The Structural and Functional Correlates of Frailty in Persons Living With HIV

Jeremy F. Strain[1]*, Sarah Cooley[1]*, Collin Kilgore[1], Brittany Nelson[1], John Doyle[1], Regina Thompson[1], Elizabeth Westerhaus[1], Kalen J. Petersen[1], Julie Wisch[1], Beau M. Ances[1]

* Equally contributed to manuscript

[1]Department of Neurology, Washington University, St. Louis, MO 63110, USA

Author Correspondence to: Jeremy F. Strain PhD
Department of Neurology
Saint Louis, MO 63110
United States
strainj@wustl.edu

Running Title: Neuroimaging correlates of HIV Frailty

Summary: Increased susceptibility to brain structural and functional damage was observed in individuals with both HIV and frailty compared to individuals with HIV and without frailty. Therefore, imaging metrics may have clinical utility for monitoring individuals with both HIV and frailty.

Abstract

Background: Chronically-infected persons living with HIV (PWH) are at increased risk of frailty, a clinically recognizable state of increased vulnerability due to aging-associated decline in multiple physiologic systems. Frailty is often defined by the Fried criteria which includes subjective and objective standards concerning health resiliency. However, these frailty metrics do not incorporate cognitive performance or neuroimaging measures.

Methods: We compared structural (diffusion tensor imaging; DTI) and functional (cerebral blood flow; CBF) neuroimaging markers in PWH to frailty and cognitive performance. Virologically controlled PWH were dichotomized as either frail (≥3) or non-frail (<3) using the Fried criteria. Cognitive Z-scores, both domain (executive, psychomotor speed, language and memory) and global, were derived from a battery of tests. We identified three regions of reduced CBF, based on a voxel-wise comparison of frail PLWH compared to non-frail PWH. These clusters (bilateral frontal and posterior cingulate) were subsequently used as seed regions (ROIs) for DTI probabilistic white matter tractography.

Results: White matter integrity connecting the ROIs was significantly decreased in frail compared to non-frail PWH. No differences in cognition were observed between frail and non-frail PWH. However, reductions in WM integrity among these ROIs was significantly associated with worse psychomotor speed and executive function across the entire cohort.

Conclusions: We conclude that frailty in PWH can lead to structural and functional brain changes including subtle changes that are not detectable by standard neuropsychological tests. Multi-modal neuroimaging in conjunction with frailty assessment could identify pathological brain changes observed in PWH.

Keywords: DTI, Probabilistic Tractography, Frailty, Cognition, CBF

INTRODUCTION:

With the introduction of combination antiretroviral therapy (cART), HIV is now a chronic disease with the life expectancy of persons with HIV (PWH) similar to persons without HIV (PWoH)[1]. This has led to an aging population, with more than half of all PWH greater than 50 years old. Consequently, age-related comorbidities are becoming more common and are an increasing concern for clinicians treating PWH.

Frailty is a clinically recognizable state of increased vulnerability due to age-associated declines in multiple physiologic systems such that an individual is unable to cope with acute or consistent stressors[2]. Frail individuals, especially those greater than 50 years old, are at higher risk for adverse health outcomes, such as falls, hospitalizations, and death[3]. Frailty is defined by the Fried criteria as having three or more of the following symptoms: unintentional weight loss, self-reported exhaustion, low physical activity, slowed gait, and/or reduced grip strength. A higher incidence of frailty has been observed in PWH compared to PWoH[4-5]; and the presence of frailty has been linked to several clinical markers of HIV disease, including lower CD4 T-cell counts[6]. Worse neuropsychological performance, particularly in executive functioning and motor/psychomotor speed, have also been observed in frail PWH[7-8].

There is increasing interest in identifying the biological basis of cognitive changes and frailty that are seen in PWH. A potential role exists for neuroimaging as it provides a noninvasive method to evaluate brain function and structure at the region, network, and global levels. With regards to functional neuroimaging measures, cerebral blood flow (CBF), as measured by arterial spin labeling (ASL), has been identified as a potentially valuable method to identify regions of interest (ROIs) that are affected by frailty in PWH[9]. Recent studies have observed that CBF is reduced within subcortical brain structures (i.e. pallidum, amygdala, caudate, hippocampus, thalamus) of older frail PWH[8,10]. Notably, a machine learning model revealed that CBF was the best predictor of frailty amongst multiple neuroimaging modalities (CBF, brain volumetrics, and resting state functional connectivity) and cognitive performance

measures[10]. However, it remains unknown if the CBF changes seen with frailty relate to white matter (WM) changes that are also often present in PWH[11,12].

We utilize CBF and WM in a multi-modality approach that allows for a greater understanding of brain structural changes in frail PWH. Measures of WM integrity were quantified with diffusion tensor imaging (DTI), a sensitive biomarker for evaluating microstructural changes in WM[13]. In a systematic review of PWoH and frailty, frailty was shown to consistently associate with worse white matter integrity particularly with lower grip strength and slower gait. [14-16]. Reductions in WM pathways have previously been proposed to underlie impairments in motor function and worse cognitive performance in frail PWH[17]. Prior work has shown that frail PWH have decreased WM volume suggesting that disruption of white matter pathways may be more pronounced in these individuals.[18] However, these hypotheses have not yet been tested in PWH despite increasing evidence suggesting alterations in WM microstructure are more prevalent in PWH compared to PWoH[19,20]. The current study utilized a data-driven multi-modal neuroimaging approach to identify affected WM tracts in older (≥50 years of age) virologically well-controlled (undetectable viral load; <200 copies/mL) frail (n=16) compared to non-frail (n=100) PWH. Additionally, WM integrity, as quantified by fractional anisotropy (FA), was compared to cognitive performance (both global and domain specific).

METHODS

Participants

All PWH were recruited from the Washington University School of Medicine (WUSM) Infectious Disease Clinic, and the WUSM AIDS Clinical Trial Unit (ACTU). Participants provided informed written consent that was approved by the Institutional Review Board at WUSM. All PWH were ≥ 50 years old and were screened using the following exclusion criteria: current or past history of confounding neurological disorders, severe depressive symptoms as assessed by the Beck Depression Inventory II (score ≥29)[21], current alcohol or substance abuse,

head injury with loss of consciousness greater than 30 minutes, contraindications for MRI including metal in the body or claustrophobia, seizures, or fewer than 8 years of education. All PWH had confirmed serological status, were receiving a stable combination anti-retroviral therapy (cART) regimen for at least three months prior to time of assessment, and were virally suppressed (<200 copies/ml). Demographic information is provided in Table 1.

Frailty Criteria

PWH were classified as either frail or non-frail based on subjective and objective measures as previously defined[3]. PWH were evaluated for unintentional weight loss (>10 pounds), self-reported exhaustion, self-reported low physical activity, reduced grip strength (adjusted for sex and body mass index), and slowed gait (adjusted for sex and height). A PWH was classified as frail if (s)he exhibited ≥3 of these features. For objective measures including gait and grip strength, measures were acquired in a laboratory setting under the supervision of a trained neuropsychological technician or neuropsychologist.

Cognition

All PWH completed a comprehensive neuropsychological battery that included tests evaluating four cognitive domains: psychomotor speed (Trail Making Test A[23], Digit Symbol[24], Grooved Pegboard dominant and non-dominant hands[25], Symbol Search[24]) learning and memory (Hopkins Verbal Learning Test free recall and both learning trials[26], Brief Visuospatial Memory Test free recall and both learning trials[27]), executive function (Color-Word Interference Test[28], verbal fluency[29], Trail Making Test B[23], Letter Number Sequencing[24]) and language (Letter Fluency[30], Category Fluency[31]). These tests have previously been used to assess cognitive impairment in PWH[22]. Raw test scores were converted to standardized scores (Z-scores) using published norms that adjusted for demographic variables (age, sex, race and years of education)

when applicable. Test Z-scores within a single cognitive domain were averaged to create domain Z-scores. These domain Z-scores were then averaged to create a global cognition Z-score.

Imaging Acquisition

All imaging was performed on a 3T Siemens Tim TRIO scanner (Siemens AG, Erlangen Germany). The imaging protocol included structural T1-weighted, DTI, and pseudocontinuous arterial spin labeling (pCASL) sequences. High-resolution 3D magnetization-prepared rapid acquisition of gradient echo (MP-RAGE) images were collected in the sagittal plane using a 12-channel head coil. A total of 176 slices, 1.0-mm slice thickness, and voxel dimensions of 1.0x1.0x1.0mm were acquired. CBF was derived from the pseudo continuous arterial spin labeling (pCASL) method using the following sequence: 1.5-second labeling time, 1.2-second post-labeling delay, TR of 3,500 ms, TE of 9.0 ms, 64 x 64 acquisition matrix, 90° flip angle, 22 axial slices with a 1-mm gap, and voxel size of 3.4x3.4x5.0. Two pCASL scans were acquired, each containing 60 volumes (30 pairs) of control and label volumes and a duration of 3.5 minutes. Two sequential DTI scans were obtained (2x2x2 mm voxels, TR=9,900 ms, TE=102 ms, flip angle =90°, 23 directions, b-values ranging from 0 to 1400 s/mm^2), and one non-diffusion weighted image.

CBF Preprocessing

Image pre-processing was performed using the FMRIB Software Library (FSL, Oxford, UK)[32]. pCASL M_0 images were brain extracted and linearly aligned to T_1-weighted images. All T_1-weighted images, and the corresponding pCASL M_0 images, were registered to the Montreal Neurological Institute (MNI152) 1-mm brain prior to analyses. pCASL volumes were motion-corrected; frame pairs with > 0.5 mm displacement between label and control were censored.

CBF was calculated by pairwise subtraction of spin-tagged and untagged images using a standard single-compartment model that follows recommended clinical guidelines[33]. Voxels with non-physiological CBF (<0 or >120 ml/100g/min) were excluded.

CBF Post Processing

A linear regression model was used to adjust CBF values for group differences with regards to age and gender. Residuals from these models were used in subsequent analyses. PWH were dichotomized based on frailty status, and group differences were analyzed on a voxel-wise basis to evaluate for regional differences in CBF. A cluster-based technique was performed across gray-matter voxels to correct for multiple statistical comparisons. Random-effects maps, thresholded at $p<0.05$, were permuted to compute a distribution of cluster size occurrence. A minimum cluster size of 40 voxels was determined based on a $p=0.05$ occurrence threshold with all significant voxels belonging to clusters smaller than this threshold excluded.

DTI Preprocessing

Preprocessing included correction for motion and eddy current distortions followed by skull stripping using FSL[34]. Scans were inspected to ensure that head movement was < 3.5 mm for all participants during data acquisition. Tensors were estimated with FA maps created using DTIFIT in FSL[35]. FA was the primary metric evaluated. All images were smoothed with a 3 mm smoothing kernel to address potential partial volume effects. All FA maps were warped to MNI space via the reference FMRIB_FA_1mm, a template in MNI space that has been optimized for diffusion images.

White matter (WM) Tract Preprocessing

To generate WM tracts, cognitively normal healthy PWoH (age 22-35 years old; n=144) from the Human Connectome Project were selected after rigorous screening of all data

(humanconnectome.org/documentation). These individuals were only used to generate a WM connection template that was seeded from regions of differential CBF as identified above.

Significant ROIs generated from the prior CBF analysis were used as seeds for the probabilistic tractography algorithm Probtrackx in FSL[36]. WM projections connecting the interface voxels between each ROI were created by FMRIB Software Library's (FSL's) probabilistic pipeline. This pipeline consisted of correction for EPI distortions, eddy-current induced distortions, participant motion, and gradient non-linearities with TOPUP and EDDY from FSL[37].

Full details regarding the generation of WM tracts for patient populations using the human connectome project (HCP) data has been previously published[19]. In short, bedpostX from FSL was used to quantify diffusion orientation distributions from preprocessed HCP DTI data. This tool uses Markov chain Monte Carlo sampling to calculate the dominant and secondary fiber distributions for each voxel. Each ROI identified by CBF was subsequently warped into native space prior to performing tractography. For each CBF ROI pair, probabilistic tractography was performed twice with each ROI serving as the seed or the target and the average of the results used to identify connections between the two ROIs. Once completed, a threshold for each probabilistic mask was identified as 10% of the maximal intensity to reduce sporadic projections. Each of the probabilistic masks were warped into the Montreal Neurological Institute (MNI) space using a combination of linear and nonlinear alignments. Probabilistic masks pertaining to a particular tract were combined and then limited to voxels present by a simple majority.

WM Post Processing

WM tracts connecting each ROI seed identified by CBF were analyzed independently as well as compiled into a "network" that included the average WM integrity from all WM tracts that connected all ROIs. Each WM tract was overlaid onto the FA map of each PWH in order to extract FA values from voxels residing within it. Additionally, FA values were also extracted from an atlas based corticospinal tract (CS), which served as a control pathway[38]. A non-parametric Mann-Whitney of the medians was used to evaluate differences between frail and non-frail PWH after controlling for age and gender. A statistical threshold of $p<0.05$ was used for each WM tract.

Comparison Between DTI and Cognition Measures or HIV variables

Domain and global cognition Z-scores were first compared between frail and non-frail PWH using Mann-Whitney U tests. Next, the average FA from each WM tract was compared to cognitive measures. We evaluated the relationship between tract FA values and global cognitive performance across the entire cohort with linear models with age and gender treated as covariates. Similar linear regression models were also performed for each of the cognitive domains (learning and memory, language, psychomotor speed, and executive function).

Finally, the average FA from each WM tract was compared with select HIV variables measuring previous and current HIV severity (nadir and current CD4). The linear models were performed with age and gender treated as covariates.

RESULTS

Demographics

The cohort consisted of PWH (n=116) of whom 100 were non-frail and 16 were frail. The two groups were not significantly different with regards to age, race, or education but did

differ with regards to sex (p<0.01). The two groups had similar CD4 nadir, CD4 current, and plasma viral loads. For additional details regarding demographic information please see Table 1.

CBF Analysis

After correcting for multiple comparisons, frail PWH had significantly lower CBF in three clusters compared to non-frail PWH. Two clusters resided within the frontal cortex and one was in the posterior cingulate (Figure 1). No regions were identified where non-frail PWH had significantly lower CBF compared to frail PWH. These three ROIs were subsequently used as seed regions for WM tract analyses.

WM Tract Analysis

Average fractional anisotropy (FA) values for the tracts that connected each of the ROIs identified by CBF were compared for non-frail and frail PWH. Frail PWH had a significant reduction in FA compared to non-frail PWH for tracts that connected frontal ROIs to the posterior cingulate (left frontal p=0.0097; right frontal p=0.0177). Connections between the two frontal ROIs were also reduced but at a trend level (p=0.067). Overall, the average FA from WM tracts that connected these three ROIs was significantly lower for frail compared to non-frail PWH (p=0.026). No differences were seen between frail PWH and non-frail PWH for the corticospinal tract (p=0.22) which served as a control. These results suggest a specificity in WM tracts involved.

Cognition and HIV Factors

No differences were observed in terms of cognition for either domain or global metrics between frail and non-frail PWH (p-values >.05). Across all PWH, the average FA from the WM "network" was significantly correlated with global cognition (F=5.41, R^2=0.037, p=0.022). When analyzing each domain separately, WM integrity was significantly associated with

psychomotor speed domain (F=9.62, R^2=0.067, *p*=0.003) and executive function (F=7.17, R^2=0.051, *p*=0.009) but not language (F=0.3, R^2=0.004, *p*=0.79) or memory (F=0.674, R^2=0.006, *p*=0.41). Figure 2 shows the relationship between the structural connectivity among the ROIs and psychomotor speed. No relationship was observed for any of the WM tracts with either current or nadir CD4 as an analysis of HIV severity.

DISCUSSION

Frailty is categorized as a signature of a possible underlying comorbidity and is traditionally more prevalent in PWH compared to HIV- controls. For our cohort, we observed a prevalence of 14% which is within an expected range for PWH.[39-41] We observed that PWH who were frail had worse brain integrity. Our findings revealed that in the absence of cognitive impairment characterized by neuropsychological assessment, imaging correlates of structural and functional integrity were reduced in frail compared to non-frail PWH. PWH who had higher structural integrity, as assessed by FA using DTI, performed better on tests of psychomotor speed and executive function. Therefore, incorporating multi-modal imaging metrics with frailty assessment may identify PWH who are potentially at greater risk for future cognitive decline.

This novel methodological approach utilized CBF to derive data-driven ROI's to evaluate WM pathways. Treating these regions as subsequent seed ROIs allowed us to generate more accurate representations of WM pathways in PWoH (HCP individuals). We focused on these WM pathways instead of implementing techniques like tract-based spatial statistics (TBSS) that are designed for studies without a specific hypothesis[42]. We assessed the localizability of our findings by including the corticospinal tract that was not identified by functional ROI's. This tract did not differ between the frail HIV and the non-frail HIV groups, suggesting our findings were not global but specific to frailty in HIV.

We observed regional reductions in CBF in frail PWH compared to non-frail PWH. Frontal regions, including the dorsal lateral prefrontal cortex (DLPFC), are often affected in PWH and could lead

to impairments in decision-making[9]. The precuneus and cingulate cortices were also identified, and these results corroborate prior findings that showed an association between atrophy in this region with reduced quality of life in PWH[44]. WM integrity between these ROIs differed by frailty status. Previous work for evaluating frailty in PWoH has led to mixed results. Some studies have shown robust DTI changes throughout the brain[43], while others found more localized changes, with primarily callosal regions or frontal WM regions affected, similar to our findings[16,45].

Across all participants regardless of frailty status, reductions in WM integrity were associated with worse performance in the psychomotor speed and executive function domains. Both cognitive domains are known to be affected by HIV[46]. Prior work has identified significant relationships between these domains and changes in white matter microstructure in older PWoH[47]. We did not observe differences between frail and non-frail PWH with regards to cognition. In contrast, significant differences in neuroimaging metrics of both structure and function were observed between the two groups. Our cognitive results are similar to previous studies that did not observe significant differences between frail and non-frail PWH after sex was included as a covariate[8]. Our results suggest that brain imaging measures of integrity may be more sensitive than behavioral assessments for evaluating frailty in older PWH.

There are several limitations with the current analyses. Future studies with larger sample sizes are needed to improve our understanding of the findings discussed in this paper. Our cohort did not contain sufficient data on activities of daily living (ADLs) to determine HAND criteria. Longitudinal data is necessary to determine the trajectory of the frail individuals and to monitor their cognitive and imaging outcomes. We focused on older (≥ 50 years old) frail individuals and cannot be extrapolated across the entire age range. Finally, the Fried Frailty measurement is a generic tool for underlying comorbidity but has been extensively used in PWH as an indicator of increased risk of possible future cognitive decline and poorer disease outcomes.

Overall, these results implicate an underlying reduction in brain integrity imaging measures for frail PWH compared to non-frail PWH. Frailty associated with reductions in brain structure and function in virologically well-controlled older PWH. Lower CBF and reduced WM integrity was observed in frail compared to non-frail PWH despite no differences in cognitive or virological measures (e.g. CD4 nadir or current). Our data demonstrated that reductions in WM integrity due to frailty associated with worse performance on psychomotor speed and executive function tasks. HIV associated variables did not associate with WM integrity, suggesting that the changes are due to frailty and not severity of HIV disease. Further longitudinal studies are needed to determine if observed changes in brain structure and function remain stagnant or continue to progress and lead to cognitive decline in older PWH.

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Potential conflicts:

BMA reports a patent for use of plasma NfL for CAR-T neurotoxicity (to institution and not relevant to manuscript); and an unpaid leadership or fiduciary role on the Editorial Board of J Neurovirology. None of the other authors has any potential conflicts.

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Table 1. Demographic and clinical characteristics of participants by group

	Frail (n=16)	Non-Frail (n=100)	p-value
Age (years old)	56.0 (7.0)	56.9 (7.2)	0.31
Range	50 - 74	50 - 85	
Sex, N (%)	7 (44%) M	85 (85%) M	**<0.01**
	9 (56%) F	15 (15%) F	
Race, N (%)	10 (62.5%) AA	55 (55%) AA	0.91
	6 (37.5%) C	43 (43%) C	
	0 (0%) MR	2 (2%) MR	
Education (years)	13.0 (2.7)	13.5 (2.6)	0.46
Range	9 - 18	8 - 18	
Recent CD4 T-cell count; median (IQR)	688 (414, 741)	563 (359, 827)	0.13
Nadir CD4 T-cell count; median (IQR)	180 (40, 273)	78 (19, 247)	0.20
Plasma viral load (copies/mL, log_{10})	1.3 (0.1)	1.4 (0.2)	0.49
Global cognition Z-score	-0.5 (0.7)	-0.2 (0.6)	0.08
10- year Framingham Risk Score	17.7 (10.5)	18.1 (9.2)	0.88
Range	11 - 23	16 - 20	
Area Deprivation Index National Rank	76.7 (22.7)	70.1 (24.9)	0.34
Range	38 – 99	8 - 100	

M= Male; F = Female; AA = African American; C = Caucasian; MR = More than one race; IQR = Inter-quartile range

FIGURE LEGENDS

Figure 1. Persons with HIV (PWH) who were frail had significant decreases in cerebral blood flow (CBF) within three regions of interest (ROIs) including the frontal left (F1)=blue, frontal right (F2)=green, and posterior cingulate (PC) =red) compared to non-frail PWH. The connections between the various CBF ROIs are displayed in magenta. The boxplots represent the structural integrity of the designated white matter (WM) tracts for the frail and non-frail PWH groups. Significant differences were observed for WM connections between F1-PC and F2-PC.

Figure 2. The relationship between average WM connections among the ROIs identified by CBF as a function of psychomotor speed for the entire PWH cohort. Frail PWH are indicated in red and non-frail PWH are indicated in green.

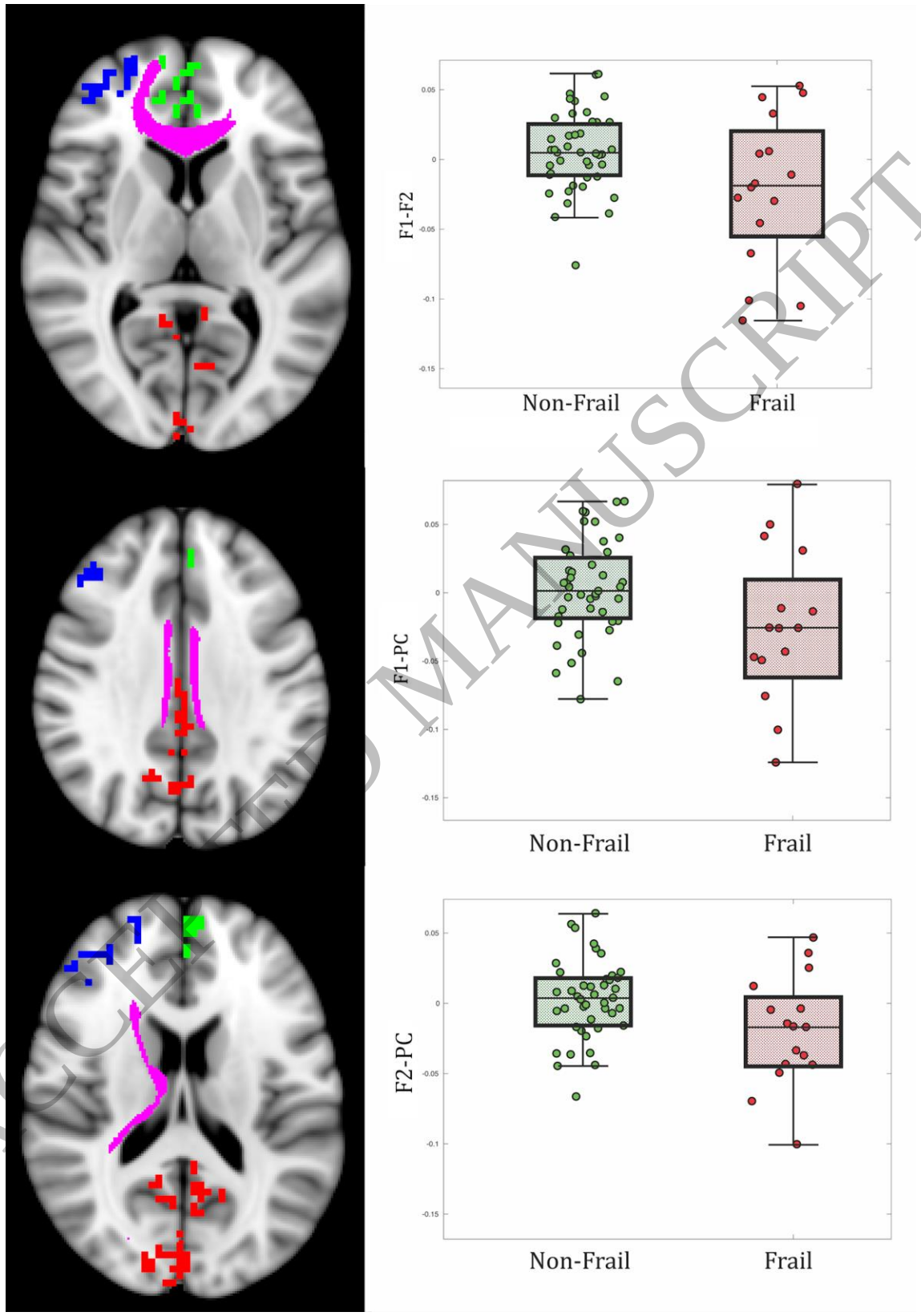

Figure 1
158x229 mm (5.7 x DPI)

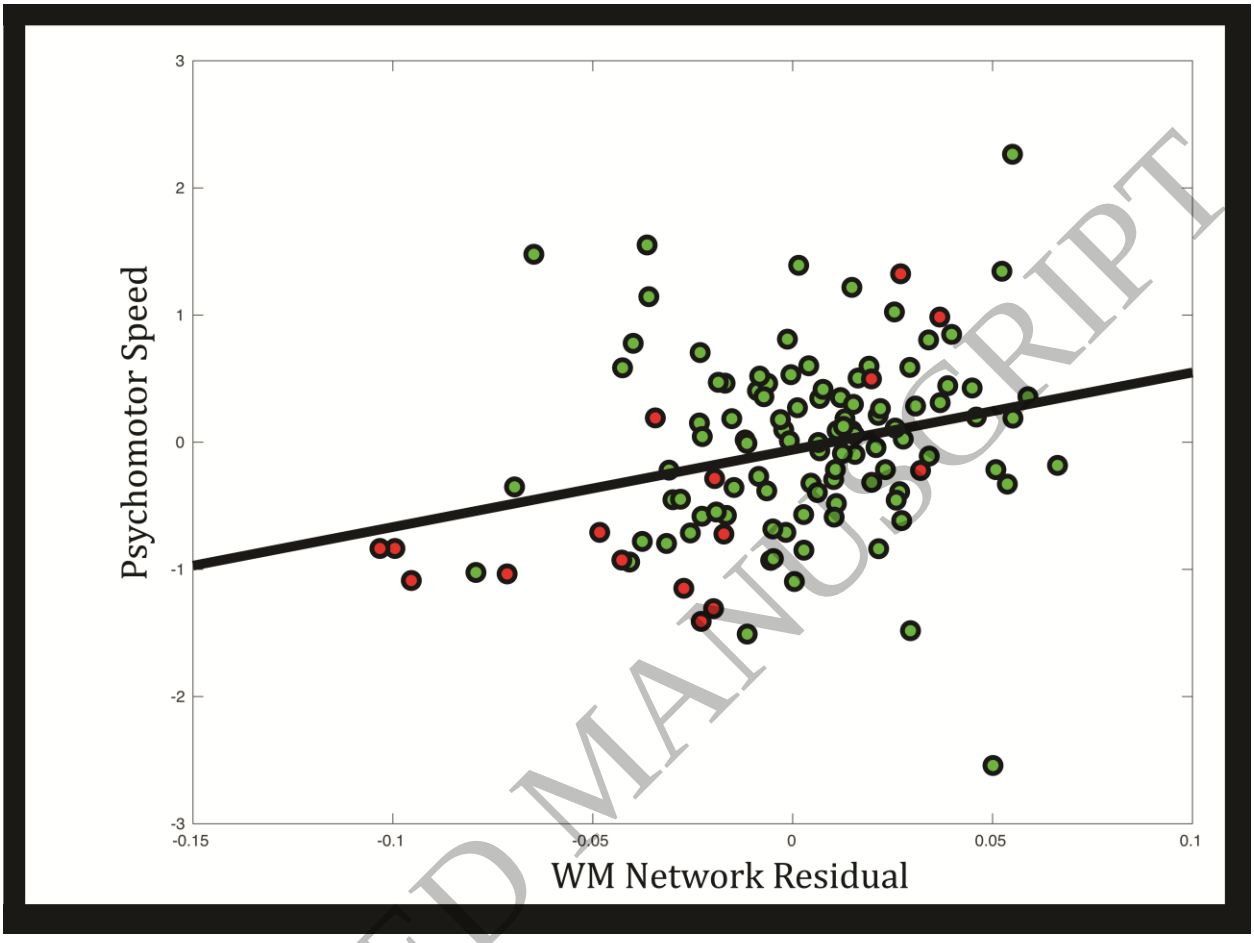

Figure 2
165x123 mm (5.7 x DPI)