A Pairwise Approach for fMRI Group Studies using the BrainSync Transform

Anand A. Joshi[a], Soyoung Choi[a], Jian Li[a], Haleh Akrami[a], and Richard M. Leahy[a]

[a]University of Southern California, Los Angeles, USA

ABSTRACT

Due to the spontaneous nature of resting fMRI (rs-fMRI) signals, cross-subject comparison and group studies of rs-fMRI are challenging. Existing group comparison methods typically reduce the fMRI time series either to lower-dimensional connectivity features or use ICA to reduce dimensionality. We previously developed BrainSync, an orthogonal transformation that allows direct comparison of fMRI time-series across subjects.[1] This orthogonal transform performs a temporal alignment of time-series at homologous locations across subjects allowing a direct comparison of scans. In contrast with existing fMRI analysis methods, this transform does not involve dimensionality reduction and preserves the rich functional connectivity information in fMRI data. BrainSync Alignment (BSA) is an extension of this approach that jointly synchronizes fMRI data across time-series data for multiple subjects.[2] Point-wise distance measures, or Pearson correlations, can be computed between the reference and synchronized time-series as measures of inter-subject differences in functional connectivity at each location in the brain. In group studies, especially in the case of spectrum disorders, distances to a single atlas do not fully reflect the differences between subjects that may lie on a multi-dimensional spectrum. Here we describe an approach that measures the distances between pairs of subjects instead of to a single reference point.[3] We present novel pairwise statistical methods for fMRI that can be used for regression and also for identifying group differences. We demonstrate the effectiveness of our method in two studies: (i) pairwise comparisons of fMRI data in subjects for performing regression to an ADHD index, and (ii) an F-test using pairwise statistical analysis to compare traumatic brain injury (TBI) subjects that develop post-traumatic epilepsy (PTE) to those that do not.

Keywords: fMRI, statistical methods

Author's accepted version
For research purpose only
Copyright (c) SPIE
Full article and citation at
https://doi.org/10.1117/12.2580980

1. DESCRIPTION OF PURPOSE

The fMRI signal acquired during rest (rs-fMRI) has been used extensively to measure functional connectivity between different brain regions.[4–8] It is also widely used for longitudinal studies of brain development and as a diagnostic biomarker in cross-sectional studies for various neurological and psychological diseases and conditions.[9]

Since rs-fMRI data reflect spontaneous brain activity, it is not possible to directly compare resting-state signals across subjects. Instead, comparisons typically make use of connectivity features,[10] which are often computed from pairwise correlations of the rs-fMRI time-series between a point of interest and other locations in the brain.[11] In this work, we present novel pairwise statistical methods and use it for (i) a regression problem that use pairwise comparisons of fMRI data of subjects for performing regression to a clinical variable,[12] and (ii) identifying group differences, y performing an F-test using pairwise statistical analysis to compare two groups of subjects.

2. METHODS

2.1 Data

2.1.1 ADHD200 Dataset

The data for the study consisting of 259 subjects (typically-developing controls: 146, ADHD combined: 46, ADHD inattentive: 66, ADHD hyperactive: 1) was acquired on a Siemens Trio 3-Tesla scanner at the Peking University which was collected as a part of the ADHD-200 Global Competition (Peking University data).[13,14] The data is available for download through the ADHD 200 competition website(http://fcon_1000.projects.

nitrc.org/indi/adhd200). Of the 265 subjects, only subjects with ADHD indices measured using the ADHD Rating Scale IV (ADHD-RS) were retained. This ADHD index measures symptoms based on Inattention and Hyperactivity-Impulsivity.[15] 150 subjects were used as test subjects and comprised of 85 ADHD subjects (age=12.0 ± 2.0; 75M:10F; ADHD Index=50.6 ± 8.5) and 65 control subjects (age=11.1 ± 1.8; 39M:26F; ADHD Index=29.2 ± 6.3). 50 additional control subjects (age=11.3 ± 1.8; 29M:21F; ADHD Index=30.1 ± 6.5) were used to create a reference fMRI atlas.

2.1.2 Maryland MagNeTs data

A second set of imaging data was obtained from 215 subjects which are publically available from FITBIR (https://fitbir.nih.gov). The data was collected as a part of a prospective study that includes longitudinal imaging and behavioral data from TBI patients with a Glasgow Coma Scores (GCS) in the range of 3-15 (mild to severe TBI). Imaging was performed on a 3T Siemens TIM Trio scanner (Siemens Medical Solutions, Erlangen, Germany) using a 12-channel receiver-only head coil. For statistical analysis, we used 37 subjects with epilepsy (26M/11F) from this dataset and 37 randomly selected subjects without epilepsy (27M/10F) from the same dataset.[16] The age range for the epilepsy group was 19-65 years (yrs) and 18-70 yrs for the non-epilepsy group. Injury mechanisms included falls, bicycle or sports accidents, motor vehicle collisions, and assaults. The individual or group-wise GCS, injury mechanisms, and clinical information is not shared. For this study, we used imaging data acquired within 10 days after injury. Seizure information was recorded using follow-up appointment questionnaires. Exclusion criteria included a history of white matter disease or neurodegenerative disorders including multiple sclerosis, Huntington's disease, Alzheimer's disease, Pick's disease, and a history of stroke or brain tumors.

2.2 Preprocessing

The rs-fMRI data was processed and analyzed using the BrainSuite Functional Pipeline (BFP). The processing and statistical analysis pipelines are publically available online (https://github.com/ajoshiusc/bfp). BFP is a software workflow that processes fMRI and T1 data using a combination of software that includes BrainSuite (https://brainsuite.org), AFNI (https://afni.nimh.nih.gov), FSL (https://www.fmrib.ox.ac.uk/fsl), and MATLAB scripts. Unique features of the BFP pipeline include cortically-constrained volumetric registration,[17,18] Global PDF-based non-local means filtering (GPDF)[19,20] and BrainSync alignment of resting fMRI time series.[21,22] Starting from raw T1 images, BFP uses BrainSuite to perform brain extraction, tissue classification, generation of brain surfaces and coregistration to a reference anatomical atlas. fMRI processing includes motion correction, skull stripping, grand mean scaling, temporal filtering, detrending, spatial smoothing, nuisance signal regression and GPDF filtering. fMRI images are coregistered to T1 images and then transformed onto atlas space.

BFP produces processed fMRI data represented both on surface and volume co-registered with BrainSuite's BCI-DNI atlas[23] as well as a grayordinate based representation.[24,25] The grayordinate representation is a common space containing both cortical surface vertices and subcortical volume voxels where the cerebral cortex is modeled as a surface mesh, whereas the globular subcortical nuclei are modeled as volume parcels.[26] Secondly, the volumetric space generated by BFP comprise of a $51 \times 70 \times 70$ voxel-matrix volume at 3mm isotropic resolution in BCI-DNI atlas space.[23] We performed statistical analysis in both coordinates for demonstration.

2.3 Regression Study

To explore the effects of ADHD on the brain, we performed a pairwise regression analysis by selecting 2000 random pairs from 150 test subjects of the Peking University data (Section 2.1.1). For each pair, we synchronized the two subjects and computed the euclidean distance between the two time series at each vertex (fmri-diff). We also computed the difference between the ADHD indices of the two subjects (var-diff) in each pair. Then we computed Pearson correlation between fmri-diff and var-diff across 2000 random pairs at each vertex and converted to p-values ($\alpha \leq 0.05$) using a permutation test (2000 permutations). False discovery rate (FDR; q=0.05) was controlled for using the Benjamini-Hochberg method.[27] To test the reproducibility of the tests, we repeated the entire experiment for the pairwise statistic with a second set of 2000 randomly selected pairs. For additional verification that the significance that we find is not by chance, randomly permuted ADHD indices were assigned to the subjects and the test was repeated.

Authors' accepted version
For research purpose only
Copyright (c) SPIE
Full article and citation at
https://doi.org/10.1117/12.2538090

For comparison, we used the atlas-based method (BSA)[2] to create an average atlas from 50 control subjects not already included in the testing group, then synchronized the 150 test subjects to the atlas. At each point, we used the euclidean distance between the synchronized time-series of the subject and the atlas as a voxel-wise univariate statistical feature. We correlated this measure to the ADHD indices and p-values were obtained using a permutation test (2000 permutations, $\alpha \leq 0.05$, FDR q=0.05).

2.4 Group Comparison study

We also demonstrate the use of pairwise statistics for group differences by comparing TBI subjects with PTE to those without (non-PTE). We compared 37 PTE and 37 non-PTE subjects from the Maryland MagNeTs dataset.[28] Pairwise differences were computed in PTE and non-PTE groups. Variance for each group at each point in the brain was computed from a pairwise statistic by comparing their synchronized time-series. A voxel-wise F-statistic was computed by taking the ratio of variances of the PTE and non-PTE groups and was converted to the p-value at each point in the brain. FDR correction was performed on the p values ($\alpha \leq 0.05$; q=0.05). For comparison, we also repeated the experiment using an atlas based method. A reference atlas was created using BSA from the 37 non-PTE subjects. Euclidean distances were computed from each subject to the atlas and group tests were performed. To test for the group differences between the PTE and non-PTE groups, at each point the brain, we used distance of fMRI signals between each subject and the atlas as the test statistic. We performed F-test to compare functional heterogeneity within PTE group compared to the heterogeneity within non-PTE groups. We expect that PTE group will have higher functional heterogeneity compared to the nonPTE group.

Authors' accepted version
For research purposes only
Copyright (c) SPIE
Full article and citation at
https://doi.org/10.1117/12.2580980

3. RESULTS

3.1 Regression study

Results of the correlation tests between ADHD Indices and fMRI measures substantially differed between the atlas-based method and pairwise test (Fig. 1). In the atlas-based methods, strongly correlated points were found sparsely throughout the brain with clusters in the frontal pole, temporal lobe and insular cortices. However, after FDR correction, only 3 small clusters remained. The pairwise test, on the other hand, showed large, highly significant clusters across the frontal, temporal and insular cortices, even after FDR correction. Significant, yet sparser clusters of regions were also found posteriorly.

The resulting spatial map of the cortex in Fig. 1 shows an association of executive function networks to the ADHD indices. Especially, large clusters can be found throughout the frontal lobe, motor cortices, temporal lobe and anterior insular cortex. Similar results were found between the repeated pairwise tests (Fig. 2, top) while randomly permuting ADHD indices (Fig. 2, bottom) showed inconsistent and sparse results.

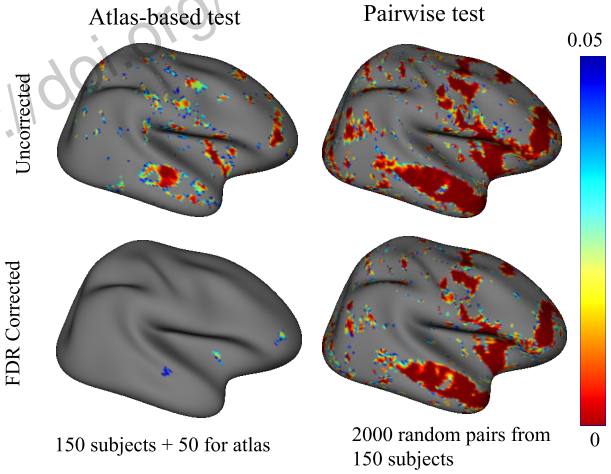

Figure 1. Results of regression using pairwise testing in the volumetric space after FDR correction ($\alpha \leq 0.05$).

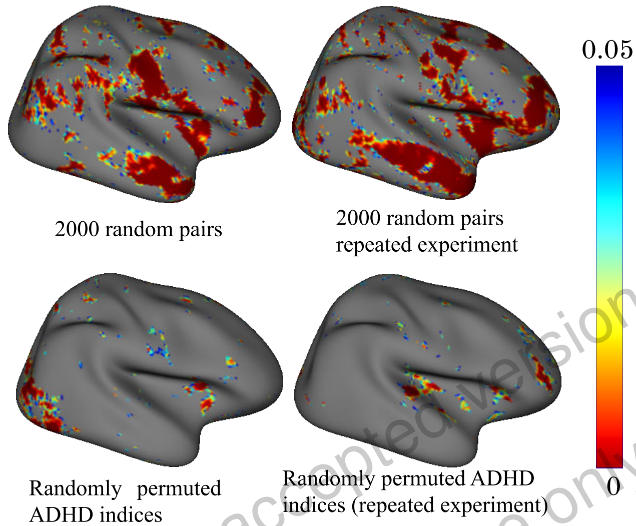

Figure 2. Top row: Repeated pairwise experiment using 2000 random pairs; Bottom row: same experiment as that in the top row but with random permutation of ADHD indices

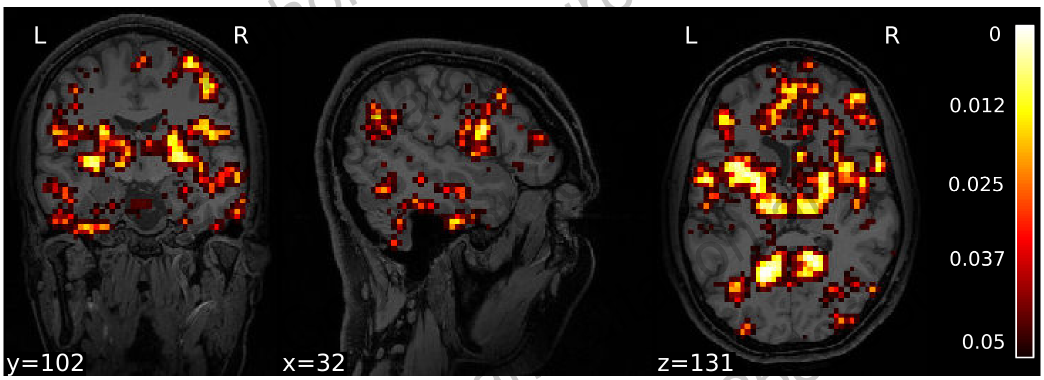

Figure 3. The results of linear regression using pairwise statistical analysis for ADHD in the volumetric space. The thresholded map of p-values is shown after FDR correction ($\alpha = 0.05$), overlaid on the USCBrain atlas in the background.

Pairwise tests performed volumetrically in the BCI-DNI brain atlas coordinates resulted in similar results to those performed in grayordinate space. Large clusters remained in the frontal, temporal, motor and insular cortices. We can see additionally in Figure 3, involvement of the striatal and thalamic nuclei.

3.2 Group comparison study

In the group comparison study between PTE and non-PTE subjects, the pairwise statistical method in grayordinate space showed significant group differences throughout the brain (Fig. 4). Some of the larger clusters found in the dorsolateral-prefrontal cortex, temporal-occipital-parietal junction, precuneus, motor areas and visual cortex. Large distributed patterns were observed rather than a localized effect possibly indicating that changes in connectivity in large distributed networks are responsible for the development of PTE. These results are largely consistent with the lesion analysis results obtained earlier in the same population.[29] The atlas-based method on the other hand, did not show significance after FDR correction.

4. CONCLUSIONS

In comparison to the atlas-based method, the pairwise test was found to be more sensitive to localizing regions correlated with ADHD Indices and in identifying group differences in PTE vs non-PTE subjects. The rs-fMRI data provides a high dimensional feature at each point in the brain, and group comparisons of these features could be performed in the high dimensions directly. For comparing distributions in high dimensional spaces, use

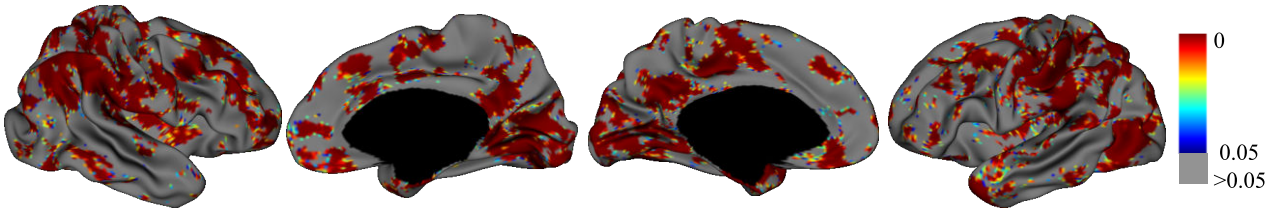

Figure 4. Results of the pairwise F-test between PTE and nonPTE group in grayordinate space after FDR correction was performed on the p-values.

of reproducing kernel Hilbert space (RKHS) has been desribed in the literature.[3,30,31] Our current analysis uses Euclidean distance, after BrainSync synchronization, as the metric. Using RKHS may lead to further gains in statistical power. Our preliminary results using kernel-based methods show promising results.[32]

ACKNOWLEDGMENTS

This work is supported by the following grants: R01 NS074980, W81XWH-18-1-0614, R01 NS089212, R01 EB026299, and 1F31NS106828-01A1.

Authors' accepted version
For research purpose only
Copyright (c) SPIE
Full article and citation at
https://doi.org/10.1117/12.2550980

REFERENCES

[1] Joshi, A. A., Chong, M., Li, J., Choi, S., and Leahy, R. M., "Are you thinking what I'm thinking? Synchronization of resting fMRI time-series across subjects," *NeuroImage* **172**, 740–752 (May 2018).

[2] Akrami, H., Joshi, A. A., Li, J., and Leahy, R. M., "Group-wise alignment of resting fMRI in space and time," in [*Medical Imaging 2019: Image Processing*], Angelini, E. D. and Landman, B. A., eds., 103, SPIE, San Diego, United States (Mar. 2019).

[3] Sejdinovic, D., Gretton, A., Sriperumbudur, B., and Fukumizu, K., "Hypothesis testing using pairwise distances and associated kernels," in [*Proceedings of the 29th International Conference on Machine Learning*], 1111–1118, Omnipress, New York, NY, USA (2012).

[4] Horwitz, B., "The elusive concept of brain connectivity," *NeuroImage* **19**, 466–470 (June 2003).

[5] Lang, S., Duncan, N., and Northoff, G., "Resting-state functional magnetic resonance imaging: review of neurosurgical applications," *Neurosurgery* **74**, 453–464; discussion 464–465 (May 2014).

[6] Smith, S. M., Miller, K. L., Salimi-khorshidi, G., Webster, M., Beckmann, C. F., Nichols, T. E., Ramsey, J. D., and Woolrich, M. W., "Network modelling methods for FMRI," *Neuroimage* **54**(2), 875–891 (2011).

[7] Smitha, K. A., Akhil Raja, K., Arun, K. M., Rajesh, P. G., Thomas, B., Kapilamoorthy, T. R., and Kesavadas, C., "Resting state fMRI: A review on methods in resting state connectivity analysis and resting state networks," *The Neuroradiology Journal* **30**, 305–317 (Aug. 2017).

[8] van den Heuvel, M. P. and Hulshoff Pol, H. E., "Exploring the brain network: A review on resting-state fMRI functional connectivity," *European Neuropsychopharmacology* **20**, 519–534 (Aug. 2010).

[9] Redcay, E., Moran, J. M., Mavros, P. L., Tager-Flusberg, H., Gabrieli, J. D. E., and Whitfield-Gabrieli, S., "Intrinsic functional network organization in high-functioning adolescents with autism spectrum disorder.," *Frontiers in human neuroscience* **7**(September), 573 (2013).

[10] Iraji, A., Calhoun, V. D., Wiseman, N. M., Davoodi-Bojd, E., Avanaki, M. R. N., Haacke, E. M., and Kou, Z., "The connectivity domain: Analyzing resting state fMRI data using feature-based data-driven and model-based methods," *NeuroImage* **134**, 494–507 (2016).

[11] Fan, L., Li, H., Zhuo, J., Zhang, Y., Wang, J., Chen, L., Yang, Z., Chu, C., Xie, S., Laird, A. R., and others, "The human brainnetome atlas: a new brain atlas based on connectional architecture," *Cerebral Cortex* **26**(8), 3508–3526 (2016).

[12] Alho, J. M., Kolehmainen, O., and Leskinen, P., "Regression Methods for Pairwise Comparison Data," in [*The Analytic Hierarchy Process in Natural Resource and Environmental Decision Making*], von Gadow, K., Pukkala, T., Tomé, M., Schmoldt, D. L., Kangas, J., Mendoza, G. A., and Pesonen, M., eds., **3**, 235–251, Springer Netherlands, Dordrecht (2001). Series Title: Managing Forest Ecosystems.

[13] Cao, Q., Zang, Y., Sun, L., Sui, M., Long, X., Zou, Q., and Wang, Y., "Abnormal neural activity in children with attention deficit hyperactivity disorder: a resting-state functional magnetic resonance imaging study," *Neuroreport* **17**, 1033–1036 (July 2006).

[14] Cao, X., Cao, Q., Long, X., Sun, L., Sui, M., Zhu, C., Zuo, X., Zang, Y., and Wang, Y., "Abnormal resting-state functional connectivity patterns of the putamen in medication-naive children with attention deficit hyperactivity disorder," *Brain research* **1303**, 195–206 (2009).

[15] Pappas, D., "Adhd rating scale-iv: Checklists, norms, and clinical interpretation," *Journal of psychoeducational assessment* **24**(2), 172–178 (2006).

[16] Gullapalli, R. P., "Investigation of prognostic ability of novel imaging markers for traumatic brain injury (tbi)," tech. rep., BALTIMORE UNIV MD (2011).

[17] Joshi, A. A., Shattuck, D. W., Thompson, P. M., and Leahy, R. M., "Surface-constrained volumetric brain registration using harmonic mappings," *IEEE transactions on medical imaging* **26**(12), 1657–1669 (2007).

[18] Joshi, A. A., Shattuck, D. W., and Leahy, R. M., "A method for automated cortical surface registration and labeling," in [*International Workshop on Biomedical Image Registration*], 180–189, Springer (2012).

[19] Li, J., Choi, S., Joshi, A. A., Wisnowski, J. L., and Leahy, R. M., "Temporal non-local means filtering for studies of intrinsic brain connectivity from individual resting fmri," *Medical Image Analysis* **61**, 101635 (2020).

[20] Li, J., Choi, S., Joshi, A. A., Wisnowski, J. L., and Leahy, R. M., "Global pdf-based temporal non-local means filtering reveals individual differences in brain connectivity," in [*2018 IEEE 15th International Symposium on Biomedical Imaging (ISBI 2018)*], 15–19, IEEE (2018).

[21] Joshi, A. A., Chong, M., Li, J., Choi, S., and Leahy, R. M., "Are you thinking what i'm thinking? synchronization of resting fmri time-series across subjects," *NeuroImage* **172**, 740 – 752 (2018).

[22] Joshi, A. A., Chong, M., and Leahy, R. M., "Brainsync: An orthogonal transformation for synchronization of fmri data across subjects," in [*International Conference on Medical Image Computing and Computer-Assisted Intervention*], 486–494, Springer (2017).

[23] Joshi, A. A., Choi, S., Chong, M., Sonkar, G., Gonzalez-Martinez, J., Nair, D., Wisnowski, J. L., Haldar, J. P., Shattuck, D. W., Damasio, H., et al., "A hybrid high-resolution anatomical mri atlas with sub-parcellation of cortical gyri using resting fmri," *bioRxiv* (2020).

[24] Smith, S. M., Vidaurre, D., Beckmann, C. F., Glasser, M. F., Jenkinson, M., Miller, K. L., Nichols, T. E., Robinson, E. C., Salimi-Khorshidi, G., Woolrich, M. W., Barch, D. M., Uğurbil, K., and Essen, D. C. V., "Functional connectomics from resting-state fmri," *Trends in Cognitive Sciences* **17**(12), 666 – 682 (2013). Special Issue: The Connectome.

[25] Barch, D. M., Burgess, G. C., Harms, M. P., Petersen, S. E., Schlaggar, B. L., Corbetta, M., Glasser, M. F., Curtiss, S., Dixit, S., Feldt, C., Nolan, D., Bryant, E., Hartley, T., Footer, O., Bjork, J. M., Poldrack, R., Smith, S., Johansen-Berg, H., Snyder, A. Z., and Essen, D. C. V., "Function in the human connectome: Task-fmri and individual differences in behavior," *NeuroImage* **80**, 169 – 189 (2013). Mapping the Connectome.

[26] Glasser, M. F., Sotiropoulos, S. N., Wilson, J. A., Coalson, T. S., Fischl, B., Andersson, J. L., Xu, J., Jbabdi, S., Webster, M., Polimeni, J. R., et al., "The minimal preprocessing pipelines for the human connectome project," *Neuroimage* **80**, 105–124 (2013).

[27] Benjamini, Y. and Hochberg, Y., "Controlling the false discovery rate: a practical and powerful approach to multiple testing," *Journal of the Royal Statistical Society: Series B (Methodological)* **57**, 289–300 (1 1995).

[28] Gullapalli, R. P., "Prognostic Value of MR Imaging Markers in the Assessment of Traumatic Brain Injury Patients," Clinical trial registration NCT01196299, clinicaltrials.gov (Mar. 2020). submitted: September 3, 2010.

[29] Akrami, H., Leahy, R. M., Irimia, A., Kim, P. E., Heck, C., and Joshi, A., "Neuroanatomic markers of post-traumatic epilepsy based on magnetic resonance imaging and machine learning," *medRxiv* (2020).

[30] Székely, G. J. and Rizzo, M. L., "Testing for equal distributions in high dimension," *InterStat* **5**(16.10), 1249–1272 (2004). Publisher: Citeseer.

[31] Székely, G. J. and Rizzo, M. L., "Brownian distance covariance," *The annals of applied statistics* **3**(4), 1236–1265 (2009). Publisher: JSTOR.

Authors' accepted version
For research purpose only
Copyright (c) SPIE
Full article and citation at
https://doi.org/10.1117/12.2580980

[32] Joshi, A. A., Choi, S., Akrami, H., and Leahy, R. M., "fmri-kernel regression: A kernel-based method for pointwise statistical analysis of rs-fmri for population studies," *arXiv preprint arXiv:2012.06972* (2020).

Authors' accepted version
For research purpose only
Copyright (c) SPIE
Full article and citation at
https://doi.org/10.1117/12.2580980