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Apathy and Striatal Gray Matter Patterns in Schizophrenia and Huntington's Disease

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Abstract

Apathy is a symptom of many neurodegenerative and neuropsychiatric disorders, such as Huntington's disease and schizophrenia. Apathy is often conceptualized as a combination of three domains, cognitive, behavioral, and emotional, characterized by impaired goal-directed behavior. The striatum has been shown to be significantly associated with executive functions and planned motor behavior via projection to the prefrontal cortex (PFC). Due to its connection to the PFC and its involvement in the basal ganglia motor circuit, the striatum is thought to be a significant part of the circuit that controls goal-directed behavior. The purpose of this study was to investigate the relationship between apathy severity and dorsal striatal grey matter concentration across several disorders, specifically Huntington's disease and schizophrenia. With access to the PREDICT-HD and FBIRN datasets, structural MRI images and clinical assessments were collected from 823 and 178 participants, respectively. We employed the use of SBM to isolate relevant basal ganglia components and used the resulting loading coefficients for a multivariate analysis. In parallel, we also conducted a univariate analysis using segmented subcortical volumetric data. We then constructed a mixed linear model to examine the relationship between apathy and any gray matter patterns in the striatum. In Huntington's disease, our results indicate that apathy is significantly related to the caudate and putamen atrophy with covarying in the medial PFC. In schizophrenia, our results indicate that apathy is significantly related to the putamen with covarying regions in the gyrus rectus and orbital medial PFC. We concluded that Huntington's disease and schizophrenia manifest apathy in different ways in unique structures.

Apathy and Striatal Gray Matter Decay in Schizophrenia and Huntington's Disease

Huntington's disease (HD) is a progressive neurodegenerative disorder characterized by involuntary movement and cognitive impairments stemming from a genetic abnormality in the *HTT* gene (Ciarochi et al., 2016). Schizophrenia is a progressive disorder characterized by an array of psychotic, affective, and cognitive symptoms, including hallucinations, anhedonia, and attention deficits. Despite being different classes of disorders, HD and schizophrenia share a specific negative symptom in the form of apathy, which is often conceptualized as a lack of motivation to act and quantified as a pathology of goal-directed behavior. Furthermore, the striatum, consisting of areas such as the caudate, putamen, pallidum, and nucleus accumbens, is an area often associated with both disorders and is heavily implicated in the physiological mechanisms behind apathy. If it is the case that the physiological underpinnings of apathy reside in the dorsal striatum and this area is also a common target implicated in both disorders, then it stands to reason that comparing gray matter volume in the dorsal striatum and apathy scores of patients of both diseases might yield a similar pattern.

Even though apathy is a common symptom reported in both disorders, defining the construct of apathy has been a challenge for researchers. Currently, apathy is generally defined as a reduction in goal-directed behavior. However, goal-directed behavior requires a series of cognitive steps, including planning, initiation, and execution, which means that apathy represents a break down at any point during processing. There are three general types of apathy: emotional, cognitive, and auto-activation. The emotional domain of apathy refers to reduced ability to appropriately associate affective signals to behavior and external stimuli, which can lead to the misrepresentation of rewards and the inability to process behavioral consequences. The cognitive domain of apathy refers to deficits in the cognitive ability to plan the intended action; apathy, in

this case, could stem from issues with working memory and the generation of strategies. The auto-activation domain of apathy refers to difficulty in engaging the motor program necessary for the behavior or any thought process related to the intended behavior. Given these three conceptualizations of apathy, the one most related to the dorsal striatum is the cognitive domain, since it is highly related to executive function, which might implicate the striatal projections to the PFC.

The basal ganglia, more specifically the striatum, has been found to be heavily implicated in the development and execution of goal-directed behaviors, especially in aspects of motivation like reward prediction and learning, through its projections to the prefrontal cortex (PFC) (Levy & Dubois, 2006; Gradin et al., 2011). As a whole, the basal ganglia is thought to transform cortical signals into directed behavior and, as such, is implicated in motor learning, habits, and the selection of actions. Furthermore, it also thought that, through the co-activation of the direct and indirect pathway, the basal ganglia could promote and suppress specific motor programs based on cortical input (Cui et al., 2013). If this is the case, then lesions in the basal ganglia could definitely be a critical factor in the onset of apathy. The striatum has several key cortical inputs that have been found to be related to apathy. The dorsal striatum, more specifically the caudate, is connected to the lateral PFC; lesions to this circuit has been found to impair working memory, ability to generate strategies and other related abilities that represent the disruption of the cognitive process, which may lead to apathy. Other areas, such as the pallidum and nucleus accumbens, have also been implicated in the onset of apathy since they are involved in a functional circuit with the orbital-medial PFC, which seems likely to play an important role in the flow of affective information due to its limbic and sensory inputs (Levy & Dubois, 2006). The orbital-medial PFC projects to the caudate and ventral striatum; subsequent output from

these structures end up terminating at the pallidum and substantia nigra pars reticulata. This connection between orbital-medial PFC and striatum seems to play an essential role in the processing and allocation of emotional information. For these reasons, the present study will focus on the striatum, particularly the caudate, putamen, and globus pallidus.

Apathy is one of the most reported symptoms in HD with reported rates of 48% or higher depending on the sample and methodology (Rosenblatt & Leroi, 2000; Paulsen et al., 2001; van Dujin et al., 2010). Although the basal ganglia and PFC are heavily implicated in apathy in other disorders, the neural mechanisms are not very well understood in the context of HD (Levy & Dubois, 2006). However, recent HD studies looking at gray matter concentration in the basal ganglia have found that dorsal striatal gray matter concentration decreases across prodromal HD stages and that apathy is related to these gray matter patterns (Ciarochi et al., 2016; Misiura et al., 2019). Considering the literature on apathy, results implicating the caudate and putamen are not surprising, since they've been found to be significant in other neurodegenerative disorders (Carriere et al., 2014; Gradin et al., 2011; Bruen et al., 2008). Other areas that are usually implicated in apathy, such as the pallidum and nucleus accumbens, have yet to be discovered in the context of HD.

Barch & Dowd (2010) suggest that individuals with schizophrenia suffer from apathy because they have a hard time using information from previous experiences to drive current and future behavior. The implication here is that other facets of goal-directed behavior, such as the hedonics and planning aspect, theoretically remain intact. Fronto-striatal circuits are thought to underlie relevant behaviors, such as reward prediction and some aspects of reinforcement learning. Evidence from fMRI studies using reward anticipation tasks specifically identify the dorsal striatum as a key structure in predicting rewards and differentially activating to prediction

errors (Knutson et al., 2000; Mucci et al., 2015). The dorsal striatum has also been implicated in learning deficits from reward feedback (Koch et al., 2010). In addition, the caudate and nucleus have been found to be differentially responsible for different aspects of reward expectancy. Haruno & Kawato (2006) found that the putamen was correlated with stimulus-reward association, while the caudate was correlated with reward prediction error. Furthermore, there are studies that use monetary incentive tasks on schizophrenic patients that find reduced activation exclusively in the putamen, caudate, or both (Knustson et al., 2000; Koch et al., 2010; Mucci et al., 2015). The ventral striatum is a well-known area in the field of reward due to its role in the dopaminergic mesolimbic pathway. Several fMRI studies confirm its involvement in the manifestation of apathy in schizophrenia patients, especially with positive prediction errors of reward (Berns et al., 2001; Kirschner et al., 2016; Simon et al., 2010). As a result, it stands to reason that a decrease in activation within the striatum could lead to an inability to process future rewards properly and, therefore, be unable to initiate the proper mechanisms that lead to behavior. Studies using structural imaging of schizophrenia patients have yet to identify the basal ganglia and have mostly identified gray matter decreases in frontal regions and the ACC (Bortolon et al., 2018). Theoretically, it is thought that apathy should be related to the fronto-striatal circuits since there are known connections between these regions and they've been implicated in key processes related to apathy, such as emotional processing, executive planning, and motor function. This seems to be supported by the functional evidence that identifies both frontal and striatal regions in the same and different tasks.

This study will examine the relationship between apathy and gray matter volume in the striatum across schizophrenia and HD. To do this, we will use structural T1 images and psychiatric measurements from the Neurobiological Predictors of Huntington's Disease

(PREDICT-HD) and the Function Biomedical Informatics Research Network Data Repository (FBIRN) datasets. Independent component analysis (ICA) will then be used to isolate components that maximally represent the specific structures within the striatum and, in combination with apathy measures from the corresponding scale in each dataset, a regression model will be built to examine the relationship between apathy and each of these components. In addition, we will also make separate regression models with subcortical volumetric data for the relevant structures. Since apathy is one of the most reported prodromal HD symptoms and correlates with increasing severity of HD symptoms, this study included participants in various prodromal stages of HD to maximize participants. The central hypothesis is that apathy will be highly related to decreased striatal, specifically caudate, putamen, and globus pallidus, gray matter, and this pattern will hold in schizophrenia and HD.

Methods

Participants

For HD, the data was extracted from the PREDICT-HD dataset, which includes data from 32 different sites (Paulsen et al., 2008). This dataset includes over 1400 prodromal and healthy controls over the age of 18. In this data set, demographic information, such as sex and age, and HD specific symptomology information, such as motor, cognitive, and psychiatric scores, were included for the participants, although some participants are missing certain items. In this study, we used all participants who had neuroimaging data along with the following variables: apathy, depression, intracranial volume, and subcortical volume (n = 823) (Table 1). Out of these participants, 174 of them were healthy controls, which means even though their family history indicates a risk of HD, they lack the genetic mutation. For more information regarding data collection, please refer to Paulsen et al., (2014).

For schizophrenia, the data was extracted from the FBIRN dataset, which includes data from 7 different sites (Keator et al., 2016). This dataset includes sMRI, fMRI, DTI, behavioral, and demographic data. It also included clinical assessments, such as the SANS, providing symptological information about schizophrenia patients. In this study, we used all participants that had neuroimaging data along with the following variables: apathy, depression, intracranial volume, and subcortical volume (n = 178) (Table 2).

Table 1
PREDICT-HD Demographics

Characteristics	prHD (n = 649) Mean (SD)	Controls (n = 174) Mean (SD)
Sex (M/F)	236/413	61/113
Age	39.81 (10.61)	44.1 (11.93)
Low/Medium/High	201/226/222	N/A
Apathy	12.29 (5.42)	10.84 (4)
Depression	52.7 (13.31)	48.8 (10.34)

Note. Low/Medium/High group categories denote prHD disease stage, based on CAPd scores, as defined by Zhang et al., 2011.

Table 2
FBIRN Demographics

Characteristics	Schizophrenia (n = 178) Mean (SD)
Sex (M/F)	133/45
Age	39.06 (11.49)
Apathy-Avolition	3.33 (2.22)
Global Apathy	4.75 (3.27)
Depression	2.21 (1.3)

Clinical Scores

For prHD, the apathy scores used for this study were from a modified 24-item form of the UHDRS apathy subscale, which asks questions about recent behavior (Grace, 2011). This apathy subscale score is calculated as a summation of eight apathy related items (Duff et al., 2010). We used companion-reported apathy scores for this analysis because previous research suggests that companion ratings are more consistently associated with disease progression. Depression scores for this study were taken from the Symptom Checklist 90 (SCL90) depression subscale. Companion reported scores were used to maintain consistency with apathy items.

For schizophrenia, the apathy scores used were from two measures of the SANS. The first measure we used was the global apathy score, which is a subjective rating of apathy as a whole without any specific restrictions, and the second measure consisted of averaging avolition and apathy measurements in an attempt to represent apathy better. Depression scores were sourced from the PANSS depression item.

Preprocessing

For PREDICT-HD, the segmentation methods of SPM5 were used to normalize images to Montreal Neurological Institute (MNI) space, reslice to 2×2×2 mm, and segment into gray, white, and CSF images (Ashburner & Friston, 2000). Data quality was checked by correlations against the segmented templates with a threshold of 0.9. When the subject's segmented gray matter data did not meet or exceed the threshold, it was removed from consideration. Data were smoothed by a Gaussian filter of 10 mm Full Width Half Maximum (FWHM). See Ciarochi et al., (2016) for further details.

For FBIRN, we used T1-weighted structural MRI images that were normalized to the standard MNI template using a 12-parameter affine model, resliced to a voxel size of $2 \times 2 \times 2$ mm, and segmented into GM, white matter, and CSF using SPM12. Data were smoothed by a Gaussian filter of 10 mm Full Width Half Maximum (FWHM). See Menningen et al., (2019) for further details.

Brain Volumes

For PREDICT-HD, we used subcortical volumes extracted from high-resolution T1 images using the BRAINSTools algorithm (Ghayoor, Vaidya, & Johnson, 2013; Kim, Magnotta, Liu, & Johnson, 2014). For FBIRN, volumes were extracted using FreeSurfer 5.1 (van Erp et al., 2016). The subcortical volumes that were used in this study included the caudate, putamen, and thalamus. The caudate and putamen are areas of interest that have been found to be related to apathy, while the thalamus was used as a control (Aylward, Nopolous, et al., 2011). For the models using these volumes, we calculated them as a percentage of ICV.

Source-Based Morphometry

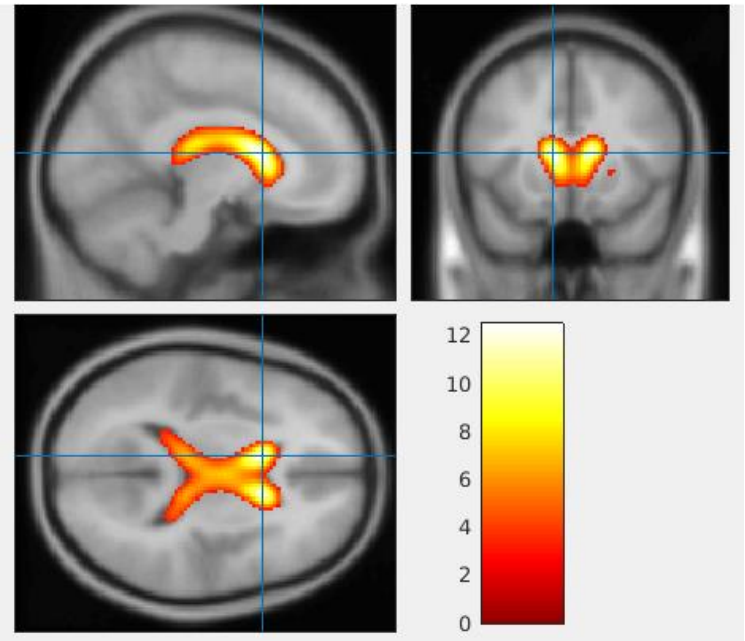
Using the GIFT toolbox in MATLAB, source-based morphometry was used to extract components, via ICA, from preprocessed (segmented, normalized, unmodulated, and smoothed)

gray matter images. The number of components was determined to be 23 for the PREDICT-HD dataset and 25 for the FBIRN dataset by a minimum description length (MDL) criterion. Using the infomax algorithm, the resulting one-dimensional matrix for each component was divided into a mixing matrix, which expresses the relationship between the subjects and components, and source matrix, which expresses the relationship between the components and brain voxels. For the mixing matrix, each row indicates how each component contributes to a single subject, while each column indicates the contribution of one component to all subjects. Conversely, each row of the source matrix indicates how one component contributes to different brain voxels, while the columns indicate how one voxel contributes to each component. As a result, this yields a loading coefficient and a spatial map for each component. To ensure the reliability of these components, the ICASSO software package was used to confirm the stability of each component (20 iterations and minimum stability of 0.90).

After obtaining the resulting spatial maps for the components, we manually selected components that contained significant gray matter variation in the striatum, specifically the caudate, putamen, pallidum, and nucleus accumbens. This was done by analyzing the spatial maps using xjview with a threshold of $z \geq 3$ and looking for gray matter variation in the component. First, we isolated the global maximum to see the area that experiences the most variation. If the global maximum was not in the striatum, we located the striatum and observed to see if there was any significant variation. If there was no variation in the striatum, then we moved on to the next component. Ultimately, we found three components of this nature in the HD (Figures 1-3) analysis and four components in the schizophrenia analysis (Figures 4-7). These components were included in subsequent models.

Figure 1

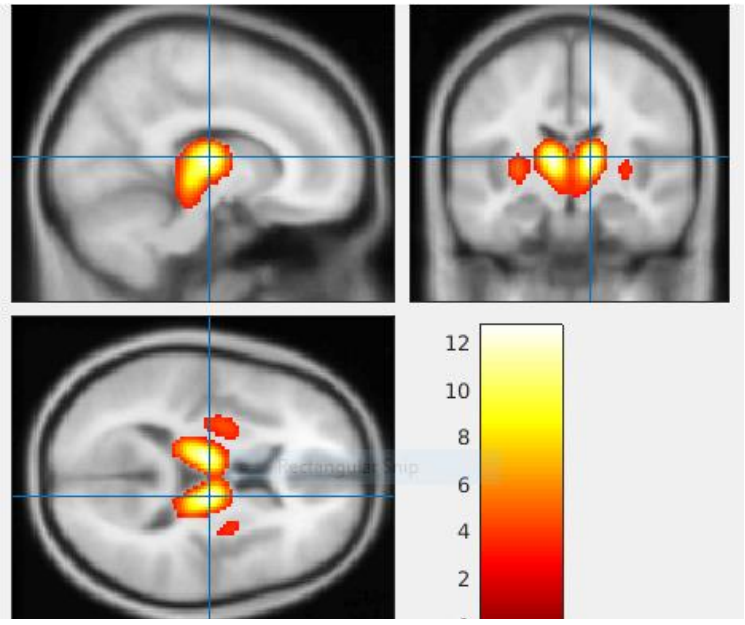
PREDICT-HD Component #3



Note. These values represent negative z values. This component mainly represents the caudate.

Figure 2

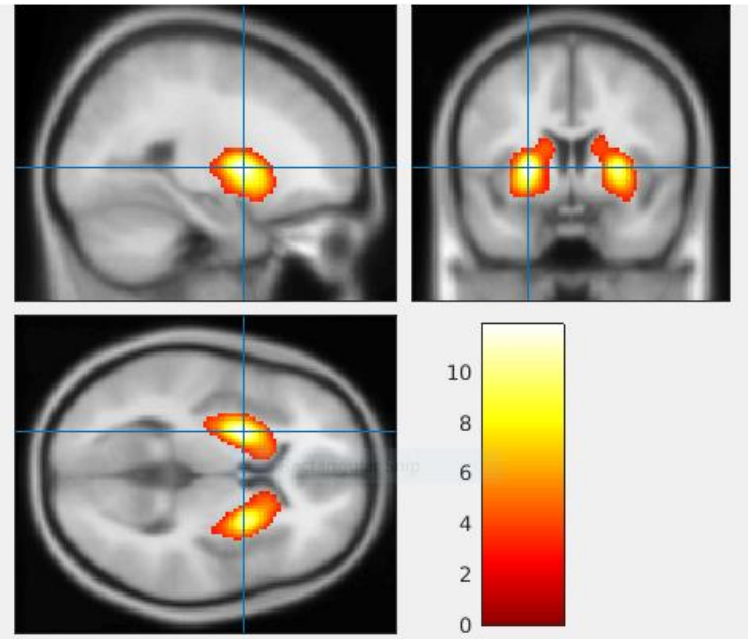
PREDICT-HD Component #5



Note. These values represent negative z values. This component mainly represents the thalamus.

Figure 3

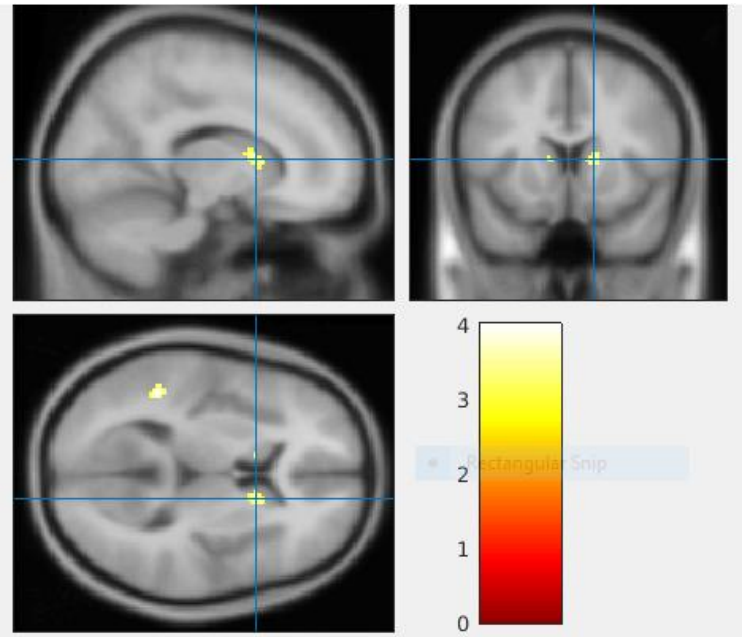
PREDICT-HD Component #17



Note. These values represent negative z values. This component mainly represents the putamen.

Figure 4

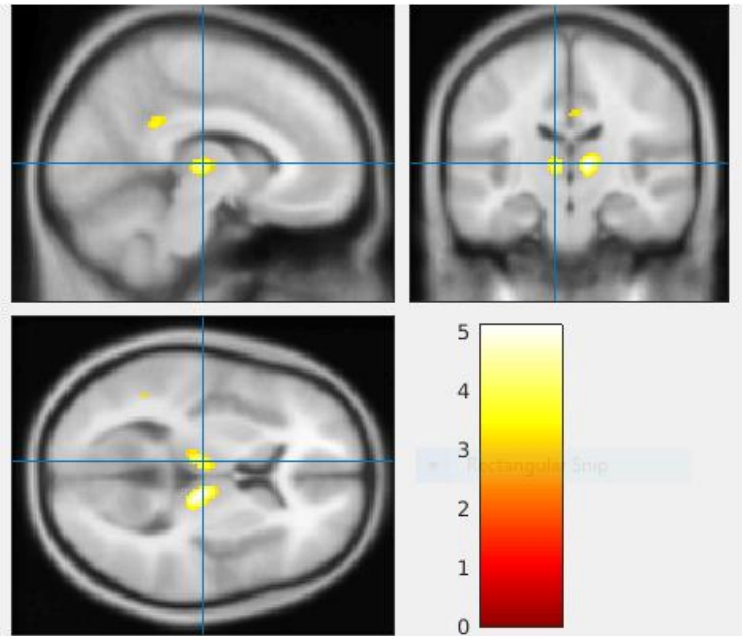
FBIRN Component #1



Note. These values represent negative z values. This component mainly represents the caudate.

Figure 5

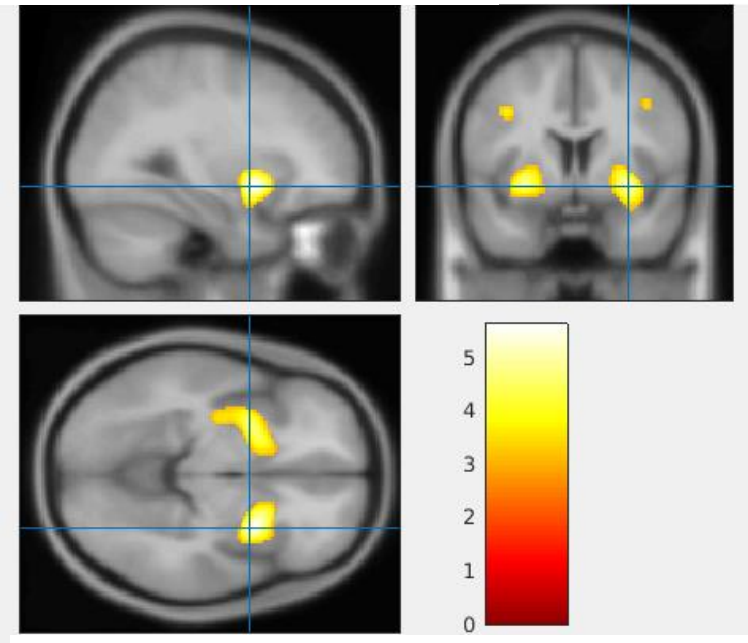
FBIRN Component #11



Note. These values represent positive z values. This component mainly represents the thalamus

Figure 6

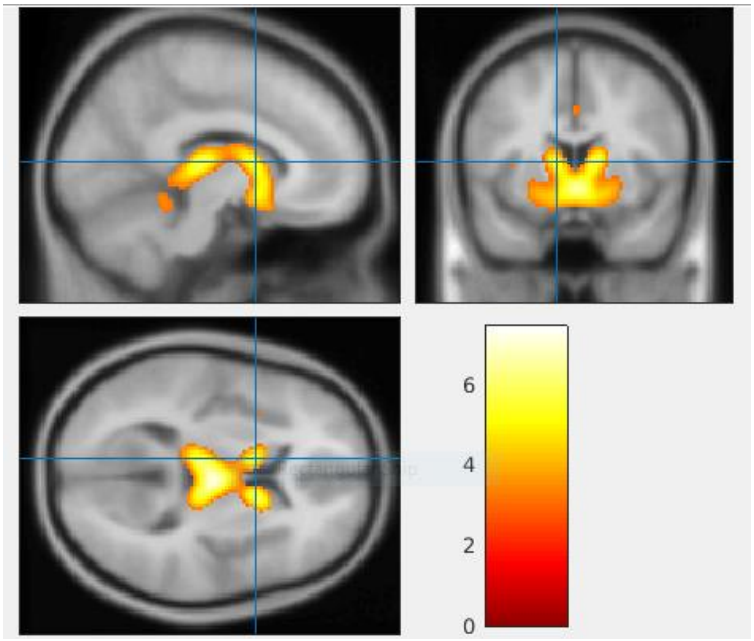
FBIRN Component #15



Note. These values represent negative z values. This component mainly represents the putamen

Figure 7

FBIRN Component #16



Note. These values represent positive z values. This component shows gray matter variation in the caudate, putamen, and thalamus.

Regression Models

We constructed various mixed linear models with the lme4 package (Verbeke & Molenberghs, 2000) in R to account for the site as a random-effects factor. Sex and disease stage were included as fixed factors, while age and ICV were modeled as continuous covariates. To ensure that the models detect relationships related to apathy, we included depression as a covariate due to their potentially significant relationship. The dependent variable in each model was apathy, while the independent variables consisted of the SBM components or segmented subcortical volumes. Due to the abnormal distribution of the residuals and variables in the regression model, we decided to normalize apathy, depression, age, sex, ICV, and the subcortical volumes through a square-root transformation. Outliers greater than 3 standard deviations did not significantly affect the results.

For prHD, we constructed four regression models for the SBM analysis and subcortical volumes respectively. The first one included all the components and subcortical volumes, in their respective models, as independent variables (inclusive model). The rest of the models analyzed the relationship of apathy with each component or subcortical volume without taking into account the other measures (isolation models). Additionally, we also constructed regression models without controls for the sake of consistency with the schizophrenia data.

For schizophrenia, we initially constructed five regression models for the SBM analysis and subcortical volumes, respectively. The first one included all of the components (inclusive model) and subcortical volumes, in their respective models, as independent variables. The rest of the models analyzed the relationship of apathy with each component or subcortical volume without taking into account the other measures (isolation models).

Results

Prodromal Huntington's Disease

Apathy was significantly related to caudate gray matter volume in both the SBM ($\beta = -0.09$; $t(814) = 2.31$; $p < 0.05$) and BRAINSTools isolation models ($\beta = -0.12$; $t(814) = -3.43$; $p < 0.05$). These significant relationships with the caudate were also found in the inclusive model. There seems to be a negative relationship between apathy and gray matter in the caudate, so apathy increases as gray matter volume in the caudate decreases. This pattern holds for the putamen in the BRAINSTools model ($\beta = -0.12$; $t(814) = -3.06$; $p < 0.05$), but only for the isolation model. No such relationship was found with the resulting SBM component most representative of the putamen ($\beta = -0.02$; $t(814) = -0.66$; $p > 0.05$). There was no significant relationship between the thalamus in the BRAINSTools model ($\beta = -0.02$; $t(814) = -0.789$; $p > 0.05$) or SBM model ($\beta = -0.02$; $t(814) = -0.62$; $p > 0.05$). Age displayed a significant negative

relationship with apathy (β = -0.08; t(814) = - 2.5; p < 0.05). All of these results were replicated in the models that excluded controls (*n* = 649). As expected, apathy was significantly related to depression in all models. See table 3 and 4 contain for further details.

Table 3
prHD Apathy and caudate (SBM model)

Independent Variable	β Estimate	SE	t Value	t Value (No controls)
Low/Medium/High	0.004/-0.03/0.02	0.09/0.08/0.08	0.05/-0.33/0.26	NA/-0.36/0.24
ICV	-0.02	0.04	-0.51	-0.01
Sex	0.08	0.06	1.4	0.92
Age	-0.08	0.03	-2.5**	-2.6**
Depression	0.66	0.03	22.8***	20.68***
Component #3	-0.09	0.03	-2.76**	-2.71**

Note. * p < 0.05
** p < 0.01
*** p < 0.001

Table 4
prHD Apathy and caudate (BRAINSTools model)

Independent Variable	β Estimate	SE	t Value	t Value (No controls)
Low/Medium/High	-.01/-0.07/-0.05	0.08/0.08/0.09	-0.06/-0.85/-0.59	NA/-0.85/-0.64
Sex	0.08	0.06	1.473	0.87
Age	201/226/222	N/A	-2.48**	-2.62**
Depression	0.66	0.03	22.96***	20.9***

Caudate volume	-0.12	0.03	-3.43***	-3.63***
Putamen volume	-0.12	0.04	-3.01**	-3.8***

Note. * $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

Schizophrenia

Apathy was significantly related to the putamen gray matter volume in the SBM model ($\beta = -0.69$; $t(170) = -2.48$; $p < 0.05$) (Table 4), while the FreeSurfer model didn't show any significant relationships. This result was replicated when the dependent variable was a combination of the SANS avolition and apathy scores ($\beta = -0.43$; $t(170) = -2.31$; $p < 0.05$). However, this result was only true in the models that included all components/volumes. The isolation model that only included the putamen component did not find a significant relationship with apathy ($\beta = -0.43$; $t(173) = -1.71$; $p > 0.05$). Post-hoc models including only components that had some overlap or relation to the putamen region (components 1 and 16) yielded a significant result ($\beta = -0.62$; $t(171) = -2.24$; $p < .05$). However, any combination of the three components yielded a significant relationship between component #15 and apathy. Volumetric data and components representative of the thalamus and caudate were not found to be significantly related to apathy. As expected, apathy was significantly related to depression in all models.

Table 4
SZ Apathy and putamen (SBM model)

Independent Variable	β Estimate	SE	t Value
ICV	-0.26	0.31	-0.82
Sex	1.05	0.64	1.65

Age	0.02	0.03	0.92
Depression	0.41	0.18	2.24*
Component #1	0.46	0.27	1.67
Component #11	-0.37	0.31	-1.2
Component #15	-0.69	0.28	-2.48*
Component #16	-0.23	0.28	-0.81

Note. * $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

Discussion

In HD, the results indicate a significant negative relationship between apathy and gray matter volume in the caudate and the putamen in the volumetric model, while the SBM model found a significant negative relationship only with the caudate. In schizophrenia, the results indicate a significant negative relationship between apathy and gray matter volume in the caudate in the SBM model, while the volumetric model didn't find any significant relationship with apathy. On top of this distinction, the SBM regression model that evaluated apathy as a function of the putamen component in the absence of the other components did not yield a significant result.

In the schizophrenia analysis, regression models differed on results based on the number of components included in the model. When all of the components were included in the model, there was a significant relationship between the putamen component and apathy. In contrast, when analyzing the relationship between apathy and the putamen component in isolation, no significant relationship is detected. This suggests that a significant relationship is only detectable when taking into account the error variance of the other components. One possibility is that there

are other components that also include the putamen, which introduce more variance into the model. To examine this a bit closer, we constructed models that examined the relationship of apathy three of the four components at a time with the putamen component being the only constant. All models were significant in this situation. This means that the putamen component does not seem to explain apathy in isolation and something from the other components is important for the putamen component's relationship with apathy. Prior literature supports the role of the putamen in apathy within the context of schizophrenia (Knustson et al., 2000; Koch et al., 2010), so we do not think this finding is insignificant. That being said, the state of the current analysis makes a bit complicated to clearly interpret these results, but it seems to us that the putamen component is related to apathy and is, therefore, worth discussing further.

While there does seem to be a similar physiological relationship with apathy in both disorder in the case of the putamen, HD models also implicated the caudate as region related to apathy. One reason for this discrepancy could be that HD and schizophrenia both induce apathy at different points in the process of goal-directed behavior, so these disorders could be affecting different structures that are associated with different features of apathy. Another reason could be due to the difference in how apathy is measured on the respective scales for each disorder (FrSBe vs. SANS).

Multidimensionality of Apathy

In this study, like most others, we used scales that define apathy along one dimension. The SANS and FrSBe have an apathy subscale, but both measure it as a one-dimensional concept. The main problem with using these scales is that it results in an attempt to collapse several dimensions, which potentially have different physiological profiles and forms of manifestation, into one. There is evidence to suggest that the three general dimensions of apathy,

cognitive, emotional (affective), and behavioral (auto-activation), manifest in unique structures within the fronto-basal ganglia circuit (Bortolon et al., 2014). In Levy & Dubois (2006), the authors describe the three aforementioned dimensions and review some evidence indicating that each dimension differentially affects unique frontal and striatal regions. They found that cognitive apathy, which is related to executive dysfunctions, is related to lesions in the lateral PFC and the head of the caudate nucleus. In the emotional domain of apathy, they found that it is related to the orbital and medial PFC projections to the ventral striatum. For the auto-activation domain, they found that it is related to the internal portion of the globus pallidus (GPi) and caudate. A more recent study found some similar results, showing that different neural circuits are involved with different profiles of apathy (Quaranta et al., 2012). This suggests that apathy isn't a one-dimensional symptom and it requires a multidimensional approach to fully encompass.

There are various problems with analyzing apathy with this paradigm. First, the number of items representing apathy varies. Depending on the items, this causes one scale to measure along a certain dimension more than the other, so the definition of the construct that is apathy is shifted in each scale. The global avolition/apathy item on the SANS can potentially mitigate the effect, but that also introduces a purely subjective rating of a symptom that requires caretakers to simultaneously consider the full range of their patient's behavior, which doesn't make for a good measurement in isolation. Second, the nature of the items is different. There may be items on one scale that try to measure some aspect of apathy (e.g., persistence) but no comparable items on the other scale. This can lead to one scale defining apathy more along a certain dimension than the others compared to the other scale, which leads to a difference in definition. Third, the items are worded differently. At first glance, this may seem a bit nitpicky to point out but years of

psychological research has shown that even the smallest of changes in the framing of questions or statements can cause people to perceive it differently. Following the same line of logic, the lack of standardization when it comes to the wording can create a serious issue when it comes to rating because the person rating could be rating apathy differently. This is, in no small part, due to the lack of consensus around a standard definition and diagnosis of apathy. All this being said, a lot of these scales may, in part, measure the other dimensions of apathy in some of its other items. For example, the SANS has an apathy subscale, which mainly focuses on behavioral apathy, but some of its other subscales, such as asociality and affective blunting, obviously delve into the territory of other domains. Even though these scales provide limited measurements of multiple dimensions of apathy, they also tend to measure more of one dimension than another. The lack of standardization prevents these scales to truly achieve construct and biological validity. When it comes to psychometric scales and accurate measurements, it is imperative that the construct is clear and items are standardized to ensure construct validity.

Schizophrenia and Huntington's Disease Neuroanatomy

Our results indicate that different areas in HD and schizophrenia were associated with apathy. For prodromal HD, we found that apathy was significantly related to a decrease in caudate and putamen gray matter volume. It is important to note that both the SBM and volumetric models indicated a significant relationship with the caudate, but only the volumetric model identified a relationship with the putamen. For schizophrenia, we found that apathy significantly related to a decrease in putamen gray matter volume. In this case, only the SBM model identified this relationship. These results are interesting in two ways: 1) different striatal structures were identified in each disorder and 2) the SBM and volumetric models produced different results.

The fact that certain structures were identified in each disorder is something that necessitates further discussion and study. Within the context of this study, this could be due to several reasons. The first reason is that apathy could manifest itself differently in each disorder, which is to say that it manifests through different structures and pathways. For HD, the main striatal region we found to be significantly related to apathy, with the SBM model, is the caudate nucleus. In this component, we also found other covarying areas, such as the putamen and medial frontal region, that also showed a decrease in gray matter volume. This makes sense within the context of other studies that have found similar results when looking at the relationship between apathy and striatal gray matter in prodromal HD (Misiura et al., 2019). The neuroimaging literature on prodromal HD has also repeatedly found both striatal and frontal dysfunctions with functional and structural analyses (Paulsen 2009). Although this correlation between gray matter patterns does not directly imply any type of connection between the caudate and covarying areas, there is some anatomical evidence to suggest connectivity between these regions (Levy & Dubois, 2006). In addition, the caudate nucleus and medial PFC are both implicated in the cognitive and auto-activation domains of apathy (Levy & Dubois, 2006). Given this neurological profile, it seems as if the apathy items in the FrSBe are mainly related to the aforementioned dimensions. This makes sense to an extent when one takes a look at the items on this scale, but, from just reading the items, it seems as if the scale is more biased towards the auto-activation domain since most items ask about initiative and self-initiation. Given the coinciding prevalence of the striatum and frontal regions in HD and apathy, it makes sense that the type of apathy that manifests in this disorder is within the cognitive and auto-activation domain. For schizophrenia, the main striatal region we found to significantly related to apathy is the putamen. Several imaging studies have identified hypoactivation of the putamen in schizophrenia in reward, with

primary and secondary reinforcers, and reinforcements tasks (Knustson et al., 2000; Koch et al., 2010; Waltz et al., 2009). The dorsal striatum, as a whole, is usually implicated in similar reward functions, although some studies have independently identified one or the other. The literature on this differentiation, however, is not developed enough to analyze the difference in function within the context of apathy. While our finding that putamen gray matter decrease is related to apathy is expected, it is a bit unexpected to only find that area. This could be due to the fact that the SANS apathy/avolition subscale only has three items with a global item. Models with the three items and the global rating as the independent variable yielded the same results. Having such a small number of items restricts out the ability to measure apathy in all of its complexity, opting instead for a perhaps an oversimplified model. Interestingly, the neural correlates of the SANS mostly coincide with the emotional and cognitive apathy, while its neuropsychological correlates coincide more with the cognitive domain (Morris et al., 2015; Levy & Dubois 2006). This is interesting because the items on the SANS apathy subscale seem to be constructed to measure behavioral apathy since the items mostly inquire about hygiene, persistence, and spontaneity. This might be another indication of the necessity to measure apathy with a multidimensional paradigm because it seems like the apathy items are measuring dimensions that do not coincide with their wording. The SBM component representative of the putamen covaries with the rectus and orbital medial frontal areas. The connection between the dorsal striatum and orbital/medial PFC is mostly associated with the emotional and cognitive domain (Bortolon et al., 2018; Levy & Dubois, 2006). From these results, it seems that the schizophrenic profile of apathy mainly consists of the emotional and cognitive domain. As shown above, it is very possible that these disorders, in which apathy is an important symptom, manifest different types of apathy. Having this type of biological validity associated without apathy measurements is

crucial to constructing effective pharmacological and/or therapeutic interventions. These different apathy profiles could also potentially serve as biomarkers for certain disorders. However, the lack of standardized items and multidimensional scales for apathy hinders our ability to properly assess apathy, which, in turn, prevents researchers, working in different disorders, to communicate and compare results effectively.

Interestingly, the observed differences between results in the SBM and segmented subcortical volume analyses are unique. In the prHD analysis, the volumetric model found a significant relationship with the putamen, while SBM did not. This could be due to the fact that component #3, which was designated as most representative of the caudate, also included the putamen. It could be that the putamen alone isn't predictive of apathy but is significantly related when in conjunction with the caudate. This would explain why component #3 was significant since it there are covarying voxels in both regions. This is further evidenced by the fact that the putamen was only found to be significantly related to apathy in the isolation model. In the inclusive model, this effect disappeared while the effect of the caudate remained. Again, this seems to suggest that, since the putamen is predictive apathy when you are not accounting for the caudate variance, the putamen's role might exist only in conjunction with the caudate. This might imply that the connectivity between the putamen and the caudate is the extent of the putamen's role. In the schizophrenia analysis, the SBM model found that component #15, which was designated as most representative of the putamen, was significantly related to apathy, while the volumetric models found no such relationship. This could be due to the different nature of the analyses. SBM is a multivariate approach that considers the relationship between the voxels, which can then be compared across groups, while the segmented subcortical volumes analysis was a univariate approach. SBM has been previously found to be able to detect the same regions

as other univariate analyses and other regions of interest that the univariate analysis could not (Xu et al., 2008). It is possible that this could just be representative of SBM being a more powerful analysis.

Limitations

This study had several limitations that need to be considered before interpreting the results. Broadly speaking, the type of analysis used was correlational in nature. SBM analysis examines the correlation between voxels to reveal underlying spatial patterns that are independent of one another. Although this method is a powerful multivariate way to evaluate the relationship between voxels and compare between groups, it relies on correlations between voxels. While it is tempting to assume that this correlation between voxels implies anatomical and functional connectivity, this may not be the case. As a result, the results of the regression analysis cannot be used to draw specific causal links on its own merit. Another problem is that we picked the SBM components manually and, therefore, introduced a subjective factor that is vulnerable to error. An automatic classification system, perhaps via machine learning, would greatly increase the validity of studies using the SBM approach.

With respect to PREDICT-HD and FBIRN, one of the differences is that our sample for PREDICT-HD included controls, while the sample for FBIRN did not. We do not think this had much impact on the results since we were studying apathy in the context of the disorders. However, we took measures to mitigate whatever effect this could have by running a parallel analysis on the prHD sample without controls. The results turned out to be the same, which supports the idea that this discrepancy did not have a significant impact on the results. Another difference was the algorithm used to segment the subcortical volumes; BRAINSTools was used for PREDICT-HD, while Freesurfer was used for FBIRN. This can introduce unneeded error

variance between the models, which could skew the results. Although we don't have any reason to believe this difference had a significant impact, the models should be treated as similarly as possible for the sake of valid comparison. There was also the issue of using different scales that are disease specific and attempting to compare one of their subscales. Even though this subject has already been thoroughly discussed above, it does present an issue because the relationships found in this study could have been based on the scales measuring different constructs or different dimensions of the same construct. The scale scores themselves pose an issue since they represent a simplification of a multidimensional symptom.

Conclusion

Our results suggest that there is different apathy related striatal gray matter patterns in HD and schizophrenia. Even though both disorders exhibited a decrease in gray matter volume, each disorder had a different structure that was significantly related to apathy. In HD, we found that caudate and putamen atrophy was significantly related to apathy, while, in schizophrenia, we found that putamen atrophy was significantly related to apathy. By using the multivariate analysis SBM, we were also able to identify other covarying areas within the significant components. For HD, we found that the caudate covaried with the putamen and medial frontal PFC. For schizophrenia, we found that the putamen covaried with the recuts and orbital medial frontal regions. Using previous studies indicating the multidimensionality of apathy, we discussed how the structures significantly related to apathy potentially mapped on to previously identified fronto-striatal circuits unique to certain dimensions. The fact that the results from both disorders mapped onto the different neural correlates of different dimensions could suggest that HD and schizophrenia manifest different profiles of apathy with unique neural underpinnings. It could also reflect the fact that scales used to measure apathy in these disorders defines it as a

one-dimensional symptom when the literature indicates that apathy is multifaceted. In other words, it could be that the scales measure one dimension more than the rest and this leads to the bias in our results.

Future studies attempting to compare apathy across several disorders should consider using scales that account for the different dimensions of apathy. To our knowledge, there are only two scales that take a multidimensional approach to measuring apathy: AES (Faerden et al., 2008) and LARS (Yazbek et al., 2014). By using these scales to compare across a population of both disorders, we could begin to have an effective and meaningful conversation about a standard definition for apathy. It will also allow researchers to start verifying the physiology of apathy, especially since the literature has contradictory results possible due to the lack of scales that consider the multidimensionality of apathy (Bortolon et al., 2018). Another reason the apathy literature is in such an erratic state is that there is no base that unifies or enables the comparison of the current findings. If there is no consensus around a definition of apathy, then there's no way to uncover its true physiology since the scales we depend on will measure different aspects of the construct. Future studies should also focus more on the actual connections between regions, which can be achieved through analyses like DTI. It is essential to verify the impact of the previously implicated dopaminergic fronto-striatal projections directly as opposed to inferring it from similar symptomology due to independent lesions of two different regions.

To construct proper pharmacological and therapeutic interventions for apathy and these disorders as a whole, it is imperative that the psychiatric community works towards a consensus on the definition of apathy so that future scales can be standardized. It is also important that the community works towards scales that measure apathy with a multidimensional paradigm. This

will enable the community to create and verify biologically relevant apathy measurements that will enable the effective crosstalk between symptomological data across disorders. This will, undoubtedly, lead a much better understanding of apathy and its parent disorders, which could result in novel and effective treatment methods.

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