–	–	200	180
Voxel size, mm	$0.88 \times 0.88 \times 1.20$	$1.0 \times 1.0 \times 1.0$	$2.75 \times 2.75 \times 2.99^b$	$3.0 \times 3.0 \times 3.5$
Duration, min	5	6	8	6

FOV, field of view; LUMC, Leiden University Medical Centre; OCMR, Oxford Centre for Clinical Magnetic Resonance Research; TE, echo time; TR, repetition time.

^a Structural scanning at OCMR was done using a magnetisation-prepared rapid gradient echo sequence (MPRAGE).

^b Including 10% interslice gap.

FIX

Network components obtained from the individual ICA were visually judged and were labeled as signal, noise, or unknown for 12 subjects from each group. Manual classification was done by looking, firstly, at their spatial maps (typically thresholded $\text{abs}(Z) > 2.3$), then at the temporal power spectrum, and lastly at their time series. Unthresholded spatial maps were examined when necessary (Salimi-Khorshidi et al., 2014).

Using these classifications, the FIX classifier was trained and a training file was created. As described by Salimi-Khorshidi et al. (2014), FIX uses over 180 features, capturing components' spatial and temporal characteristics, which are fed into a multilevel classifier (built around several different classifiers). Temporal features include autoregressive properties, distributional properties, jump amplitudes, the Fourier transform, and the time series' correlation with grey matter-, white matter-, cerebrospinal fluid- and head motion-derived time series. Spatial features include clusters' sizes and spatial distribution, voxel intensity information indicating whether voxels are grey matter or, e.g., blood vessels, percent on brain boundary, hand-created mask-based features for components that have signal-like spatiotemporal characteristics (such as sagittal sinus, cerebrospinal fluid, and white matter), and other spatial features such as spatial smoothness.

Next, a leave-one-out test was run in order to control the quality of the classifier algorithm by estimating the level of agreement of the hand-labeled classifications and the classifier's classifications. The accordance was measured as a true-positive rate (TPR), a true-negative rate (TNR), and a composite measure, i.e., $(3 \times \text{TPR} + \text{TNR}) \div 4$, for a range of thresholds (used to determine the binary classification of components since FIX's output is probabilistic). After checking the TPR, TNR, and the composite measure, the optimal threshold (i.e., 20) was chosen and the classifier was applied to all subjects' data using this threshold in order to classify and remove the structured noise components from the data (Griffanti et al., 2014; Salimi-Khorshidi et al., 2014).

Group-level ICA

After prestatistical processing and FIX, three group-level ICA (GICA) analyses were run using MELODIC. In order to qualitatively compare FIX's effect on GICA components, GICA was run on combined English and Dutch data before application of FIX (GICA-1), and on combined English and Dutch data after application of FIX (GICA-2). For statistical analysis of FIX's effect on the multicentre differences, GICA was carried out on all data combined (GICA-3). Consequently, the data used for this analysis (GICA-3) contained four subgroups: Dutch subjects with and without use of FIX, and English subjects with and without use of FIX. Rs-fMRI data were temporally concatenated across individuals to create a single 4D data set. The data were whitened and principle component analysis was used to project the data into a 25-dimensional subspace, matching many previous rs-fMRI studies (Filippini et al., 2009; Smith et al., 2009; Cocozza et al., 2015; Gaudio et al., 2015). By optimising for non-Gaussian source estimates through a fixed-point iteration technique, we obtained component maps (Hyvärinen, 1999). After transforming the component maps to Z-maps, Gaussian/Gamma Mixture Models were fitted to them in order to obtain 25 independent spatial maps defining functional connectivity patterns across the participants (Beckmann & Smith, 2004). The GICA-derived spatial maps were then judged by eye and divided into RSN and noise components.

Dual regression

Analysis of group differences was performed using FSL's dual regression, a regression technique that allows for voxel-wise comparisons of rs-fMRI (Filippini et al., 2009; Veer et al., 2010). All spatial maps derived from GICA-3 (using English and Dutch FIX and non-FIX data) were regressed against each individual's preprocessed rs-fMRI data, resulting in a time course for each component and subject. The produced time courses were regressed against the same individual's preprocessed rs-fMRI data, resulting in subject-specific spatial maps for parameter estimates (PEs) and Z-stats. GICA noise component maps were disregarded, and RSN component maps were collected across subjects into 4D files (one per ICA component, with the fourth dimension being subject identification) and were tested voxel-wise for statistically significant differences between groups. We used a general linear model equivalent to an independent *t*-tests to test the PE- and Z-stat-driven spatial maps for differences between Dutch and English groups before use of FIX, differences between Dutch and English groups after use of FIX, and the interaction between the use of FIX and group differences (by comparing the differences before and after use of FIX to each other). Age and years of education were added to the analysis as confound regressors. Non-parametric permutation-based testing was done by running 5,000 random permutations using the randomise algorithm, a tool based on the Freedman-Lane methods within FSL (Winkler et al., 2014). Afterwards, threshold-free cluster enhancement (TFCE), a method for finding clusters in data without defining

clusters in a binary way, was applied (Smith & Nichols, 2009), and a family-wise error corrected cluster significance threshold of $p < 0.05$ was used. In a more qualitative approach, non-family-wise error corrected results and raw t -stat maps were also investigated.

Result masking

In order to fully appreciate the impact that FIX has on the data, results of the differences between groups for all components were thresholded, binarised, and merged. The resulting imaging volumes display the total number significant voxels for all different components together, with colour variation showing the number of components with significant change in each voxel.

Statistical analysis

Statistics of non-imaging variables were performed using SPSS version 20 (SPSS, Chicago, IL). Demographic variables were tested using independent t -tests for continuous variables and chi-square tests for categorical variables.

Results

Sample demographics

Demographic information for the Dutch and English subjects is shown in **Table 5.2**. Age and sex were matched across groups.

Table 5.2 Participant demographics

	OCMR (<i>n</i> = 36)	LUMC (<i>n</i> = 36)	<i>p</i> -value
Age, mean (SD) years	49.9 (11.5)	49.8 (11.3)	0.94
Sex, <i>n</i> (%) ♀	19 (52.8)	18 (50.0)	1.0
Education, mean (SD) years ^a	16.6 (3.2)	12.6 (2.9)	<0.001

LUMC, Leiden University Medical Centre; OCMR, Oxford Centre for Clinical Magnetic Resonance Research.

^a Scores of education level in years were missing for two individuals (both LUMC subjects).

Individual ICA and FIX

Table 5.3 shows the number of extracted independent components by individual ICA for each group (OCMR and LUMC), as well as the number of components classified as noise and RSN by FIX. Significantly more independent components were extracted from Dutch data, compared to English data. Also, significantly more components from Dutch data were classified as noise by FIX. The number of components classified as RSN by FIX was not found to be different between groups.

Table 5.3 FIX classifications

	OCMR (<i>n</i> = 36)	LUMC (<i>n</i> = 36)	<i>p</i> -value
ICs, mean (SD)	36.1 (4.8)	44.3 (7.9)	<0.001
Noise ICs, mean (SD)	23.6 (3.9)	31.8 (8.2)	<0.001
RSN ICs, mean (SD)	12.6 (3.0)	12.7 (3.0)	0.88

FIX, FMRIB's ICA-based X-noiseifier; FMRIB, Functional Magnetic Resonance Imaging of the Brain Centre; IC(A), independent component (analysis); LUMC, Leiden University Medical Centre; OCMR, Oxford Centre for Clinical Magnetic Resonance Research; RSN, resting-state network.

Group-level ICA

Figure 5.1 shows spatial maps derived from GICA for data before (GICA-1, **Figure 5.1A**) and after (GICA-2, **Figure 5.1B**) application of FIX (numbers in text correspond to numbers in figure). RSN components are shown with a green frame, whereas noise components are shown with a red frame. FIX's effect on GICA seems to be two-fold: some noise components are eliminated (i.e., motion artefacts [**5.1A**: numbers 6, 22, 23], brain stem/vascular artefacts [**5.1A**: numbers 14, 18, 25], and sagittal sinus artefacts [**5.1A**: numbers 8, 19]) and others are 'pushed back' (i.e., have a higher index number after the use of FIX: white matter [**5.1A**: number 4, **5.1B**: number 23] and frontal sinus susceptibility noise [**5.1A**: number 9, **5.1B**: number 21]). Both observations rely on the same mechanism: FIX removes variance explained by noise components from the data. As

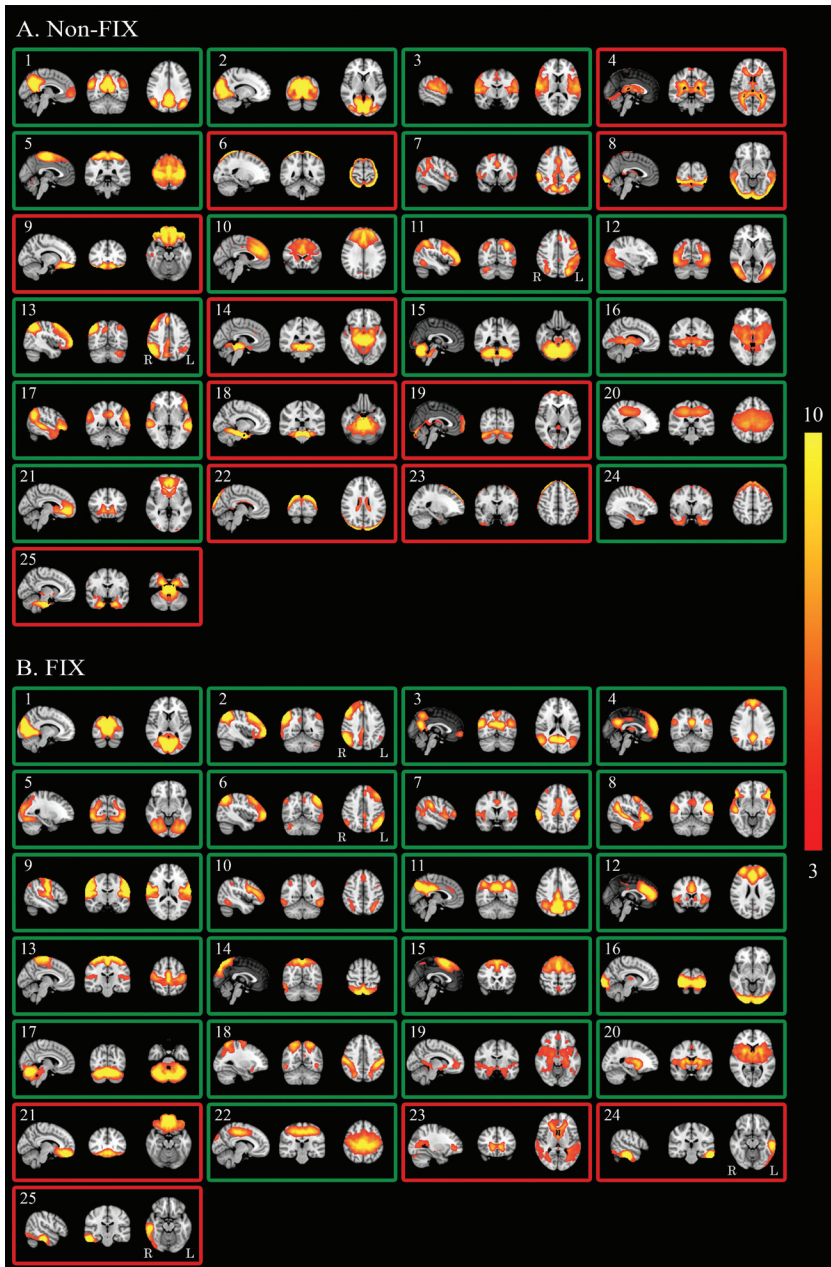


Figure 5.1 GICA spatial maps before and after FIX

Maps illustrate the 25 GICA networks' most informative orthogonal slices before (A, GICA-1) and after (B, GICA-2) applying FIX. Green frames indicate RSNs; red frames indicate noise networks. Colour bar represents Z-scores.

FIX, FMRIB's ICA-based X-noiseifier; FMRIB, Functional Magnetic Resonance Imaging of the Brain Centre; GICA, group-level ICA; ICA, independent component analysis.

MELODIC shows components in order of decreasing explained variance, the removal of variance explained by noise components results in higher component numbers or even exclusion.

Spatial maps that were used as spatial regressors for dual regression (GICA-3) are shown in **Figure 5.2**. Identified RSNs were the default mode network (1), primary/medial (2) and lateral (7, 13) visual networks, lateralised higher order cognitive networks involved with working memory (3, 5), a network showing the dorsal attention network combined with the salience network (4), the auditory network (6), a network combining features of the default mode network and the ventral stream (8), the executive control network (9), networks that describe different parts of the sensorimotor network (10, 11), cerebellar network (14), a network describing the basal ganglia (17), and a network showing frontal default mode network features as well as features from the executive control network (21).

Dual regression

All RSNs' combined results based on PE-driven spatial maps are shown for family-wise error corrected group differences before the use of FIX (**Figure 5.3A**), group differences after the use FIX (**Figure 5.3B**), and for the interaction between applying FIX and group differences (**Figure 5.3C**). Dual regression results for each RSN are shown separately in **Supplemental Figure S5.1** (numbers in **Supplemental Figure S5.1** correspond with numbers in **Figure 5.2**).

Before the use of FIX, large areas of statistically significant differences were shown in all (15) RSNs. After applying FIX, the size and number of areas with significant differences between groups was strongly reduced: only 7/15 RSNs showed statistically significant differences and the number of significantly different voxels was reduced by 98%. The RSN with the largest area of significant differences after using FIX was the primary/medial visual network (PVN), containing 85% of all significantly different voxels after applying FIX. This network is associated with a difference in scan protocol (eyes open vs. closed) and showed greater activation in English than in Dutch subjects.

The interaction between the use of FIX and site differences was significant in 13/15 RSNs.

Dual regression results based on Z-stat-driven spatial maps were similar on visual inspection.

Additionally, for a more qualitative view of the results, **Supplemental Figure S5.2** shows dual regression results without family-wise error correction for each component. Another point of view on FIX's effect is offered in **Supplemental Figure S5.3**, demonstrating a reduction in raw *t*-stats for group differences in each component after applying FIX.

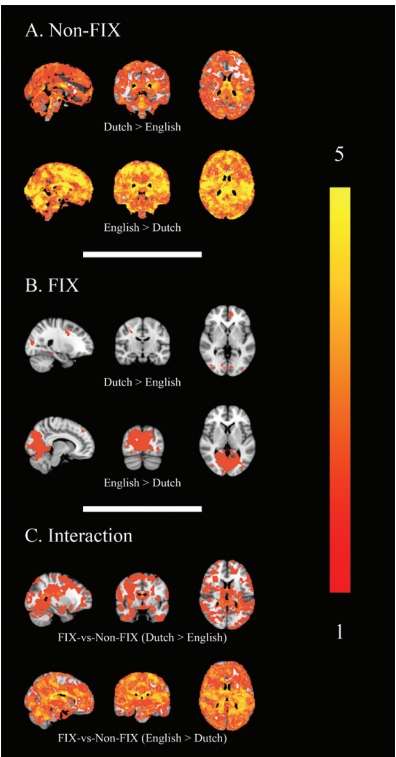


Figure 5.2 GICA spatial maps for statistical analysis

Maps illustrate the 25 GICA networks' most informative orthogonal slices of data before and after applying FIX combined (GICA-3). Green frames indicate RSNs; red frames indicate noise networks. Colour bar represents Z-scores. FIX, FMRIB's ICA-based X-noiseifier; FMRIB, Functional Magnetic Resonance Imaging of the Brain Centre; GICA, group-level ICA; ICA, independent component analysis.

Figure 5.3 Combined group differences

Maps show statistically significant ($p < 0.05$) differences between groups: without the use of FIX (A), after the use of FIX (B), and the interaction between FIX and group differences (C) in all (15) RSNs combined. Colour bar represents the number of significantly differing networks. FIX, FMRIB's ICA-based X-noiseifier; FMRIB, Functional Magnetic Resonance Imaging of the Brain Centre; ICA, independent component analysis; RSN, resting-state network.



Discussion

In this study, FIX was found to be helpful in the comparison of multicentre rs-fMRI data. FIX significantly reduced structured noise resulting from hardware, software, and environmental differences in a multicentre group comparison, as demonstrated by **Figure 5.3** and **Supplemental Figures S5.1, S5.2**. Additionally, **Supplemental Figure S5.3** shows an intra- and inter-component reduction in raw *t*-stat variability after applying FIX. The significant interaction between the application of FIX and group differences (**Figure 5.3** and **Supplemental Figure S5.1**) shows that site differences are not just pushed below significance threshold, but are significantly changed by applying FIX. Importantly, the remaining differences between sites after FIX (**Figure 5.3** and **Supplemental Figure S5.1**) are primarily confined to the primary/medial visual cortex, which reflects differences in experimental design (Dutch participants had eyes closed, whereas English participants had eyes open). This implies that FIX removes structured noise, but retains physiologically driven differences.

Dual regression is usually run using PE-driven spatial maps; alternatively, Z-stat-driven spatial maps can be used. Our results using PE- and Z-stat-driven spatial maps were similar on visual inspection, suggesting that the use of FIX is of value for both types of analysis. However, in order to assess whether FIX works better for either one, a more specific analysis is required.

Structured noise in fMRI has various origins: hardware differences (e.g., scanner manufacturer, type of head coil), software differences (filters, k-space acquisition methods, and scan parameters), and radio-frequency noise (Casey et al., 1998; Zivadinov & Cox, 2008). As demonstrated in **Figure 5.3** and **Supplemental Figures S5.1–3**, FIX helps to deal with noise from these origins, inasmuch as they present themselves as separate noise components in individual subjects' ICA. Still, it cannot account for all potential between-site differences. For example, it cannot deal with differences that present themselves within RSN components such as differences in sensitivity to RSNs based on hardware configurations or RSN spatial variability relating to head coils. However, due to the nature of ICA, the most striking differences caused by structured noise are presented as separate noise components. Therefore, intra-component variability is much smaller than inter-component variability, implying that the scope of this drawback is altogether limited. Also, FIX cannot account for differences in the magnitude of the blood-oxygen-level-dependent effect. Voxel-wise intensity normalisation may help to reduce this problem, but site-wise confound regressors should be used when they do not correlate with the regressors of interest.

Although eyes-open and eyes-closed differences cannot be mathematically disentangled from site/scanner differences, we suggest that the remaining differences in the PVN after using FIX are a manifestation of this protocol discrepancy since the differences in all other networks are substantially reduced. Recently, a number of studies have investigated the effect of eyes-open vs. eyes-closed conditions on functional connectivity without yet reaching a clear consensus. For example, reduced activation (Feige et al., 2005), amplitude of low frequency fluctuations (ALFF; Yang et al., 2007; Yan et al., 2009; Liu et al., 2013; Liang et al., 2014; Yuan et al., 2014), and regional homogeneity (Liu et al., 2013) have all been reported in eyes-closed relative to eyes-open conditions. Conversely, other studies showed higher blood-oxygen-level-dependent response (McAvoy et al., 2008) and higher mean ALFF (Jao et al., 2013) for the eyes-closed condition, or no difference in seed-based correlations (Patriat et al., 2013). Aside from these local changes in functional connectivity between conditions, Jao et al. (2013) discovered that the mean ALFF of the whole brain was greater in eyes-closed vs. eyes-open conditions. Some of these studies also reported functional connectivity differences in other networks than the PVN, including the sensorimotor, default mode, and

auditory networks. The family-wise error corrected changes found in this study in non-PVN networks were small, scattered and generally did not follow the independent component's anatomy closely. Therefore, it is difficult to infer if these changes are due to the experimental design or if they reflect a small quantity of remaining noise. The changes we found in independent component 2 are extensive and follow the PVN anatomy well. As it is unlikely that false positive results or leftover noise would take this form and since similar PVN differences between eyes-open and eyes-closed conditions have been described in rs-fMRI multiple times before, it seems reasonable to assume that this effect is due to reported differences in experimental design.

Whilst groups were matched for age and sex, there was a significant difference in level of education. This may be attributable to the recruitment protocols. The English recruitment protocol selected subjects from the general population near Oxford, a relatively highly educated region (Filippini et al., 2009, 2011; Trachtenberg et al., 2012a), whereas the Dutch sample was recruited from known FTD families (Dopper et al., 2014). In order to account for this, demeaned education values were added to the general linear model as a regressor of no interest.

Previous studies on multicentre fMRI primarily focused on data collected using standardised protocols. Glover et al. (2012) argue that hardware, software and procedural aspects should be carefully matched and managed in order to successfully perform multicentre fMRI research. Zivadinov & Cox (2008) suggest the use of quality assurance methods and careful subject selection and matching across centres, such as used by Wegner et al. (2008), in order to control for scan site by adding centre as covariate in the analysis. Whereas these recommendations are naturally important for the correct set-up of a new multicentre study, our results suggest reanalysis of existing non-standardised rs-fMRI data may also be possible across sites. Additionally, although it would be interesting to see how these different sources of structured noise are dealt with individually by FIX (whilst controlling for the others), this study importantly shows that even with more of these problems present simultaneously, FIX adequately diminishes structured noise.

Conclusion

Previous studies using FIX have considered the theoretical and practical use of spatial ICA, classifier training and noise detection (Salimi-Khorshidi et al., 2014), and denoising (Griffanti et al., 2014). They showed that FIX is a useful tool for noise clean-up and therefore helps in making data more sensitive to changes related to neuronal activity. This study is the first to show FIX's additional value in multicentre rs-fMRI analysis. By improving multicentre fMRI research and efficient reanalysis of acquired data, comparisons of rare diseases and at-risk populations will be more efficient and convenient, leading to a better insight in neurological disorders. Furthermore, as free data sharing is an upcoming way to create large rs-fMRI data sets (Biswal et al., 2010; The ADHD-200 Consortium, 2012; Di Martino et al., 2014), FIX may be a valuable tool to ensure valid comparison of data acquired at different centres.

Acknowledgements

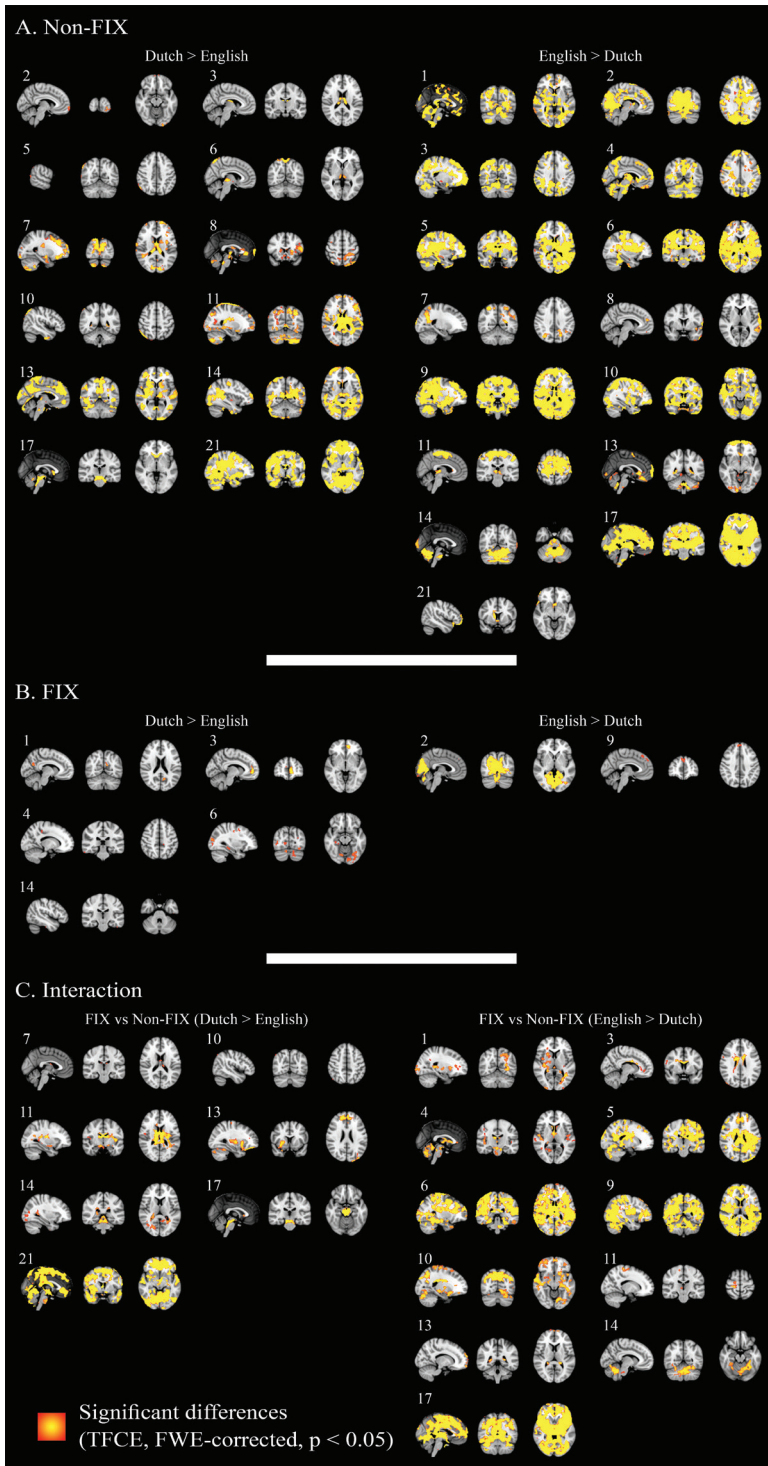
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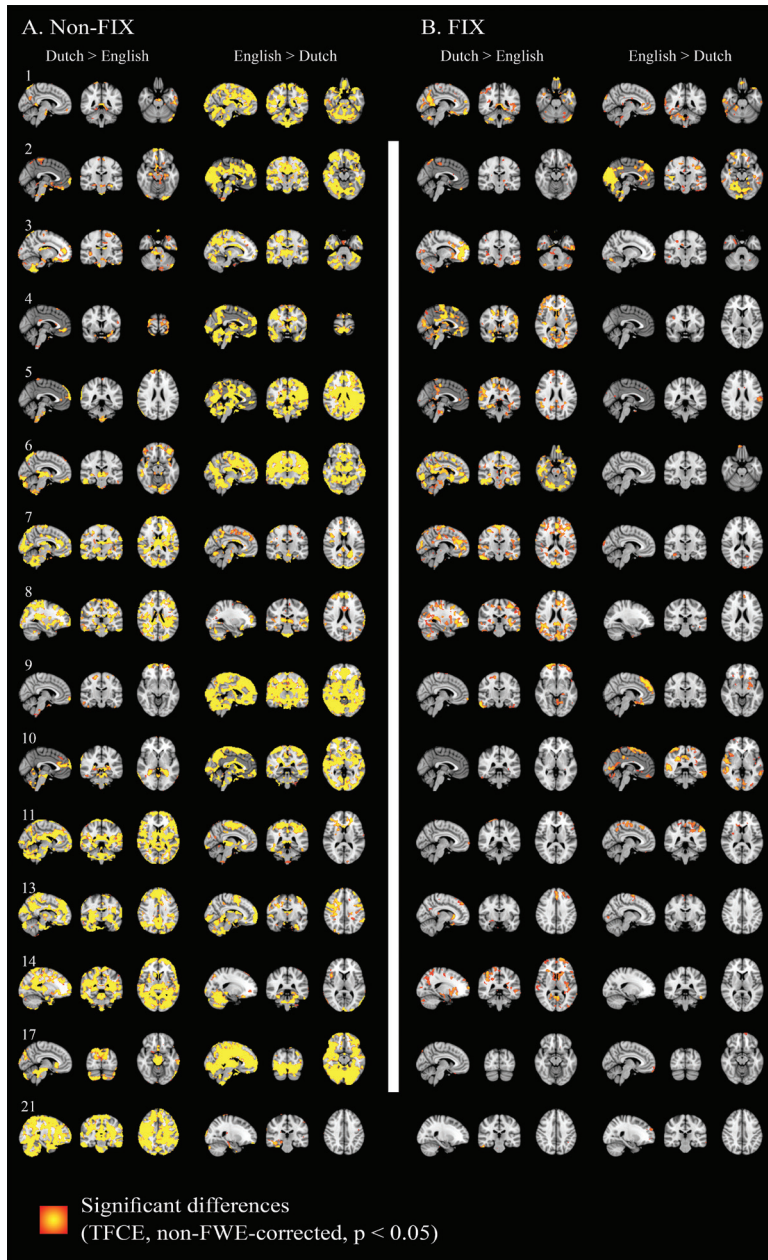
Supplemental material

Supplemental Figure S5.1 Separate FWE corrected group differences (opposite page)

Maps show FWE corrected statistically significant ($p < 0.05$) differences between groups: without the use of FIX (A), after the use of FIX (B), and the interaction between FIX and group differences (C) for each of 15 RSNs. Colour bar represents significance.

FIX, FMRIB's ICA-based X-noiseifier; FMRIB, Functional Magnetic Resonance Imaging of the Brain Centre; FWE, family-wise error; ICA, independent component analysis; RSN, resting-state network; TFCE, Threshold-free cluster enhancement.

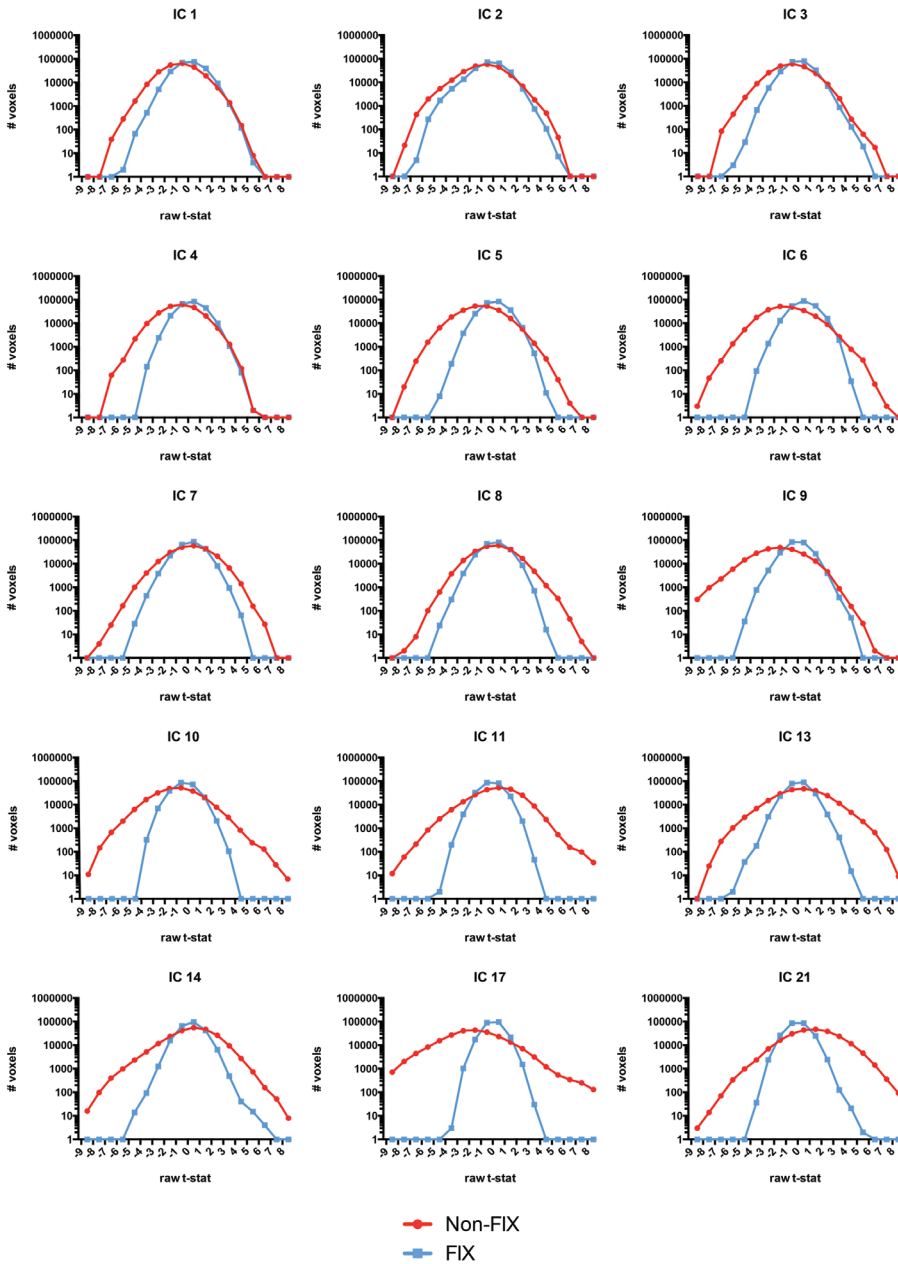




Supplemental Figure S5.2 Separate uncorrected group differences

Maps show uncorrected statistically significant ($p < 0.05$) differences between groups: without the use of FIX (A) and after the use of FIX (B) for each of 15 RSNs. Colour bar represents significance.

FIX, FMRIB's ICA-based X-noiseifier; FMRIB, Functional Magnetic Resonance Imaging of the Brain Centre; ICA, independent component analysis; RSN, resting-state network; TFCE, Threshold-free cluster enhancement.



Supplemental Figure S5.3 Raw t -stats variability

Graphs show raw t -stats between groups (positive t -stats signify Dutch > English, negative t -stats signify English > Dutch) before and after FIX for each of 15 RSNs on a logarithmic scale.

FIX, FMRIB's ICA-based X-noiseifer; FMRIB, Functional Magnetic Resonance Imaging of the Brain Centre; ICA, independent component analysis; RSN, resting-state network.