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Resting State Functional Connectivity of the Supplementary Motor Area and the Caudate Nucleus in Prodromal Huntington's Disease

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RESTING STATE FUNCTIONAL CONNECTIVITY OF THE SUPPLEMENTARY MOTOR
AREA AND THE CAUDATE NUCLEUS IN PRODROMAL HUNTINGTON'S DISEASE

A Thesis

Georgia State University

2017

by

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RESTING STATE FUNCTIONAL CONNECTIVITY OF THE SUPPLEMENTARY MOTOR
AREA AND THE CAUDATE NUCLEUS IN PRODROMAL HUNTINGTON'S DISEASE

by

Elizabeth Fall

Under the Direction of Jessica Ann Turner, PhD

ABSTRACT

Huntington's disease (HD) is a fatal neurodegenerative genetic disease that causes motor difficulties, mood impairment, and cognitive dysfunction. Prodromal Huntington's disease (PrHD) refers to people who carry the mutated huntingtin (htt) gene, but do not yet fit the criteria needed for a full diagnosis. Changes in mood typically begin in the prodromal phase, and apathy is a particularly devastating change that progresses in severity throughout the course of the disease. We investigated neural connectivity changes that could be associated with apathy severity within this population. We performed a seed-based connectivity analysis on resting state scans of 89 (PrHD) patients, with the supplementary motor area, bilateral caudate and caudate head as our regions of interest. We found that apathy severity was significantly correlated with increased connectivity between the caudate head and the supplementary motor area ($p = 0.03$). Further analyses are needed to establish the extent of the effect of caudate atrophy on this relationship, which we would predict would be highly related due to the degenerative nature of the disease.

INDEX WORDS: prodromal Huntington's disease, apathy, caudate head, supplementary motor area

DEDICATION

This project would not have been possible without the support of my closest friends and family. Sean Lachenberg, your unwavering love and encouragement has sustained me through this entire process. I would also like to dedicate this to my parents, Peter and Astrea Fall, my grandparents Gloria and Michael Fall, my Grandmother Bertha Wolf and late Grandfather David Wolf. Last but certainly not least, my best friends, Julia Morris and Golda Steinberg.

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TABLE OF CONTENTS

DEDICATION iv

ACKNOWLEDGMENTS v

INTRODUCTION 1

 PREDICT-HD Research Group 1

 Emergence of Mood Changes in Prodromal HD 2

 Fronto-striatal Dysfunction 3

 Cognitive Apathy 4

 Supplementary Motor Area 5

 Purpose 6

METHOD 7

 Participants 7

 Measures 7

 Data Acquisition and Imaging 7

 Data Preprocessing 7

 Statistical Model 9

RESULTS 9

DISCUSSION 9

 Tables 12

 Figures 14

REFERENCES 24

INTRODUCTION

Huntington's disease (HD) is a fatal neurodegenerative genetic disease that causes motor impairment, emotional dysregulation, and cognitive decline. The HTT gene implicated in Huntington's disease is present in all humans, but in HD affected individuals, an abnormal amount of trinucleotide cytosine, adenine, guanine (CAG) repeats (Paulsen et al., 2014) is present. The mutated huntingtin gene causes a toxic accumulation of protein within the striatum, resulting in neuronal dysfunction, and eventually cell death (Graveland, Williams & Difiglia, 1985). In HD, progressive neuronal atrophy occurs most severely in regions of the striatum responsible for executive function, reward/reinforcement, and voluntary movement (Halliday et al., 1998; van den Bogaard et al, 2011). The disease affects approximately 2.71 people out of 100,000 worldwide (Pringsheim et al., 2012), with an average age of onset of age 40 (Myers, 2004). Though clinical diagnosis does not typically occur until middle age, mild symptoms of the disease become apparent many years in advance, in the prodromal phase of the disease (Epping et al., 2016). Clinical diagnosis requires the gene positive individual carrying the abnormal amount of CAG repeats to present a certain degree of motor impairment as dictated by the Unified Huntington's Disease Rating Scale (Huntington Study Group, 1996).

PREDICT-HD Research Group

Our study was done in collaboration with The Neurobiological Predictors of Huntington's Disease (PREDICT-HD) group, whose overarching goal is to identify biomarkers associated with symptoms prior to the onset of Huntington's disease (Paulsen et al., 2008). The group has compiled one of the largest prodromal Huntington's disease datasets and contributed significant insight into the symptoms preceding motor diagnosis. The aim of the longitudinal PREDICT-HD study is to provide information that could result in behavioral or pharmacological

interventions to slow the onset and progression of the disease. To better predict time to diagnosis, the team has developed a predictive measure called the CAP score (Paulsen et al., 2014). CAP score, which stands for CAG-AgeProduct, is an interaction term that includes age and number of CAG repeats as a predictor of years to motor onset. $CAP\ score = (age\ at\ study\ entry) \times (CAG - 33.66)$ (Zhang et al., 2011). CapD, is a dynamic version of CAP score that uses current age rather than age at scan. We used this variable as a measurement of disease burden in our study.

Emergence of Mood Changes in Prodromal HD

The PREDICT-HD team has identified a wide range of mood changes that occur prior to motor onset of HD. Mood changes typically emerge prior to clinical diagnosis, and apathy and depression are particularly prevalent symptoms (Paulsen et al., 2001; Duff et al., 2007; Martinez-Horta et al., 2016). Depressive symptoms have been reported in up to 70% of the diagnosed HD population (Epping et al., 2013). Apathy has been reported anywhere from 32% in prodromal HD patients far from diagnosis to 62% in early manifest HD patients (Martinez-Horta et al., 2016). These symptoms emerge slowly, but over the course of the disease often lead to strained interpersonal relationships and poor quality of life (Licklederer, Wolff, & Barth, 2008; Hartelius et al., 2010). Because of this, it is important to study the neural correlates related to dysfunctional mood symptoms to gain a better understanding of why these changes are occurring and what can be done to mitigate these effects.

Delineation of Apathy and Depression in Huntington's Disease

Apathy, characterized by a loss of motivation and a decrease in goal directed behavior, affects up to half the Huntington's disease population (Paulsen et al., 2006). Apathy is often considered a symptom of depression in the general population, but in movement disorders such

as Huntington's disease or Parkinson's disease, apathy can be present without depressive symptoms (Baudic et al., 2006). Apathy that accompanies these clinical diagnoses appears to be more related to impairment of cognitive and motor function, but depression is not associated with these impairments (Pluck and Brown, 2002; van Duijn et al., 2010). A large meta-analysis of 5388 patients with Parkinson's disease found that half of patients with apathy do not suffer from depression (Meyer et al., 2014; den Brok et al., 2015). A study of 34 HD patients demonstrated that while apathy severity was significantly related to cognitive function, as measured by the Mini Mental State Examination, as well as motor score (UHDRS), depression was not (Naarding et al., 2009). Additional studies have yielded similar results. These findings, though not exhaustive, suggest an alternative mechanism responsible for the presentation of apathy in Huntington's disease, independent of depression.

Fronto-striatal Dysfunction

Fronto-striatal dysfunction has been consistently associated with apathy in neurodegenerative conditions (Kos et al., 2016) and may be involved in non-pathological apathy in a small portion of the healthy population as well (Bonnelle et al., 2015). We would expect the striatum to be involved in apathy, as it is essential in cognitive functions such as decision making, and self-generated behavior. Prodromal HD patients tend to do poorly on tests of cognitive function such as the Symbol Digit Modality Test. (Paulsen et al., 2014) Similarly, Parkinson's disease patients exhibit impairment in tests of semantic verbal fluency and set shifting (Pagonabarraga, Kulisevsky, Strafella, & Krack, 2015). Although fronto-striatal dysfunction appears to be a commonality in pathological apathy, it is not necessarily homogenous. The specific regions and mechanisms involved in fronto-striatal dysfunction have an effect on the way apathy manifests itself. Researchers (Levy and Dubois, 2006) studying the

unique features of apathy in patients with lesions of the basal ganglia characterized apathy into subtypes. The sub-type of particular relevance to Huntington's disease is cognitive apathy.

Cognitive Apathy

Cognitive apathy, sometimes referred to as "cognitive inertia" is characterized by an inability to initiate the executive functions needed for goal directed behavior (Levy and Dubois, 2006). Patients with this type of apathy have difficulty on psychometric tests that assess set-shifting or cognitive flexibility (Levy, 2011). Studies in diagnosed HD validate this apathy profile. A cross-sectional analysis of 82 clinically diagnosed HD patients investigating the relationship between behavioral measures and cognitive test scores found that apathy was significantly related to poor performance on tests of object recall, word fluency, and the Stroop test (Thompson et al., 2002). Additionally, apathy score was strongly related to motor impairment severity. Depression on the other hand, was not strongly related to measures of cognition or motor impairment.

Cognitive apathy is observed in patients with lesions to the dorsal portion of the caudate head (Cognat et al., 2010; Mendez et al., 1989). The caudate is of especial relevance in Huntington's disease, as it is one of the first regions to exhibit marked atrophy, even before clinical diagnosis (Papp et al., 2011). Reduction in caudate volume is associated with poorer performance on tests of executive function (Liu et al., 2016). It would make sense then that atrophy that begins in the prodromal phase of Huntington's disease would produce a similar expression of apathy that is seen in patients with caudal lesions. Surprisingly, there is limited literature on the neural correlates of apathy in prHD.

Levy (2011) states that apathy may be the result of abnormalities or disruptions that occur in the process of initiating a plan. In order to execute a goal directed behavior, one has to plan,

understand and find rules, use working memory, among other cognitive faculties (Zelazo and Müller, 2002). Therefore apathy could be the result of impairment or inability to employ the necessary cognitive functions to participate in goal directed behavior. The end result is the appearance of a lack of motivation or will, but the reality may be a defect in the goal selection and initiation process.

Supplementary Motor Area

The presence of apathy in many movement related disorders suggests a possible role of impaired motor planning in the presence of apathy. In the process of initiating goal-directed behavior, one needs to plan to physically move. The supplementary motor area (SMA) is a region located in the cerebral cortex that is active when planning voluntary movement (Goldberg, 1985). The SMA has been shown to be active even when thinking about making a motor movement (Leisman et al, 2016). One would presume that damage to this area would result in an apathetic like-syndrome due to the inability to initiate a planned movement. A study of post-stroke patients with basal ganglia lesions reported apathy severity was negatively correlated with cerebral blood flow in the supplementary motor area (SMA) (Okada et al., 1997). More evidence of SMA's role in apathy is supported by an amplitude of low-frequency fluctuation (ALFF) study in Parkinson's disease. Researchers reported a strong association between apathy severity and ALFF signal in the left supplementary motor area (Skidmore et al., 2013). Moreover, a severe form of apathy termed the "auto-activation deficit" is seen in patients with direct lesions of the supplementary motor area (Levy, 2011). Patients suffering from this affliction exhibit difficulty in initiating voluntary actions without the cue of an external stimulus, thus goal-directed behavior is fundamentally impaired. Taken together, it can be inferred that the activation in the supplementary motor area is involved in apathetic states.

In prodromal Huntington's disease, there are no studies to our knowledge that have specifically looked at the relationship between apathy severity and supplementary motor area function, but there is a wealth of evidence pertaining to global impairments in supplementary motor area function (Kloppel et al., 2009; Minkova et al., 2015). A resting state study of 10 prodromal HD patients reported significantly lower BOLD synchrony between the caudate nucleus and supplementary motor area (Unschuld et al., 2012).

Taken together, this evidence suggests that SMA-Caudate Nucleus functional connectivity could be affected in apathy severity in prodromal HD subjects. For this reason, and the previous evidence for alterations in neural activity in apathetic subjects, we would expect there to be a relationship in prodromal HD individuals and apathy severity. We do not anticipate that depression will be related to functional connectivity.

Purpose

Although many studies have investigated resting state functional connectivity in prodromal Huntington's (Unschuld et al., 2012; Seibert et al., 2012; Dumas et al., 2013; Poudel et al., 2014, Dogan et al., 2015; Klöppel et al., 2015, Harrington et al., 2015), none to our knowledge have studied the relationship between apathy severity and resting state functional connectivity. The aim of the current project is to identify functional connections related to apathy in prodromal Huntington's disease. We hypothesize that a reduction in functional connectivity between the supplementary motor area and the caudate nucleus will be significantly correlated with higher apathy scores.

METHOD

Participants

Our sample included 89 prodromal HD individuals (Mean age = 43.91 years; SD = 12.67). Participants in this sample were part of a larger resting state sample derived from a longitudinal PREDICT-HD dataset (Paulsen et al., 2008). There were 57 females and 32 males. The average CAG repeat length was 41.98. More information on the demographic information for our participants is presented in Table 1.

Measures

Apathy was measured using the Frontal Systems Behavior Scale (Grace & Malloy, 2001). Companion reported apathy and participant reported apathy were both used in our model. Depression scores were measured using the Beck Depression Inventory (BDI).

Data Acquisition and Imaging

Identical Siemens TIM Trio 3 T MRI scanners were used at 6 different scanning sites. T2*-weighted gradient-echo echo-planar images (EPIs) were acquired with the following parameters: voxel size = 2.0×2.0×(4.0 or 4.5) mm³; repetition time TR = 2800 ms; echo time (TE) = 29 ms; FA = 80°; field of view (FOV) = 256×256 mm²; matrix = 128×128, slice thickness = 4 mm, gap = (0 or 0.5 mm), number of slices = 31 interleaved axial oblique. Scans lasted 6 minutes, 15 seconds. Participants were instructed to close their eyes and lie still in the scanner.

Data Preprocessing

Preprocessing was done using SPM5 (www.fil.ion.ucl.ac.uk/spm/). Head motion correction was done using INRIAlign (<http://www.sop.inria.fr/epidaure/Collaborations/IRMf/INRIAlign.html>). Slice-timing correction

was set to 31 slices using slide 15 as a reference frame. Normalization to the Montreal Neurological Institute (MNI) template was done using SPM5. Scans were resliced to 3mm x 3mm x 3mm voxel size. Scans were smoothed using a 6-mm-full width half-maximum (FWHM) Gaussian kernel using SPM8. Scans were also despiked using an in-house code. Scans with a voxel-wise correlation to the MNI template of ≥ 0.97 , maximum translation ≥ 3.5 mm, and absolute mean frame-wise displacement ≥ 1.0 mm were excluded (See Figure 1).

We used the GIFT toolbox (Calhoun & Adali, 2012) in MATLAB R2013b to perform an independent component analysis (ICA) as a means of artifact detection and removal. 100 components were derived from ICA. Artefactual components were defined as those located in cerebrospinal fluid, white matter, or indicative of head movement (Allen et al., 2011). 42 of the original components were deemed artifacts and were removed from the scans. The scans were reconstructed from the remaining 58 components. Seeds were created using the WFU PickAtlas tool on SPM8 and were coregistered to the reconstructed scans. The ROI's chosen for this analysis are as follows: the caudate head, bilateral caudate and bilateral supplementary motor area (see Figure 2). The reconstructed scans were used as the input for a seed to seed functional connectivity analysis using DPARSF Advanced Edition (Chao-Gan & Yu-Feng, 2010). DPARSF extracts the averaged time course from specified seed regions, and performs a correlation analysis to create connectivity values. Connectivity values are a measure of BOLD signal correlation such that a high positive connectivity value indicates positive BOLD signal correlation, or synchronous activation, between two regions. A high negative value indicates anti-correlation between two regions.

Statistical Model

We used RStudio to construct a linear mixed effects model using the lme4 package (Verbeke & Molenberghs, 2000). Our covariates include companion-reported apathy scores, Beck Depression Inventory (BDI) total, CAG repeat length, CAP score, absolute mean frame-wise displacement, age, and gender. Absolute mean frame-wise displacement was included as a covariate to further account for variations in head motion (see Figure 1). Site by scanner was included as a random effect, to eliminate the effect of different scanning sites (see Table 4).

RESULTS

We found that higher apathy scores were significantly related to increased functional connectivity between the caudate head and the SMA ($B = 0.01$, $t(169) = 1.85$, $p = 0.03$) (See Table 2; Figure 3). As connectivity between the caudate-head and SMA increased, apathy severity also increased. The relationship between whole caudate connectivity to the SMA and apathy severity trended toward significance ($p = 0.06$) but did not meet threshold (See Table 3; Figure 10). Depression (BDI) was not significantly related to functional connectivity between either the bilateral caudate or caudate head and SMA (see Figure 4). CAP Score, CAG repeat length, absolute mean frame-wise displacement, age, and gender were also not significantly correlated with either caudate head (see Figures 5-9) or bilateral caudate connectivity.

DISCUSSION

Our aim for this study was to determine whether activation in specified regions of the brain was associated with apathy severity in prodromal Huntington's disease. Though we hypothesized that supplementary motor area – caudate head functional connectivity would be negatively correlated with apathy severity, we found the opposite to be the case. Increased SMA-Caudate Head connectivity was related to higher apathy severity. Though our results did not

replicate connectivity related reductions with increasing apathy severity as was found in other clinical populations, it did support current prHD literature on global connectivity. Wolf et al., 2014, conducted a network functional connectivity analysis on early manifest HD participants that reported increased connectivity in the caudate bilaterally within a striatal resting state network compared to controls. Additionally, they reported within a motor resting state network, early manifest HD subjects had increased connectivity of the SMA. Task based studies of prodromal HD have also found similar activations in the SMA (Scheller et al. 2013).

Moreover, it appears that in several task-based studies of apathy across clinical and healthy populations, apathetic individuals tend to have increased connectivity with the SMA compared to controls (Blakemore et al., 2017). Although intuitively, it would seem that a “negative” symptom such as apathy would result in a decrease in activation, it is theorized that apathetic individuals may need to employ more cognitive resources to initiate an action, than non-apathetic individuals.

It was surprising that companion reported apathy was the only significantly related variable to SMA-Caudate Head connectivity values. We would expect that age and number of CAG repeats would be related to our connectivity model, because the greater the number of CAG repeats, the more atrophy in the caudate, which is sometimes correlated with functional connectivity (Craufurd, Thompson, & Snowden, 2001; Julien et al., 2007; Marshall J et al., 2007; Rosenblatt, 2007). A longitudinal version of our study would prove very helpful in shedding more light on the effect of aging on the connectivity values. Additionally, we did not include caudate volume in our model. Future studies including volume would provide evidence of whether the volume loss of the caudate is the driving force behind increased apathy.

In conclusion, apathy severity is associated with hyperconnectivity of the supplementary motor area and caudate head in prodromal Huntington's disease. It is possible the supplementary motor area may be attempting to compensate for volume loss of the caudate. Our study did confirm that the caudate head is more significantly related to apathy than the whole caudate body. This is in line with previous studies of apathy in individuals with lesions of the caudate head. Additionally, our study confirmed that depression and apathy are distinct entities in Huntington's disease.

Tables

Table 1

Participant Characteristics

Fixed Effects	Mean	SD
Age at scan	43.91	12.67
CAG repeats	41.98	3.40
BDI Total	7.75	8.54
Companion Reported Apathy	13.36	5.49
Absolute Mean Framewise Displacement	0.23	0.14
Cap D Score	341.17	89.60
Participant Reported Apathy	13.96	5.71

Note: n = 89 BDI = Beck Depression Inventory

Table 2

Caudate Head – SMA Connectivity Mixed Effects Model

Fixed effects	B	Std. Error	t score	P
Companion Reported Apathy	0.02	0.01	2.11	0.03*
BDI Total	0.00	0.01	0.95	0.34
Participant Reported Apathy	-0.01	0.01	-0.88	0.38
CAG Repeats	0.02	0.03	0.58	0.56
Cap D Score	0.00	0.00	-0.77	0.44
Absolute Mean Framewise Displacement	0.28	0.26	1.07	0.28
Age at Scan	0.00	0.01	0.19	0.85
Gender	-0.04	0.07	-0.62	0.53

Note: n = 89 BDI = Beck Depression Inventory

Table 3

Whole Caudate (Bilateral Caudate) – SMA Connectivity Mixed Effects Model

Fixed Effects	B	Std. Error	t-value	<i>P</i>
Companion Reported Apathy	0.015	0.008	1.851	0.064
BDI Total	0.000	0.006	-0.085	0.932
Participant Reported Apathy	-0.006	0.009	-0.744	0.457
CAG Repeats	0.007	0.031	0.242	0.808
CAP D Score	-0.001	0.001	-0.639	0.523
Absolute Mean Framewise Displacement	0.286	0.281	1.020	0.308
Age at Scan	-0.004	0.008	-0.462	0.644
Gender	-0.069	0.075	-0.917	0.359

Note: BDI = Beck Depression Inventory

Table 4

Random effects:

Groups Name	Variance	Std.Dev.
sitebyscan (Intercept)	0.00	0.00
Residual	0.09228	0.3038

Note: Number of obs: 89, groups: sitebyscan,6

Figures

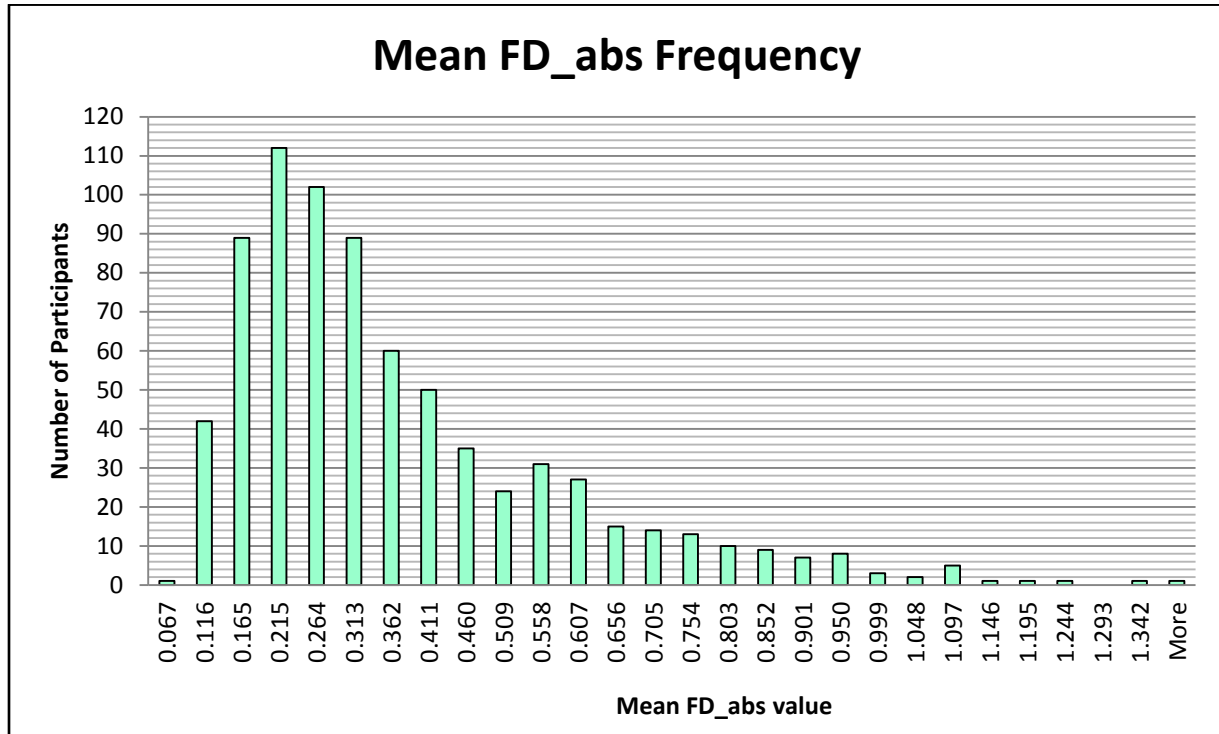


Figure 1: Absolute Mean Framewise Displacement Frequency

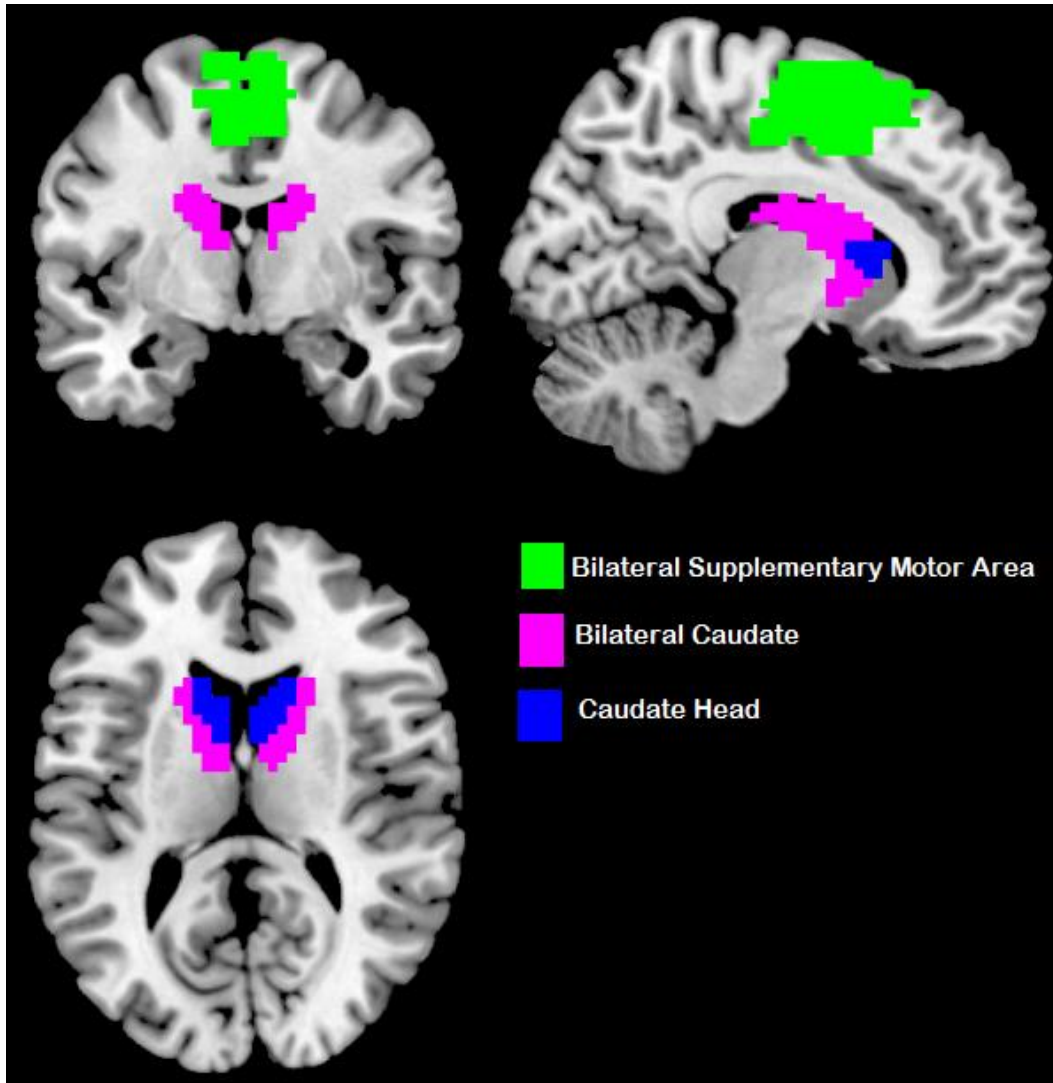


Figure 2: Seed Regions of Interest

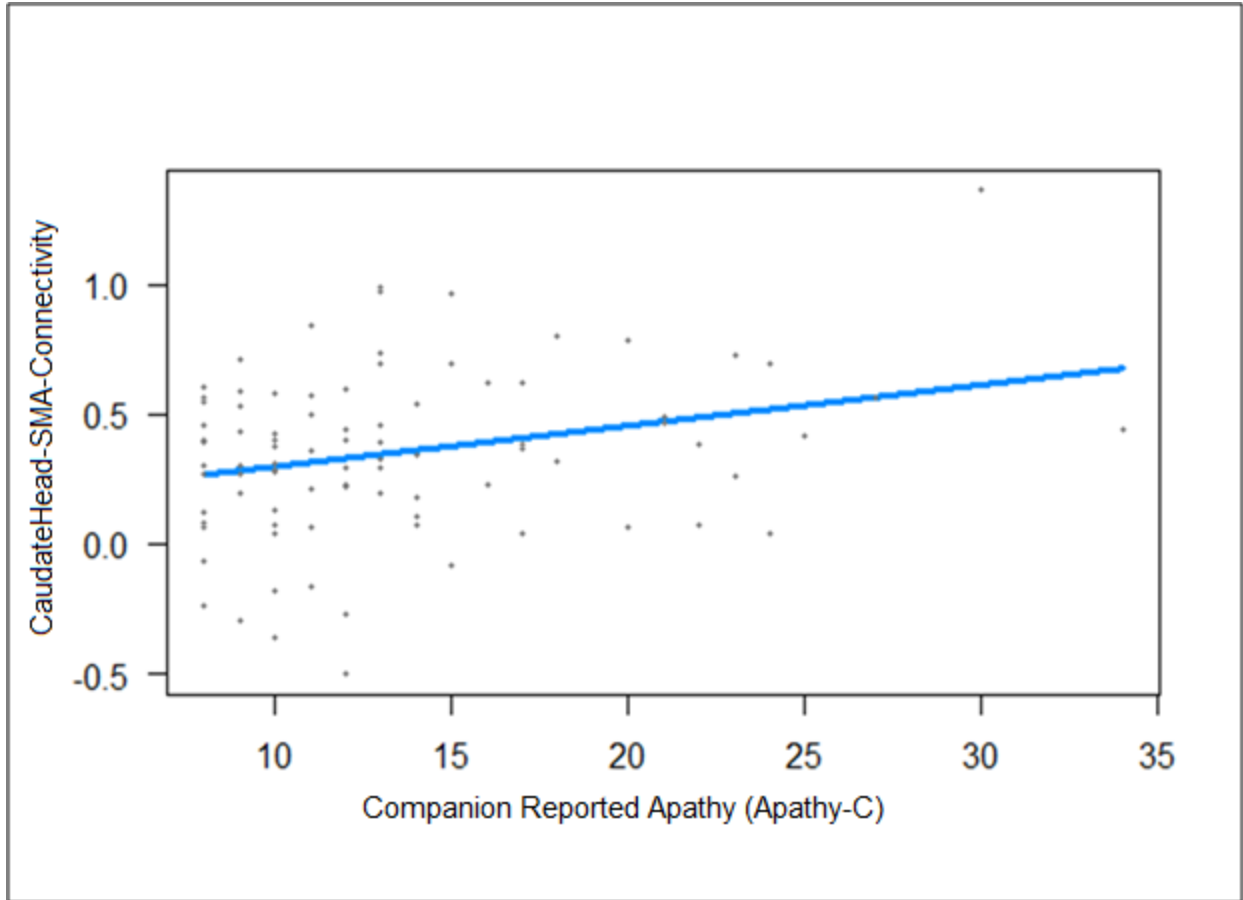


Figure 3: Companion Reported Apathy vs. CaudateHead-SMA Connectivity

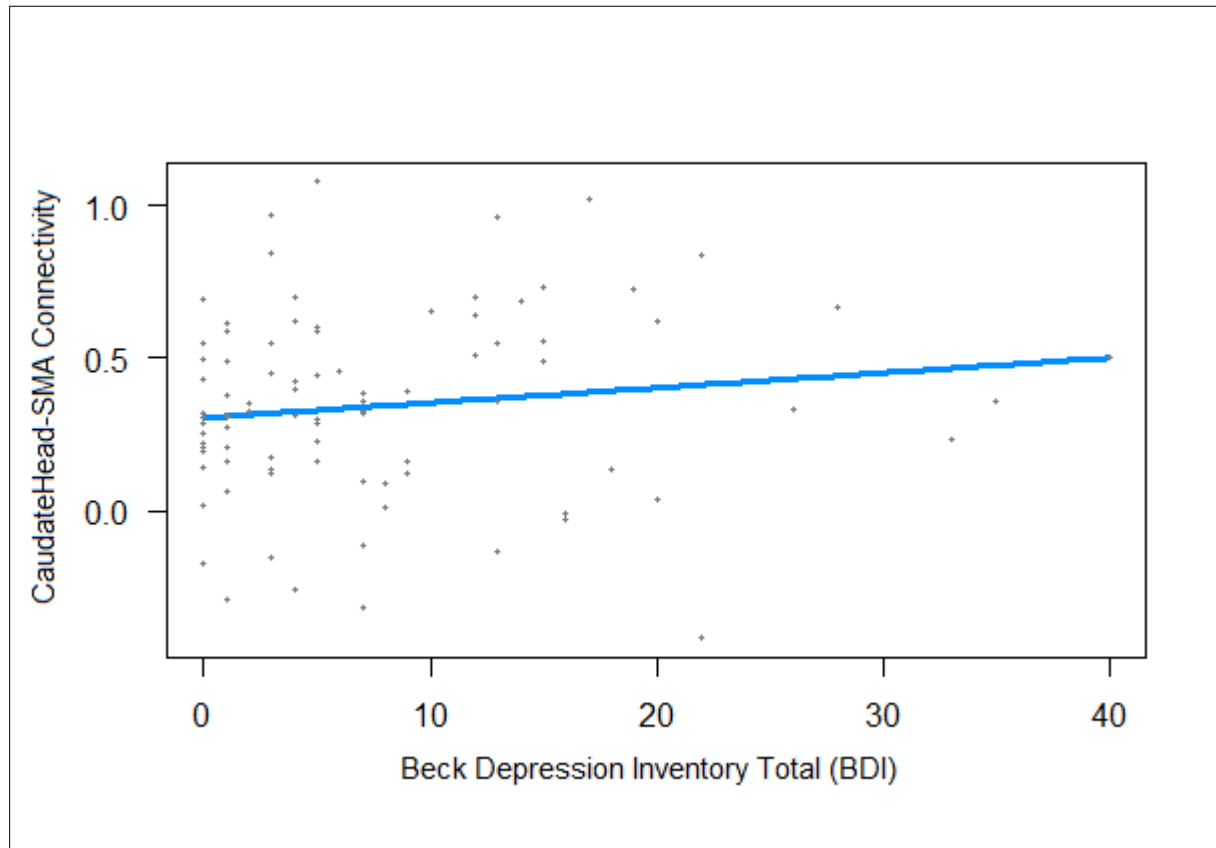


Figure 4: Beck Depression Inventory Total vs. CaudateHead-SMA Connectivity

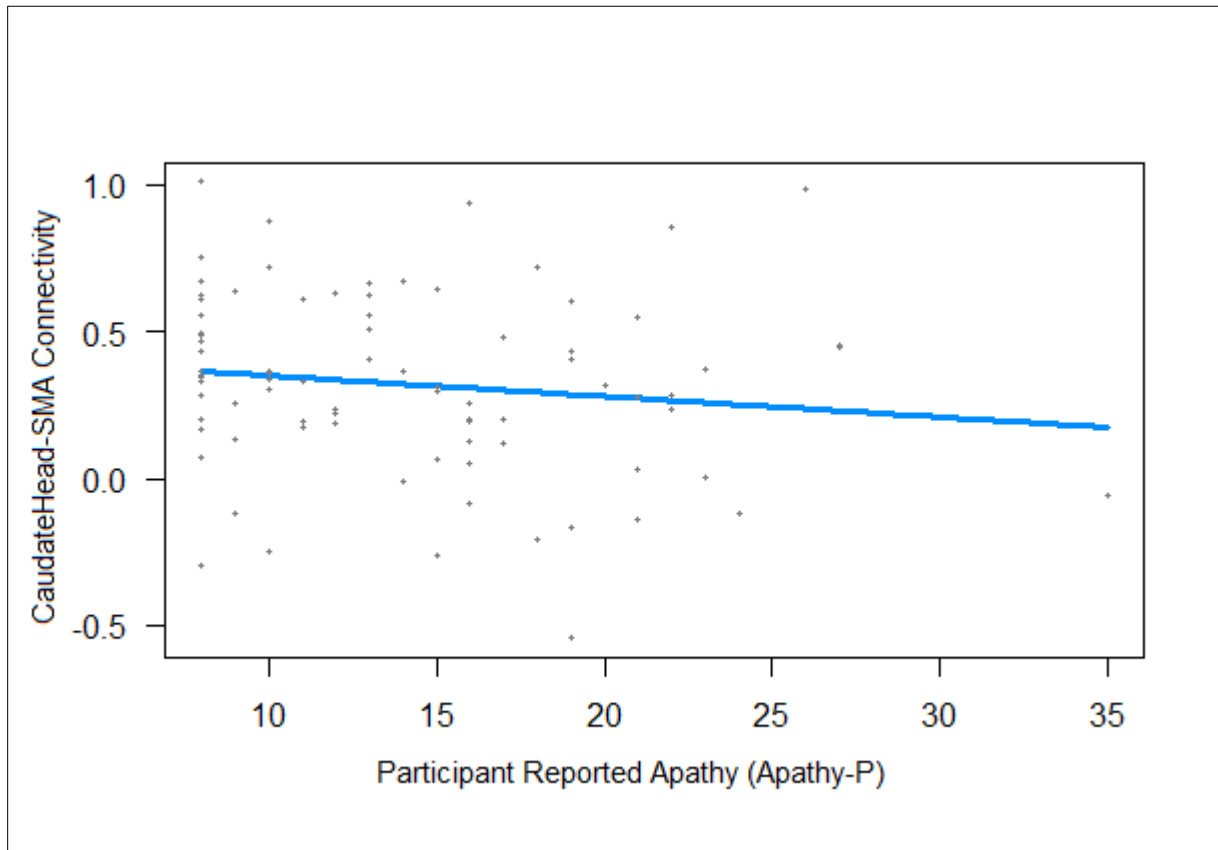


Figure 5: Participant Reported Apathy vs. CaudateHead-SMA Connectivity

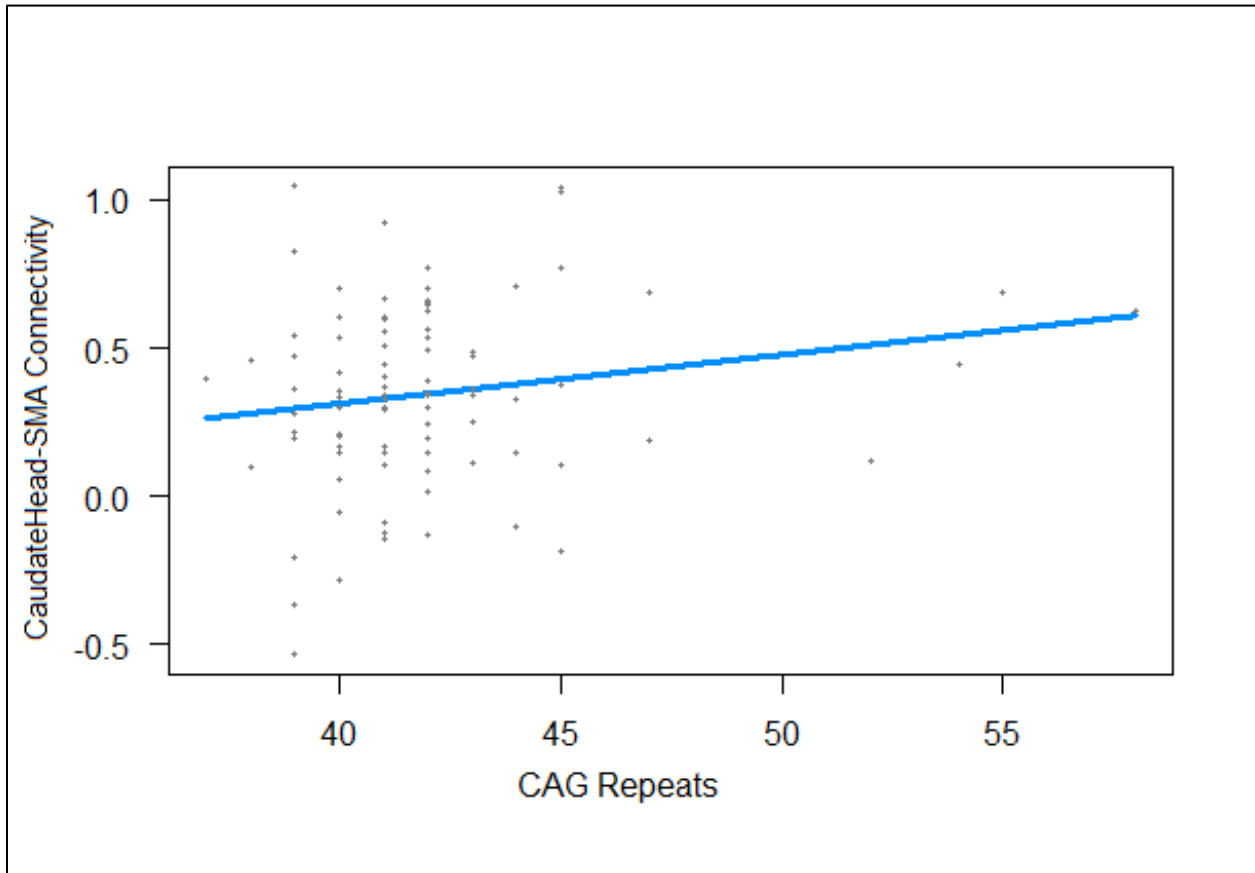


Figure 6: CAG Repeats vs. CaudateHeadSMA Connectivity

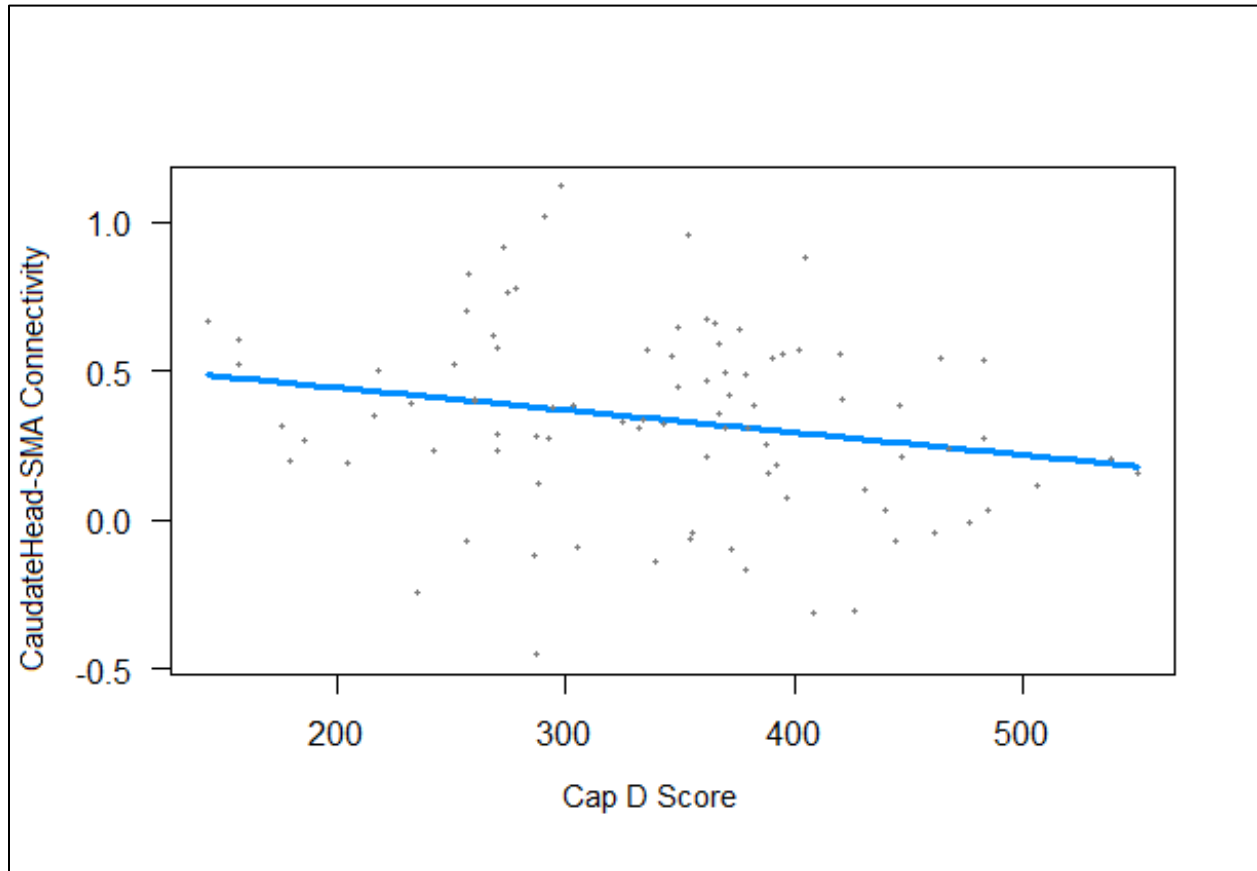


Figure 7: CapD Score vs. CaudateHead-SMA Connectivity

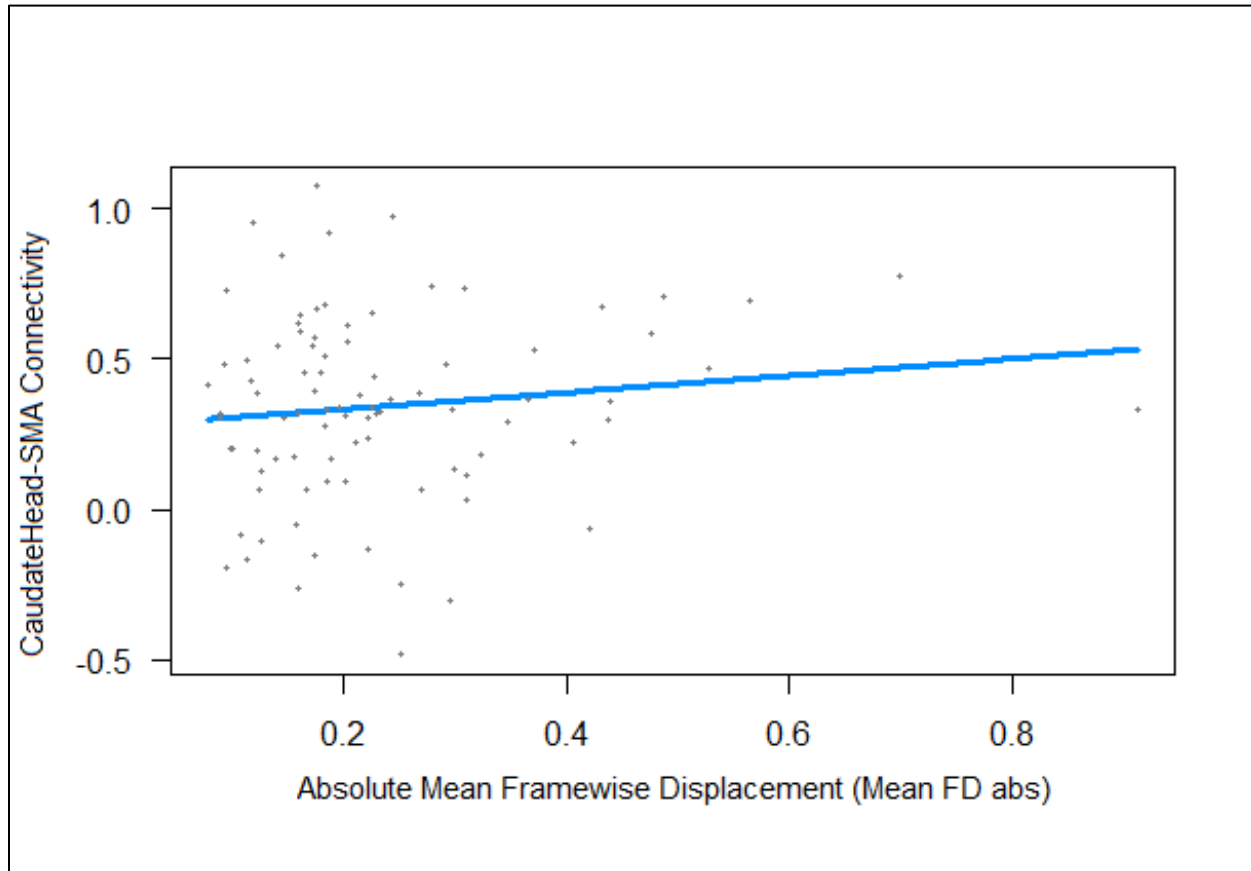


Figure 8: Absolute Mean Framewise Displacement vs. CaudateHead-SMA Connectivity

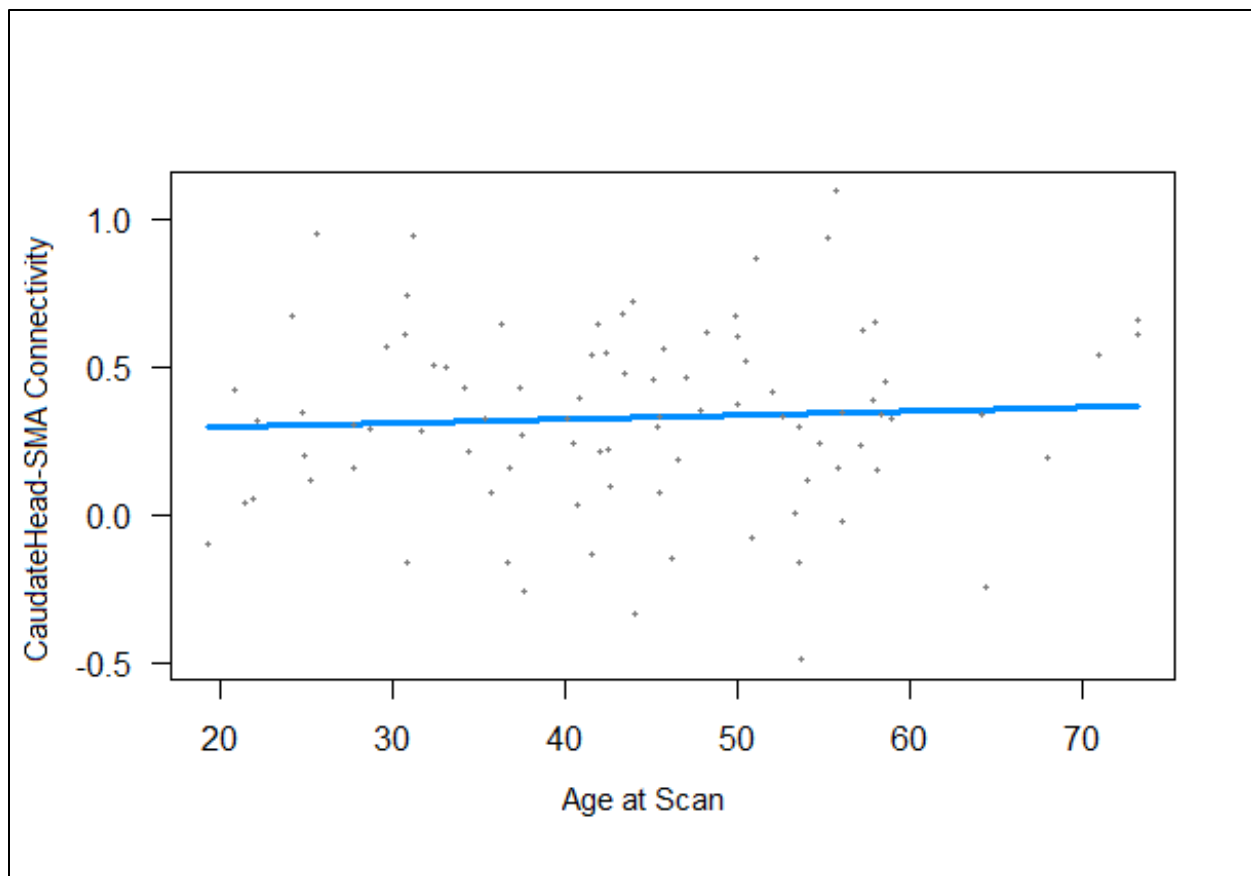


Figure 9: Age at Scan vs. CaudateHead-SMA Connectivity

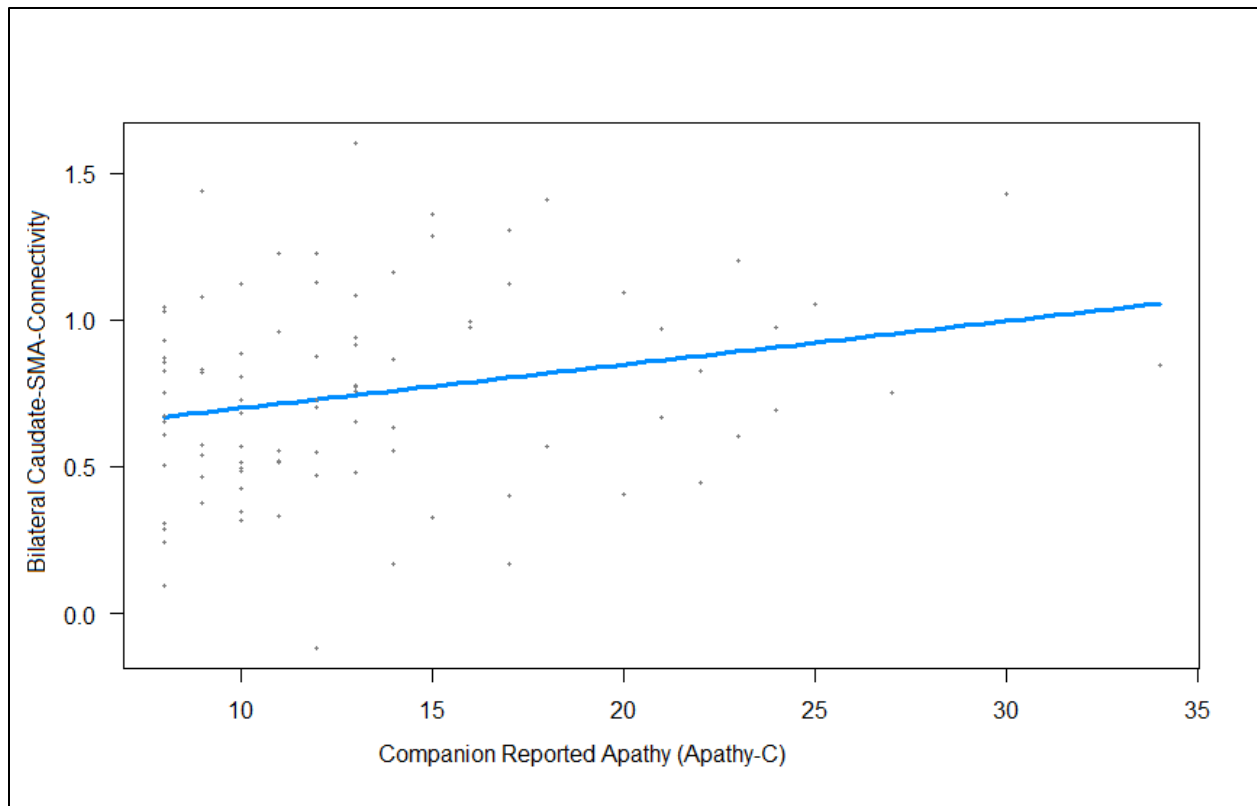


Figure 10: Companion Reported Apathy vs. Bilateral Caudate-SMA Connectivity

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