A Novel PCA-Based fMRI Noise Reducing Wishart Filter to Improve Diagnosis of Neurodegeneration

Nikhil Boddu
Washington University in St. Louis, St. Louis, MO 63110, USA
Email: nikhilvamsi31@gmail.com

INTRODUCTION

A. fMRI and Connectomes in Diagnostic Imaging

Functional MRI (fMRI) has become an increasingly popular method of scan acquisition in neuroimaging research, with an exponential growth in related publications in recent years [2]. The function of fMRI scanning is to analyze and represent common variance of blood-oxygenation-level-dependent (BOLD) signals in different regions of the brain [12], which is an effective indicator of simultaneous neural activity. fMRI can also be useful in developing functional connectivity networks, which highlight the connections between brain regions during neural activation. These connectivity networks – known as connectomes – are produced directly from fMRI data by cross-correlating every voxel with one another [5]. Having a clearer understanding of brain structure and functionality with high quality fMRI data offers solutions in diagnostic imaging for diseases such as Parkinson's and Alzheimer's [17]. Variations in specific brain regions of the connectome can also provide biomarkers for such diseases and can provide planning strategies during neurosurgery [3].

B. Unstructured Noise Reduction

Noise, or signal that does not originate from neural activity, is an element of fMRI that makes identifying neural pathways and characteristics far more difficult. In addition to the neural BOLD signal, several contributions add to the fMRI frequencies such as heartbeat, breathing, head movement, and white noise [9]. Predictable and consistent frequencies from bodily functions like these can be classified as structured noise, or artifacts, while irregular frequencies from white noise are classified as unstructured noise [12]. Isolating true neural BOLD signal is valuable to better understand brain physiology, but it is a challenge because the fMRI picks up signals from various processes in the environment [11]. The utility of an fMRI scan is heavily dependent on its ability to reduce noise and reflect real neural function. Connectomes are also susceptible to the noise in these fMRI scans, as unstructured signals can reduce correlation values between brain regions. The focus of this study was to utilize a new method for removal of unstructured "white" noise from both fMRI and connectomes to ultimately create better imaging data to for use in clinical testing. The conventional method of noise reduction is currently spatio-temporal smoothing [4]. This method utilizes a Gaussian function – given the full width at half maximum (FWHM) for a smoothing kernel – to average neighboring voxels across the scan and reduce the intensity of unstructured signals. In the temporal realm, specific frequencies over a given threshold are removed from the fMRI timeseries, reducing overall signal intensity. Although smoothing is a popular method for noise reduction, it reduces accuracy of neural signal by blurring spatial resolution, shifting neural activations, and merging multiple activation peaks [10]. Such problems are caused by the inherent blindness of spatio-temporal smoothing thresholds, which cannot actively differentiate between noise and BOLD signal. This can be harmful during clinical analysis of fMRI and connectomes for disease because altered neural functionality can cause misinterpretation of the characteristics of a subject's scan and misdiagnosis. A potential alternative to spatio-temporal smoothing is the use of Principal Component Analysis (PCA), which is a way to convert multi-dimensional data into lower dimensions. In relation to fMRI, the technique quantifies variance of signals by creating an eigenspectrum [15]. An eigenspectrum is an ordered sequence of eigenvalues, which represent the variance of each signal in the fMRI. Typically, variance caused by neural activity is much greater than that of unstructured noise, therefore the majority of it lies in the upper end of the eigenspectrum. The tail of this spectrum, therefore, typically consists of unstructured noise and can be removed by thresholding [7].

C. Human Connectome Project

PCA is a fairly new noise reduction method, with the WU-Minn Human Connectome Project (HCP) to be the first fMRI study to extensively utilize it for image processing. The HCP is a systematic effort to map human brain circuits and their relationship to behavior in large populations of healthy adults. High quality image processing techniques on the HCP have identified PCA as a potentially better method for unstructured noise reduction [7]. Based on this understanding that PCA can be used for reducing noise, a PCA-based Wishart Filter (WF) that incorporated a Wishart noise distribution to intuitively reduce noise in fMRI without using thresholds was developed in this study.

D. Objective and Hypotheses

The objective of this study was to test this novel WF as an alternative to current methods of unstructured noise reduction and to improve fMRI as a diagnostic tool. To understand the effect of WF on fMRI, this study was divided

into two major components: analysis of WF on task fMRI and analysis of WF on connectomes.

In the task analysis, spatial and temporal components of the fMRI were analyzed using a cluster mass statistic and visual analysis of z-statistic maps. To identify the optimal noise reduction method, this study proposed a null hypothesis: no significant difference in unstructured noise reduction and improvement of signal-to-noise ratio (SNR) exists between PCA-based WF and spatio-temporal smoothing.

The connectome analysis was composed of two key objectives. The first objective was to identify the optimal method of noise reduction to improve resting-state connectivity in dense and parcellated connectomes. This was measured using an average absolute Fisher transformed z-statistic of the connectome data. The second objective was to identify the optimal method of noise reduction to improve visibility of gradients in the resting-state fMRI timeseries; gradients, which are sharp shifts in signal across the timeseries, are important in creating parcellated connectomes because regions with higher gradients tend to represent borders for different brain regions. This was measured by calculating an average gradient for the volume and surface of each resting-state timeseries. For both objectives, the study proposed a null hypothesis: no significant difference in connectivity and gradient exists between PCA-based WF and spatio-temporal smoothing

METHODOLOGY

A. Study Subjects

All task and resting-state fMRI data was collected from the WU-Minn HCP's 1200 subject data acquisition perspective. All subjects of the HCP dataset were adults between the ages of 22 and 35 years. Many siblings and monozygotic and dizygotic twins were also included in the HCP, but they were excluded in this study. Individuals with severe neurodevelopmental disorders, documented neuropsychiatric disorders, or neurological disorders were excluded from the dataset; however, individuals who were smokers, heavy drinkers, recreational drug users, or overweight were included as long as they had not experienced any severe symptoms [14]. Therefore, all subjects in HCP data were considered fairly healthy. 28 unrelated subjects from the HCP dataset were randomly chosen for this study.

B. Scan Protocol

All fMRI scanning for the HCP was conducted on a 3 Tesla MRI scanner at Washington University in St. Louis. The acquisition parameters for fMRI were determined using assessments of robustness, spatial extent, and reproducibility of task activations/deactivations [14]. A 32-channel Siemens head coil and 2mm isotropic voxels were used to produce the fMRI scan. For task fMRI, 7 different tasks were performed by each subject, and data for each task was collected in 2 runs. These tasks included working memory, which tested the subjects' short term memory retention; gambling, which tested the subjects' decision-making in a risk/reward situation; motor, which tested their motor and sensory capabilities; language, which tested their reading and listening capabilities; social cognition, which tested their ability to recognize mental interactions between nonhuman objects; relational processing, which tested their ability to compare the physical features of objects; and emotional processing, which tested their ability to recognize facial expressions [1]. This fMRI scan protocol was held constant for all subjects that were analyzed in this study.

C. Task fMRI Experimental Design

Existing minimally preprocessed fMRI data that had no unstructured noise removed were used as a baseline control for this study, and altered fMRI timeseries and spatial maps were created in addition to the baseline as independent variables. Altered timeseries included 5 iterations of WF; 4mm, 6mm, and 8mm FWHM spatial smoothing; and a temporal low-pass filter with a threshold of 0.08 Hz, explained thoroughly in [6]. All quantitative data to determine the effectiveness of noise reduction was analyzed with a "cluster mass" statistic which was represented by this equation [8]:

$$\sum_{v=1}^{n} v_A * v_z * ROI$$

The region of interest (ROI) was defined binarily as 1 if the z-statistic for a given voxel was greater than 5 or less than -5 and 0 otherwise to exclude voxels that were primarily unstructured noise or outside of the task-evoked brain regions. An increase in the cluster mass statistic was interpreted as a reduction of unstructured noise, as higher z-statistic represented stronger and clearer task-evoked pathways. Cluster mass results were verified by qualitative visual analysis of z-statistic and spatial variance maps.

D. Experimental Design of Connectivity

Dense and parcellated connectomes were created from the resting-state fMRI data. To create a dense connectome, each voxel in the resting-state timeseries was cross-correlated with every other voxel to create a dense connectome. To create a parcellated connectome, a parcel label file was created by correlating fMRI volume and surface gradients using Connectome Workbench commands. This label file was then compared to the resting-state timeseries to compress the dense timeseries into a parcellated timeseries with fewer voxels. Figure 1 depicts the difference between the brain regions in parcellated connectomes and dense connectomes. Each parcel in this parcellated timeseries was then correlated to the other parcel to create a parcellated connectome. Processing of the baseline dense timeseries included 6 iterations of WF; 4mm, 6mm, and 8mm FWHM spatial

smoothing; and a 0.08 Hz temporal low-pass filter. A baseline connectome with no processing was also used as a control. An average absolute Fisher transformed z-statistic was calculated for both dense and parcellated connectomes to quantify connectivity. The absolute Fisher z-statistic is represented by the equation:

$$|z'| = \frac{ln(1+r) - ln(1-r)}{2}$$

The Fisher transformation normalized the data, and calculating an absolute value ensured that only magnitudes of z-statistics were considered. Because unstructured noise reduces the visibility of neural activation, correlations and z-statistics would be lower; therefore, increase in the z-statistic was interpreted as improvement in the visibility of resting-state connectivity.

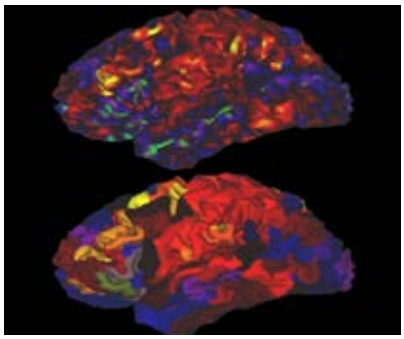

FIGURE 1
DENSE AND PARCELLATED TIMESERIES

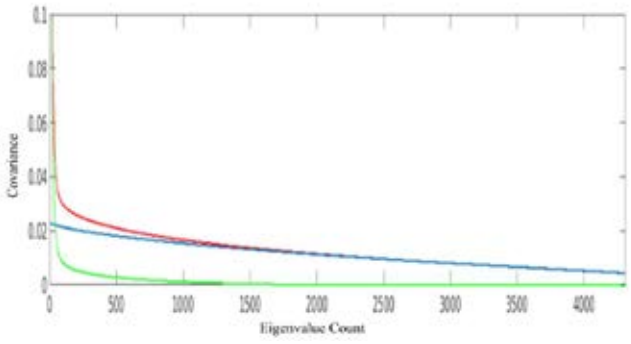

FIGURE 2
WISHART EIGENSPECTRA
RED: BASELINE, BLUE: WISHART NOISE, GREEN: RESULT

E. Wishart Filtering Method

Before using the Wishart function, PCA was conducted on the baseline fMRI to create a covariance matrix. This covariance matrix was then reduced to 2-dimensional eigenspectrum. Once the fMRI had been transformed into an eigenspectrum, a Wishart noise function was used to construct a "noise eigenspectrum" for this data using its spatial and temporal dimensions [16]. The noise eigenspectrum was then subtracted from this section of the fMRI eigenspectrum. The intention of this was to remove a significant amount of noise eigenvalues to create a higher signal-to-noise ratio (SNR), as shown by [13]. Figure 2 visually depicts this noise eigenspectrum subtraction, as the green WF eigenspectrum has far fewer trailing eigenvalues with little variance; they have been removed from the red baseline eigenspectrum by subtracting the blue noise eigenspectrum.

RESULTS

A. Task fMRI Analysis

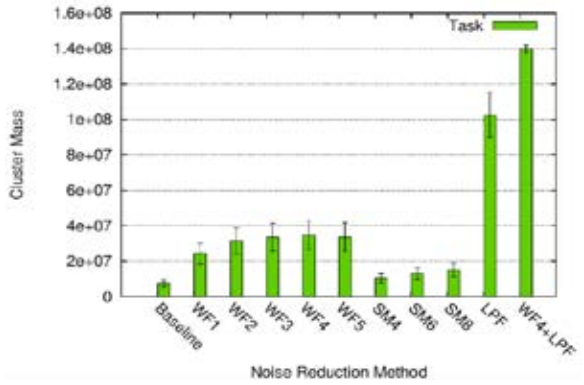

FIGURE 3
TASK CLUSTER MASS STATISTICS

Figure 3 presents the mean cluster mass statistics for each noise reduction method in the individual task analysis. In general, WF in the individual task fMRI produced higher mean cluster mass statistics. 1 iteration of WF (WF1) had significantly higher cluster masses than baseline ($t_{28} = 17.42$, $p = 0.00$), and the most effective iteration was WF4, as it had the highest mean cluster mass. As predicted, spatial smoothing also improved cluster mass statistics in comparison to baseline. 8mm spatial smoothing (SM8) was considered the most effective FWHM for spatial smoothing, as it produced the highest mean cluster mass.

Although both WF and spatial smoothing improved cluster mass statistics, WF4 had significantly higher results than SM8 ($t_{28} = 11.57$, $p = 0.00$), suggesting that WF is likely more effective at improving z-statistics and reducing unstructured noise. Figure 4 highlights the effectiveness of WF at revealing neural signal in the fMRI, as it captures substantially more regions than the baseline and SM8.

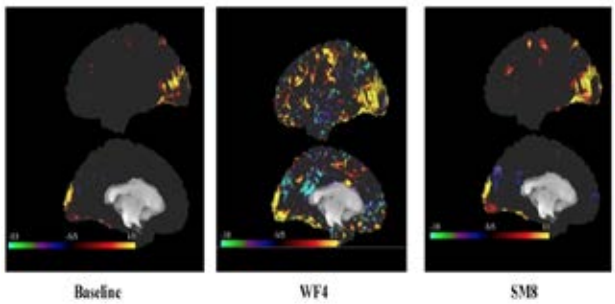

FIGURE 4
Z-STATISTIC SPATIAL MAPS OF TASK DATA

B. Connectivity Experiment

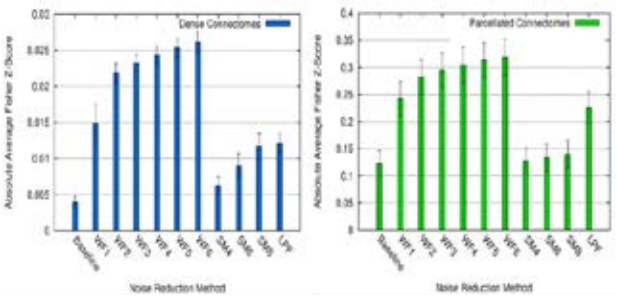

FIGURE 5
CONNECTOME AVERAGE ABSOLUTE FISHER Z-STATISTICS

Figure 5 presents the average z-statistics for each noise reduction method in dense and parcellated connectomes. WF4 significantly improved connectivity in the dense connectomes compared to SM8 (t_{28} = 33.23, p = 0.00), and low-pass filtering, LPF (t_{28} = 36.62, p = 0.00). In parcellated connectomes, WF1 yielded the same results, improving connectivity much more than SM8 and LPF. Using WF on the dense timeseries was able to clarify and strengthen correlations between neural pathways that were not clear with spatio-temporal smoothing. In general, the average Fisher z-statistics were much higher in parcellated connectomes due to the reduced presence of unstructured noise in the larger brain regions. However, the results for the parcellated connectomes follow a similar pattern. Figure 6 visually depicts WF6's ability to clarify the neural connections compared to SM8, as there are far more red points in the WF6 connectome which represent stronger positive correlations.

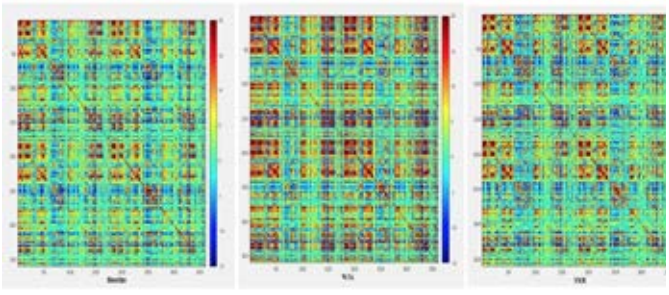

FIGURE 6
PARCELLETED CONNECTOMES
LEFT: BASELINE, CENTER: WF6, RIGHT: SM8

C. Gradient Experiment

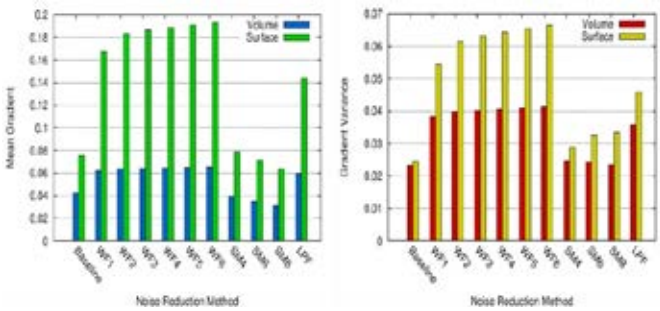

FIGURE 7
FUNCTIONAL MRI GRADIENT MEAN AND VARIANCE
LEFT: MEAN, RIGHT: VARIANCE

Figure 7 presents the results of the gradient analysis for each noise reduction method on the dense timeseries. WF1 was significantly more effective than 8mm spatial smoothing at increasing the average gradient at both the volume level and surface level (t_{28} = 29.17, p = 0.00). Although the LPF had higher average gradient than spatial smoothing, WF1 was still significantly more effective than LPF in both at the volume and surface level (t_{28} = 7.52, p = 0.00). In general, WF also had higher variance than spatial smoothing and LPF, which suggests that gradients and brain regions in the WF fMRI have greater contrasting. Figure 8 visually supports this, as WF6 seems to reveal much stronger gradients between functional regions compared to the baseline and SM8. In fact, because spatial smoothing blurs the gradients, SM8 reduces the visibility of many gradients that are visible in the baseline fMRI. This suggests that spatial smoothing is actually detrimental for determining brain regions (parcels) and for producing more accurate parcellated connectomes.

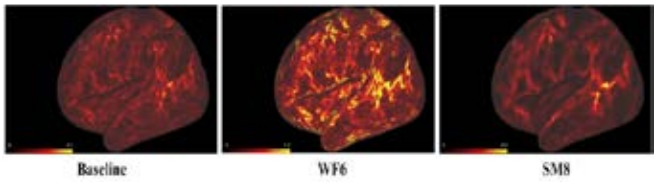

FIGURE 8
INFLATED SURFACE GRADIENT MAPS

DISCUSSION

A. Implications

As highlighted by [10], spatial smoothing results in several detrimental consequences in the fMRI spatial map and timeseries, and such effects were avoided by WF in both task fMRI and resting-state connectomes. WF produced more effective results than spatio-temporal smoothing in noise reduction, connectivity, and fMRI gradients. In general, this study showed that WF is likely a superior noise reduction and fMRI processing method. This novel method for more effectively revealing neural signals and pathways can have groundbreaking implications on the development of disease biomarkers and knowledge for diagnostic and surgical purposes. Being able to more clearly visualize fMRI without

smoothing data can provide doctors and scientists with a more confident way to understand, diagnose, and treat diseases that alter brain structure and function like Alzheimer's and Parkinson's. The detailed pathways that non-smoothed connectomes provide can give insight into the effect of different neurodegenerative proteins on the brain and how to counter these effects. As the field of connectomics and study of functional networks expands, WF can act as a key tool for identifying and understanding neurological disorders.

B. Future Research

A major step in applying WF to clinical trials and studying disease is to analyze the effects it has on diseased subjects' fMRI data. As shown by this study, functional signals and pathways would be clarified by WF, but it would be useful to study the specific pathways and characteristics that the new method can reveal. Studying these pathways can provide insight into the plasticity and adaptability of brain networks in the presence of disease. Additionally, it could be beneficial to expand the effects of WF connectomes to study the development of mental disorders and other brain related health issues that don't directly impact the brain anatomy. [3] emphasizes the potential for connectomes as a way to diagnose and treat mental disorders by identifying changes in neural function. These potential studies are the next steps in applying WF as a tool for studying functional connectomics in a clinical setting to diagnose and treat patients.

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