The Influence of Age and Sex on Resting state fMRI (rs-fMRI) Signal Temporal Complexity
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Background & Goals
Understanding the process of aging and the differences in sex can help improve the implementation of machine learning (ML) strategies when assessing concussions with large neuroimaging datasets. Concussions cause unique and potentially lasting deficits in today’s patient population and current diagnostic tools are limited and incomplete. We therefore report on a novel way of analyzing temporal complexity in fMRI images to identify functional damage present in concussion patients while taking age and sex into consideration. Investigating the effects of age and sex can help us more accurately diagnose patients with a concussion and improve the connection between imaging and clinical symptom presentation.

Patients & Methods
Assessing functional complexity across age and sex required the collection of over 10,000 resting state fMRI (rs-fMRI) datasets of healthy controls, males and females, between the ages of 18-70, and sourced from worldwide data repositories including IDA, HCP, NITRC, and OpenNeuro [1, 2, 3, 4]. TBIFinder™ (https://www.tbifinder.com) software was used to analyze all rs-fMRI data by calculating the temporal complexity (TC) of the BOLD signal [5, 6]. All data was warped to the MNI152 standardized space, eddy corrected, and brain extracted, then segmented into over 90 gray matter regions of interest (ROIs) in reference to the John Hopkins University (JHU) atlas [7]. Statistical map distributions were therefore generated for each age, sex, and ROI within the healthy control population. These maps were further used as a normal distribution to perform a Z-score statistical evaluation against individuals who have suffered a concussion. A standard deviation >2.5 in the concussion population is considered clinically relevant with typical TBIFinder™ outputs shown in the Results section below.

Results
Analysis demonstrates significant differences in temporal complexity (TC) between males and females and between age groups (30-60 year old age groups) within each ROI. Specific highlighted results are as follows:
- A reduction in mean TC associated with men compared to women (p=0.0006)
- Women had higher TC variance than men (i.e. higher standard deviations)
- A reduction in mean TC associated with aging, between the ages of 30 to 60 (p=0.03), shown in Figure 1
- Significant differences between the ages of 30 and 60 year old Males (p=0.02), shown in Figure 1
- 60 year old Males had higher TC variability compared to 30 year old Males (p=0.02), shown in Figure 1

A Z-score analysis was further performed on a 19 year old Male who had suffered a concussion and was compared against the 19 year old Male healthy distribution map for a more accurate injury assessment, shown in Figure 2.

Conclusions
This study proves that age and sex effects are important and must be considered when performing Z-score type analyses, and other ML techniques, in patient populations (i.e. concussion). This study demonstrates that personalized brain assessment can successfully be performed in subjects who suffered a concussion, as long as their comparative healthy reference is representative of their own patient population.

Future work should include more age groups and advanced statistical methods to further validate the technique in other patient populations and highlight the statistical differences in aging rates. Some specific ROIs may also require investigation due to their unique mean TC values (i.e. premotor cortex, medial geniculate bodies). Vendor contributions and patient demographics should also be investigated to identify their potential effects on the healthy distributions. Higher resolution or a more voxel-sized approach should also be considered to pinpoint very specific areas of injury and help clinical colleagues target treatment and rehabilitation efforts.

References & Funding

Figure 1. A colour coded visualization of the temporal complexity (TC) mean values across each ROI for the 30 and 60 year old male age groups. A reduction in TC is demonstrated within 60 year old males and is represented in green (outer circle). Increased TC variability is also demonstrated in light green (inner circle) for older age groups who progressively age at different rates.

Figure 2. A colour coded visualization of the personalized rsfMRI-based resting state complexity analysis (M) from a subject where outliers were detected in specific regions of gray matter in the cerebrum. In this subject, injuries have been identified and visualized via TBIFinder™ software. Axial, coronal, and sagittal slices demonstrate the location and severity of these functionally damaged regions.