Defining the distinction: neural and cognitive correlates of apathy & depression in prodromal huntington's disease

Maria Misiura

Follow this and additional works at: https://scholarworks.gsu.edu/psych_theses

Recommended Citation
https://scholarworks.gsu.edu/psych_theses/165

This Thesis is brought to you for free and open access by the Department of Psychology at ScholarWorks @ Georgia State University. It has been accepted for inclusion in Psychology Theses by an authorized administrator of ScholarWorks @ Georgia State University. For more information, please contact scholarworks@gsu.edu.
DEFINING THE DISTINCTION:
NEURAL AND COGNITIVE CORRELATES OF APATHY & DEPRESSION IN
PRODROMAL HUNTINGTON’S DISEASE

by

MARIA MISIURA

Under the Direction of Jessica Turner, PhD

ABSTRACT

Huntington’s Disease (HD) is a debilitating genetic disorder characterized by motor, cognitive and psychiatric abnormalities. Among these psychiatric symptoms, apathy and depression are some of the most common mood symptoms in the pre-diagnosed population (prHD). This study examined the role of apathy and depression and their neural and cognitive correlates. We compared apathy and depression scores to measures of cognitive control, language, and motor symptoms in a sample of individuals with prHD. Additionally, we compared apathy and depression scores to activation in the default mode network, caudate, putamen, and supplementary motor area (SMA) during a timing task. We found that as apathy increases, cognitive control decreases. Increased activation in the SMA, during the task, was related to increased apathy. Increased depression was related to increased putamen activation.
Our results further support the distinction between apathy and depression. Understanding the nature of this distinction can aid in development of interventions.

INDEX WORDS: prodromal Huntington’s Disease, fMRI, apathy, depression, cognitive control
DEFINING THE DISTINCTION:
NEURAL AND COGNITIVE CORRELATES OF APATHY & DEPRESSION IN
PRODROMAL HUNTINGTON’S DISEASE

by

MARIA MISIURA

A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of
Master of Arts
in the College of Arts and Sciences
Georgia State University
2016
DEFINING THE DISTINCTION:
NEURAL AND COGNITIVE CORRELATES OF APATHY & DEPRESSION IN
PRODROMAL HUNTINGTON’S DISEASE

by

MARIA MISIURA

Committee Chair: Jessica Turner

Committee: Bruce Crosson
            Vince Calhoun

Electronic Version Approved:

Office of Graduate Studies
College of Arts and Sciences
Georgia State University
May 2016
DEDICATION

I dedicate this thesis to Asha Sterling, Brandon Byrd, and Arianna Bird. Their ongoing support for me has been invaluable.
ACKNOWLEDGEMENTS

I would like to acknowledge my committee members Bruce Crosson for providing me with informative references that have enriched this thesis, and Vince Calhoun for his guidance regarding the GIFT toolbox and its intricacies. I also would like to express my sincere gratitude for the support and direction with which my committee chair, Jessica Turner, has provided me.
TABLE OF CONTENTS

ACKNOWLEDGEMENTS ........................................................................................................ v

LIST OF TABLES .................................................................................................................. viii

LIST OF FIGURES ................................................................................................................ ix

1 INTRODUCTION .................................................................................................................. 1
  1.1 Purpose of the Study ....................................................................................................... 1
  1.2 Cognition in Prodromal Huntington’s Disease ................................................................. 2
  1.3 Neurological profile of Prodromal HD ............................................................................. 6
  1.4 Neural Correlates of Cognition in Prodromal HD ........................................................... 7
  1.5 Mood symptoms in basal ganglia disorders ..................................................................... 8
      1.5.1 Depression ................................................................................................................ 8
      1.5.2 Apathy ....................................................................................................................... 11
  1.6 Motor Tapping Task ...................................................................................................... 15
  1.7 Summary ......................................................................................................................... 16
  1.8 Aim 1 ............................................................................................................................... 17
  1.9 Aim 2 ............................................................................................................................... 17
  1.10 Expected Results ......................................................................................................... 18

2 METHODS ............................................................................................................................ 18
  2.1 Participants ...................................................................................................................... 18
      2.1.1 Neuropsychiatric Data .............................................................................................. 18
      2.1.2 fMRI Participants ..................................................................................................... 19
  2.2 Measures ........................................................................................................................ 20
      2.2.1 Depression & Apathy Scores .................................................................................. 20
LIST OF TABLES

Table 1 Participant Demographics for the clustering dataset..............................19

Table 1 Participant characteristics for clustering dataset........................................19

Table 2 Participant characteristics for the fMRI dataset........................................20
LIST OF FIGURES

Figure 1 Neuropsychiatric domains from clustering analysis ........................................ 6
Figure 2 Model of organization of goal directed behavior ............................................. 12
Figure 3 Structural fronto-striatal circuitry .................................................................. 14
Figure 4 Putamen Component ....................................................................................... 24
Figure 5 Precuneus/ middle temporal component ......................................................... 24
Figure 6 Middle temporal component .......................................................................... 25
Figure 7 Caudate Component ....................................................................................... 25
Figure 8 Supplementary Motor Area Component ......................................................... 26
Figure 9 Motor Symptom cluster score and apathy ...................................................... 28
Figure 10 Cognitive control clusters and apathy .......................................................... 29
Figure 11 Partial plot for depression scores against putamen loading coefficients .......... 30
Figure 12 Partial plot for apathy scores against supplementary motor area loading coefficients .................................................................................................................. 31
1 INTRODUCTION

1.1 Purpose of the Study

Huntington’s Disease is a debilitating genetic disorder characterized by jerky, involuntary movements, cognitive decline, and eventual loss of bodily control and function. An extended trinucleotide CAG repetition causes the neurological atrophy responsible for these symptoms, and individuals with more repetitions of CAG will have a more severe form of the disease (Chial, 2008). Huntington’s disease (HD) currently affects 12.3 to 17.2 people per 100,000 in the western world, and many more individuals are at risk for developing the disease (Evans et al., 2013; Fisher & Hayden, 2014). Death usually occurs within 15-20 years of clinical diagnosis, and the disease usually develops around age 40 (Ross & Tabrizi, 2011). An estimate of the age of onset can be provided by a simple blood test that determines the number of extraneous trinucleotide repeats an individual has in the HTT gene; any number greater than 36 indicates that an individual will develop the disease, and a higher number signifies more rapid onset (Paulsen et al., 2014). The prodromal HD population consists of anyone who tests positive for the genetic mutation (CAG repeat length > 36) but has not yet reached full motor diagnosis. A clinical diagnosis of HD requires a variety of severe motor, cognitive, and psychiatric symptoms. However, there is a wealth of research that suggests that cognitive, motor, and psychiatric changes in the prodromal population occur well before full clinical diagnosis (Paulsen, 2010; Paulsen et al., 2006; Paulsen et al., 2008).

Because individuals can be tested for the disease well before they are clinically diagnosed, we can evaluate what factors contribute to time to onset, and develop interventions, either behavioral or pharmaceutical, that may further delay onset. The Neurological Predictors of Huntington’s Disease (PREDICT-HD) has collected and analyzed data from over 1000
participants to identify biomarkers that may lead to increased accuracy in predicting time to onset (Paulsen et al., 2014). There are a variety of mood symptoms this study has identified that precede clinical diagnosis including irritability, obsessive compulsive tendencies, apathy, and depression (Duff et al., 2007; Epping & Paulsen, 2011). The purpose of our study is to further illuminate the distinction between apathy and depression in the prodromal HD (prHD) population.

Often times, apathy is characterized as a factor of depression, but in movement disorders, apathy can exist independent of depressive symptoms (Alexopoulos et al., 2013; Marin, 1991). To determine whether apathy and depression are indeed separate mood qualities in this population, we have analyzed behavioral as well as neuroimaging data in the context of apathy and depression.

1.2 Cognition in Prodromal Huntington’s Disease

PrHD individuals often exhibit deficits in executive function tasks, including those involving cognitive control, working memory, and procedural memory (Harrington et al., 2012; Papp et al., 2013; Snowden, Craufurd, Thompson, & Neary, 2002; Stout et al., 2011; Williams et al., 2015). In the prodromal population, cognitive decline is prevalent even before motor symptoms appear. On general measures of cognition, many studies found that prHD participants perform significantly worse than healthy, gene negative controls, especially on measures of executive function (K. V. Papp et al., 2013; K. V. Papp, Kaplan, & Snyder, 2011; Snowden, Craufurd, Thompson, & Neary, 2002b; J K Williams et al., 2014). In one publication from the large PREDICT-HD study involving over 900 prHD (Stout et al., 2011), findings shows that controls outperformed prHD individuals in 16 out of 19 cognitive tasks. There is widespread
evidence that prHD individuals exhibit cognitive deficits, and that these deficits increase over time.

A longitudinal PREDICT-HD study spanning 10 years examined the progression of cognitive decline and subcortical volumes in 1030 individuals (Paulsen et al., 2014). The purpose of this study was to identify which specific functional, cognitive, and imaging measures most accurately predict time to onset. Cognitive and motor assessments with the most robust measures of decline included the symbol-digit modalities test, the Stroop-color word test and dysrhythmia (Paulsen et al., 2014). The goal of the study was to examine longitudinal cognitive decline within the prodromal population, but it also presented a variety of scores that were significantly related to poorer functioning in the prHD in a cross-sectional analysis including a variety of Stroop tests, both trails making A and B, and a few tapping tasks. While there is a general consensus that there is cognitive decline in the prodromal population, there is inconsistency in the literature about which constructs are most sensitive to prHD individuals. This is driven by the fact that different scales and tests are used in different studies, and that the number of and type of participants varies widely across each study.

In order to remedy these inconsistencies, we have aggregated scores on cognitive tasks into variables that encompass large neuropsychiatric domains (Misiura et. al, 2015). Figure 1 shows the results of a hierarchical clustering analysis that was performed using a data-driven approach to identify groups or “variable clusters” that not only group together by content, but are also supported by the data itself. We chose to divide the data into 7 different clusters that show some intuitive validity, in that the measures in each cluster theoretically measure the same constructs. Our 7 domains include functional capacity, problem solving, language and memory, executive function, tapping performance, motor symptoms, and clinical symptoms. For this
analysis, we investigated the relationships between mood symptoms and executive function, language and memory, and motor symptom cluster scores.
Using a cross section of this same longitudinal data, we take this analysis a step further by considering how psychiatric measures may relate to cognition, and if there is a difference between the relationship of depression with cognition and apathy with cognition. Because there is evidence that these two constructs are indeed separate in the diagnosed population, apathy and depression may be related to distinct cognitive domains.

Although there is clear evidence that prHD individuals do experience cognitive deficits before clinical diagnosis, exactly which tests to include in further studies, and which tests are more robust to changes in extraneous variables (CAG repeat length, age, sample size), is still unclear. Our current sample size, extensive cognitive battery, and clustering approach allow us to identify which possible constructs might be more closely related to changes in prHD. Using the cluster analysis to determine which variables group together and represent different cognitive domains, we investigate the relationships of depression and apathy to cluster scores of language and memory, executive function, and motor symptoms.

1.3 Neurological profile of Prodromal HD

Morphological and structural changes are detectable in individuals with expanded HTT CAG repeats well before clinical diagnosis. These changes are particularly centered on the striatum. The striatum seems to be the region most severely effected by the HTT protein, and is the earliest detectable region of atrophy (Halliday et al., 1998; Paulsen et al., 2006; van den Bogaard et al., 2011; Wolf et al., 2011). Even individuals 15 years out from clinical diagnosis show early signs of striatum atrophy (Paulsen et al., 2010). Individuals in the prodromal phase...
of HD show accelerated rates of atrophy in total brain volumes, striatum, and in total white matter volumes, particularly in the frontal lobe (Aylward et al., 2011). Because the striatum exhibits such profound changes within prodromal HD, it is one of the brain regions of interest for this study, the others being the default mode network and its related regions, and the supplementary motor area. There are a variety of behavioral changes linked with brain morphology, and they are outlined below.

1.4 Neural Correlates of Cognition in Prodromal HD

Within the prodromal HD literature, cognitive changes relate to morphological abnormalities. Researchers have explored these relationships through a variety of cognitive tasks and imaging methods. Disease burden correlated with worse performance on a visuomotor task, and accelerated volume loss in the prefrontal cortex (Gómez-Ansón et al., 2009). Harrington et al. (2014) took a subset of the PREDICT-HD data set and extracted regional brain volumes that correlated specifically with changes in cognitive function on a fairly large sample size with a range of prHD levels of severity. When these brain volumes were correlated with performance on cognitive tasks, and psychiatric surveys, smaller caudate and putamen were found to relate to lower scores on the symbol digit modalities test and the Hopkins verbal learning test (Harrington et al., 2014).

Our clustering analysis reinforces the relationship between structure and function within this population. (Misiura, 2016). However, striatum volumes and CAG repeat length did not account for all of the variance within these cluster scores, allowing for the inclusion of additional variables into our model. We investigate the relationship between additional psychiatric variables, specifically depression and apathy.
1.5 Mood symptoms in basal ganglia disorders

1.5.1 Depression

Prevalence of depression in prHD is significantly greater than in the total population. In a variety of sample HD populations, individuals with a full motor diagnosis of HD the prevalence of a depressed mood was as high as 33-69% (Epping & Paulsen, 2011; Kim et al., 2015; Paulsen et al., 2014; Unschuld, Joel, Pekar, et al., 2012). While some studies conclude that depression is related to time to onset, with higher symptoms present close to full manifestation (Julien et al., 2007), most studies have not identified a linear relationship between depressive symptoms and disease progression in prodromal HD (Tabrizi et al., 2009). Depression is often reported to be higher in premanifest and manifest HD relative to controls across a variety of measures used to quantify symptoms (Aziz, Anguelova, Marinus, Lammers, & Roos, 2010; Duff et al., 2007; Kingma, van Duijn, Timman, van der Mast, & Roos, 2008). The current study utilizes the Symptom Checklist-90 depression inventory to calculate measures of depression. Studies using this measure have identified significantly higher depression in the prHD population (Duff et al., 2007; Marshall, White, Weaver, et al., 2007). Depression in diagnosed and prHD does not follow linearly with CAG repeat length, making it a valid clinical variable to study independent of genetic disease burden as a possible contributing factor to time to onset.

In some prHD studies, cognition is significantly related to depression. In a study conducted with 1044 participants, researchers divided participants into mild, medium, and severe depression based on Beck Depression Inventory scores. Individuals in the high depression group performed significantly worse than individuals in the low and medium group on the Single Digit Modalities Test, Trails B, Hopkins Verbal Learning Test--Revised (HVLT-R) Immediate Recall, and Stroop interference, but showed no difference in scores on the Trails A or HVLT-R Delayed
Recall (Smith, Mills, Epping, Westervelt, & Paulsen, 2012). In this study they found that depression and gene status were significant predictors of performance on all cognitive tasks. However, in a separate longitudinal study using another measure of executive function, the towers task, depression was found to be unrelated to declining cognitive function in a sample of 781 prHD individuals (K. V Papp et al., 2013). In Major depressive disorder (MDD) depression is linked with executive dysfunction, and it is possible that the depressive symptoms in prHD also correlate with cognitive changes (DeBattista, 2005).

1.5.1.1 Neurological correlates of depression

A hyperactive default mode network is one of the most commonly reported signatures of major depressive disorder and depressive symptoms in general (Sheline et al., 2009). The default mode network (DMN) is primarily comprised of the ventromedial prefrontal cortex (vmPFC) and the posterior cingulate cortex (PCC) (Esposito et al., 2006). Activation of the default mode network is associated with self-reflection, rumination, and stimulus-independent thought (Bluhm et al., 2009; Fransson, 2006).

The DMN is generally regarded as a “task negative” network, but the degree of its deactivation during tasks is dependent upon cognitive load of the task being performed, such that during a more difficult task DMN is less active than during easier tasks (Chen, Wang, Zhu, Tan, & Zhong, 2015; Fransson, 2006). In the normal population, DMN activity decreases in response to externally directed cognition (Gusnard, Akbudak, Shulman, & Raichle, 2001). Abnormal functional connectivity and up-regulation of this network is associated with a variety of clinical and neurological disorders including depression. In the depression literature, individuals with major depressive disorder show higher activation of the DMN during task-based fMRI scans (Whitfield-Gabrieli & Ford, 2012). Our study seeks to probe this “hyper-activation” hypothesis.
to investigate whether or not individuals with prodromal HD that experience depressive symptoms exhibit this elevated activation during a motor tapping task. Furthermore, if individuals who also report apathy exhibit this same DMN signature, it would indicate that apathy and depression are indeed part of the same mood symptom.

Researchers have identified aberrant DMN functional connectivity related to depressive symptoms and activation within prHD. In a task-based study, using ICA to isolate DMN components, researchers calculated measures of functional connectivity between nodes in the default mode network (Unschuld, Joel, Liu, et al., 2012). Participants performed a Stroop-task during an fMRI scan, and found that activation of the ventromedial prefrontal cortex node of the DMN was more highly correlated with depression in prHD individuals than in healthy controls. An additional study examined the DMN during a block design attention motor task, and found that prHD had lower connectivity between the DMN subcomponents, and that some of the regions of the DMN remained more active during the task, when compared to controls. However, they found no correlation of BOLD measures with depression (Wolf et al., 2012).

There seems to be a conflict in the literature as it pertains to the default mode network in prHD, that the proposed analyses will attempt to clarify. The discrepancies between these two studies may be explained by the task itself, the large difference in sample size, or unknown factors. In our attempt to examine default mode components and their correlation with task positive networks, we hope to illuminate the reasons for the discord in the literature, and can add valuable insight to the understanding of the DMN in prHD and its relationship with depression. Our study attempts to replicate these results by comparing activation of the DMN during a task, and we compare this activation with depressive and apathetic symptoms. If apathy is indeed just a symptom of depression, we would anticipate similar relationships between apathy and
depression scores and activation of the DMN during a task.

1.5.2 Apathy

In an individual, apathy is defined as a loss of interest and emotion, especially towards activities that a person previously found rewarding (Marin, 1991). In neurodegenerative disorders, particularly disorders that involve damage to the basal ganglia, apathy can emerge without accompanying symptoms of depression. Apathy is commonly present in the absence of other depressive symptoms in other movement disorders (Duff et al., 2007; Levy et al., 1998; Litvan, et. al, 1998; Naarding, et.al, 2009).

Within Huntington’s disease, apathy is regarded as a separate construct, distinct from depression (Levy & Czernecki, 2006; Naarding, Janzing, Eling, van der Werf, & Kremer, 2009). Across many studies, apathy is related to the number of CAG repeats in individuals with the HD mutation, and greater apathy scores predict cognitive decline in the diagnosed population (Craufurd, Thompson, & Snowden, 2001; Julien et al., 2007; Marshall J et al., 2007; Rosenblatt, 2007). In the diagnosed HD population, apathy was prevalent in 52% of the participants in one sample, and depression was present only in 12% (Naarding , Janzing , Eling, van der Werf, & Kremer, 2009). Individuals in the premanifest and prodromal phases of HD are 15-88 times more likely to experience apathy, than gene-negative individuals, and some report prevalence rates as high as 62% (Duff et al., 2007; Martinez-Horta et al., 2016).

Apathy is often related to cognition within Huntington’s disease and other neurological disorders (Naarding et al., 2009). According to Levy and Czernecki (2006), apathy has three facets with distinct neurological correlates, and damage to these regions produces specific profiles of apathy. Of interest for this study is the “cognitive apathy” profile. Cognitive apathy is characterized as a dysexecutive syndrome in which an individual has difficulty shifting from one
mental or behavioral set to another (Levy & Czernecki, 2006). It is also related to “cognitive interia”, which is the inability for individuals to self-initiate or “auto-activate” and partake in behavior or thought processes that would be rewarding (Laplane & Dubois, 2001). The figure below depicts the various aspect of apathy. The caudate is involved in the intention, planning, and initiation-execution phase (Levy & Dubois, 2006).

![Model of organization of goal-directed behavior](image)

**Figure 2** Model of organization of goal-directed behavior. Adapted from Brown & Pluck, (2000). Taken from Levy & Dubois (2006).

Apathy has been correlated with worse performance on executive functioning tasks in the diagnosed HD population (Hamilton et al., 2003; Thompson, Snowden, Craufurd, & Neary, 2002; van Duijn et al., 2010). In early HD, individuals with apathy perform worse than prHD individuals without apathy on tests of executive function, memory and attention (Baudic et al., 2006). While it is established that apathy is related to executive function in the diagnosed population, the prodromal population is less researched.
The sparse literature dedicated to depression, apathy, and cognition in this prodromal population only suggests a relationship between some apathy symptoms, some depressive symptoms, and cognition but it is far from conclusive. The inconsistency in the measures used to quantify cognitive constructs yields different results between studies. Additionally, questions about apathy are included in many depression inventories, and may explain the relationship to cognition that we see in this population. We hope to remedy this inconsistency between measures used to quantify cognitive constructs using our cluster scores, as aggregated measures of cognition, to determine if depression, apathy, or both significantly relate to cognition within this population. Identifying a similar relationship may indicate that depression and apathy are in fact part of the same construct.

1.5.2.1 Neurological correlates of apathy

Apathy and depression are also posited to have different neurological mechanisms responsible for mood changes within the normal population (Bonnelle, Manohar, Behrens, & Husain, 2015; Levy et al., 1998). Individuals with lesions to the caudate, similar to the atrophy experienced in prHD, experience severe apathy (Bhatia & Marsden, 1994; Mendez, Adams, & Lewandowski, 1989). The type of apathy exhibited with damage to the caudate involves an inability to initiate in activities and thought (auto-activation) as well as the inability to plan and shift behavioral and mental sets (cognitive apathy) (Levy & Dubois, 2006). Auto-activation deficit manifests most frequently after lesions to the caudate head and the globus pallidus, and regions of the putamen (Bokura & Robinson, 1997). Cognitive apathy, or problems with set shifting are also related to caudate head atrophy (Cognat et al., 2010). In functional imaging studies, apathetic individuals exhibit aberrant connectivity between striatal and frontal regions, and increased activation in regions attempting to compensate for atrophied regions (Alexopoulos
et al., 2013; Baggio et al., 2015; Bonnelle et al., 2015; Drevets, 2001).

Even though frontal regions control many higher order cognitive functions, much of the competing processes that take place during executive function tasks are regulated by the basal ganglia (Brunner, Kornhuber, Seemüller, Suger, & Wallesch, 1982). Figure 2 shows the fronto-striatal circuitry involved in auto-activation deficit. Although the diagram depicts changes to the reward system via the pallidum in progressive supranuclear palsy, it is clear that atrophy in the striatum would have a similar effect on fronto-striatal circuitry as pallidum lesions. Atrophy in the striatum would result in decreased excitatory output to the pallidum and Dorsolateral Pre-Frontal Cortex (DLPFC). Without the necessary cortical input to the basal ganglia via the striatum, individuals have trouble initially engaging in a task.

![Figure 2](image2.png)

**Figure 2** Structural fronto-striatal circuitry involved in auto-activation deficit. (Levy & Dubois, 2006).

The prodromal HD literature has investigated the relationship between depression and neuropsychiatric variables, but there has not been an in-depth investigation in prHD with a dataset as large as the PREDICT-HD dataset. It is possible that the depressive symptoms
reported in this population could be largely explained by the experience of apathy. This study attempts to further the understanding of the distinction between apathy and depression in this population, and examine whether poor cognitive performance and neurological changes are related to one or both of these constructs.

1.6 Motor Tapping Task

Researchers studying prHD and other movement disorders have used motor tapping tasks to assess motor function, changes in basal ganglia activation, and efficacy of internal time keeping systems (Rowe et al., 2010). The advantage of using the self-paced timing tasks is that they are simple to perform by both healthy controls, and individuals with motor impairment within an MRI apparatus, but are sensitive enough to detect differences between these two groups. Simple self paced timing tasks usually involve scenarios where a participant taps in time with a metronome, and then must continue tapping in time with the previous metronome rhythm, but with no audio or visual cues (Rao et al., 1997). These tasks, although simple in their execution, do require higher order processing in various regions of the basal ganglia. An Independent Component Analysis (ICA) was performed on a set of 10 healthy controls that completed several variations of a motor tapping and internal timing task (Moritz, Haughton, Cordes, Quigley, & Meyerand, 2000). The most consistent brain regions that exhibit elevated Blood-Oxygen-Level-Dependent (BOLD) signal while performing this task across studies, and of particular interest in this study are bilateral basal ganglia, and supplementary motor area (Witt, Laird, & Meyerand, 2008).

This type of motor timing task was administered to prHD participants, and predicted time to onset and symptom severity (Michell et al., 2008; Rowe et al., 2010; Siemers, Foroud, Bill, & et al., 1996; Tavares et al., 2005). For the current study, we have analyzed functional magnetic
resonance imaging (fMRI) data collected while prHD individuals were performing this task. Previous analyses with this dataset found that even 12 years out from diagnosis, prHD individuals exhibited aberrant activation during task performance (Zimbelman et al., 2007). Individuals close to clinical HD diagnosis exhibited reduced neural activation in the left putamen, Supplementary Motor Area (SMA), left anterior insula and right inferior frontal gyrus. Individuals far from diagnosis exhibited decreased activation in the right anterior cingulate and right anterior insula, and increased activation in the left sensorimotor, left medial frontal gyrus, left precentral gyrus, bilateral superior temporal gyri and right cerebellum (Zimbelman et al., 2007). Because the SMA was active during task performance, but differentially activated between controls and prHD participants, we considered it a region of interest for this analysis.

The basal ganglia, in particular, are of interest for our proposed study as they contain the regions most heavily affected by HD. Because previous hypothesis-based and data-driven methods reveal that both caudate and putamen are reliably significantly related to self-paced timing tapping tasks, we anticipate that we will find specific striatum components and supplementary motor area components in our ICA analysis.

1.7 Summary

Within the prodromal HD literature, there are discrepancies about which measures specifically relate to depression, and whether apathy and depression are distinct mood symptoms in the prodromal population. This analysis helps determine which cognitive constructs as a whole are related to depression and apathy in prodromal HD. Additionally, we probed the possible biological correlates of apathy and depression by examining activation of disease and depression related regions during a motor tapping task.
For the first part of this study, we analyzed cognitive and psychiatric data collected on 984 prodromal HD individuals that were evaluated on a variety of neuropsychiatric tests. We compared these scores to measures of depression and apathy. The next portion of our analysis included fMRI data collected while participants performed a motor tapping self-paced timing task. The imaging data set came from a subset of the cognitive dataset, and includes 23 prodromal HD participants.

1.8 Aim 1

We first determined whether depression and apathy negatively predict measures of cognitive function within a prodromal HD population in a cross sectional analysis.

1. We regressed cognitive cluster scores onto apathy and depression scores, to investigate whether apathy is a facet of depression, or a separate mood symptom.

Hypothesis 1. We anticipate that depression will not be related to cognition or motor symptoms; and apathy will be related to cognitive and motor cluster scores, after accounting for age, gender, years of education, and CAG x age interaction.

1.9 Aim 2

We identified regions of interest related to disease progression, apathy, and depression. We identified two default mode network components, a supplementary/presupplementary motor area component, a caudate component, and a putamen component. We calculated measures of correlation between these components and the conditions of the task time course. We regressed these loading coefficients for each component and each participant onto measures of apathy and depression.

Hypothesis 2. We anticipated that depression would be related to default mode network loading coefficients. Apathy would be related to disease specific components, and supplementary
motor area component, after accounting for age, gender, CAG repeat length, and CAGxAge interaction term and mean frame-wise displacement.

1.10 Expected Results

1) Apathy, but not depression will be negatively related to cognitive control cluster scores. Apathy, but not depression will be related to language and memory scores. Apathy, but not depression will be related to motor scores.

2) Depression will be related to increased positive synchrony between DMN component time courses and the task time. Apathy will be related to decreased synchrony between disease specific components and the time course of the task.

2 METHODS

2.1 Participants

2.1.1 Neuropsychiatric Data

We extracted this data from the PREDICT-HD study wide data set (Paulsen et al., 2008). The data set includes both healthy controls and prodromal HD participants, and was collected across 32 different scanning sites across the United States, and includes over 1200 participants. In order to be involved in the PREDICT-HD study, participants had to consent to blood draws, to determine CAG length, MRI scanning sessions, neuropsychological testing, and de-identified data sharing. The PREDICT-HD study wide data set includes demographic information for each participant such as gender, age, and years of education, HD specific genetic information, and data for approximately 50 different neuropsychiatric variables. Individuals with more than 35 repeats were considered to be in the Prodromal phase of HD (prHD participants/individuals). Their CAG repeat length determines whether they are a case or a control, and for the clustering analysis, only cases were analyzed.
The prodromal HD participants tested positive for the HTT mutation (CAG repeat length >36), and will eventually develop HD. They had not yet received a clinical diagnosis of HD. All of these individuals have taken the Unified Huntington’s Disease Rating Scale (UHDRS), and did not perform at the threshold required for clinical diagnosis. Participants were recruited via the University of Iowa’s and the additional scanning sites’ interactions with HD physicians and patients. Participants provided their consent for their data to be shared and analyzed. The data collected are de-identified prior to their retrieval for our database.

The data for used the initial clustering analysis are cross sectional, and collected across a range of ages and CAG repeat lengths, with one time point collected per person. For Aim 1, we used clinical and cognitive data collected from 984 prodromal HD participants. Individuals considered for the clustering, apathy, and depression analysis was anyone with complete data for at least one cluster (data for every measure of at least one cluster score), apathy, and depression measures. Table 1 provides demographic information about our sample population for the clustering analysis.

### Table 1 Participant characteristics for clustering dataset

<table>
<thead>
<tr>
<th>prHD (N =984)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>360/624</td>
</tr>
<tr>
<td>Apathy</td>
<td>12.4 (5.54)</td>
</tr>
<tr>
<td>Depression</td>
<td>52.98 (13.48)</td>
</tr>
<tr>
<td>Age</td>
<td>41.87 (11.08)</td>
</tr>
<tr>
<td>Years of Education</td>
<td>14.46 (2.6)</td>
</tr>
<tr>
<td>CAG Repeat Length</td>
<td>42.49 (2.06)</td>
</tr>
</tbody>
</table>

#### 2.1.2 fMRI Participants

The imaging data collected for Aim 2 consists of a subset of the PREDICT-HD dataset, consisting of 78 people, both healthy controls and prHD individuals. The scans for our imaging analyses were collected at the University of Ohio and the University of Iowa. Participants
consented to data collection, as well as sharing of their de-identified data. To ensure that there was consistent and correct timing information between sites, we performed a general linear model analysis using SPM8, with site as a covariate. We found that one site did not exhibit the expected differences between the task conditions, indicating that they had the incorrect timing information. Therefore, we only used data collected at the University of Ohio, and omitted the data from the University of Iowa for this analysis. After excluding participants from this site, and excluding healthy controls, we were left with data from 21 participants.

Table 2 Participant Demographics for the fMRI Dataset

<table>
<thead>
<tr>
<th>prHD (N = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Apathy</td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>CAG Repeat Length</td>
</tr>
</tbody>
</table>

2.2 Measures

2.2.1 Depression & Apathy Scores

The depression scores were taken from the depression subset of the Symptom Checklist-90 (Derogatis & Unger, 2010). Higher scores indicate greater levels of depression. The apathy scores used for this assessment were taken from the Frontal Systems Behavioral Scale (FrSBE) apathy subscale (Grace, 2011). For our analyses we modeled apathy and depression as continuous variables.

2.2.2 Cluster Scores

Upon entering the PREDICT-HD study, participants are administered a battery of neuropsychiatric tests spanning a wide variety of psychological domains including clinical,
cognitive, and motor symptoms (Misiura et. al, 2016). To decrease the number of variables in our analyses, we performed a hierarchical clustering analysis. From this analysis, we chose a cut point that broke the variables into 7 fairly distinct neuropsychological domains: executive function; language, memory, and perception; motor symptoms; psychiatric symptoms; daily functioning; problem solving; and tapping. Cluster scores were computed by z scoring each participant’s score for each variable, to homogenize the scaling of all of the variables. We then calculated an average for each cluster score by adding all of the measures in a cluster together, and dividing by the number of measures.

Individuals who did not have all measures for a specific cluster score were not used in that specific cluster model, but may contribute to a different cluster score for which they had all measures. For example, if an individual did not have a score for the Stroop Color Word Test, he or she would not be included in the regression model for the Cognitive Control cluster, but if this individual had all blocks from the tapping tasks completed, their data would be used in the Tapping cluster regression model. This approach generated varying numbers of individuals within each model, and each model has its own number of participants, listed with the model results.

2.2.3 Motor Tapping Task

For this analysis, we used fMRI data collected while participants were performing a block design motor tapping task. While in the scanner, participants tapped one finger on their right hand in synchrony with a metronome (Sync), presented over headphones at a pace of one tap every 550 ms. After approximately 25 seconds, the metronome stopped, and participants continued tapping at the same pace, but without any auditory cues (Cont). A pilot study involving healthy controls performing this task is described in further detail in Rao et al., (1997).
Scans were collected on a Siemens TIM Trio 3T MRI scanners (Erlangen, Germany) Whole-brain fMRI scans were acquired with a gradient-echo, echo planar pulse sequence (31.4-mm thick contiguous axial slices, TE = 29 msec; TR = 2800 msec; flip angle = 80°; FOV = 256 x 256 mm; matrix = 128 x 128; in-plane resolution = 2 x 2 mm). For each trial of this task, there were 5 blocks of each condition, 145 TRs per trial, and there were two trials per participant. Using SPM we created a design matrix for each participant for each trial, for a total of 2 identical design matrices per person. We used this design matrix to define the task timecourse utilized in our independent component analysis.

2.2.4 Independent Component Analysis

Independent component analysis is a data driven approach to identifying covarying regions of interest in functional MRI. Although the components themselves are derived from the data, researchers have identified highly replicable and brain networks (Calhoun & Adali, 2012; Calhoun, Adali, Pearlson, & Pekar, 2001; Calhoun, Liu, & Adali, 2009). In task related fMRI data, while not initially specified, task related components are often predictable, based on the brain regions that researchers have previously identified as relevant. The advantage of ICA lies in its ability to detect regions that researchers may not have previously related to tasks, identify functional networks, and easily identify motion artifacts. While previously specifying regions of interest for functional analysis may lend itself to more hypotheses-based testing, ICA provides an excellent method of exploration in a dataset about populations for which there is not a solid foundation of functional imaging literature, such as prHD.

To extract components that contain our brain regions of interest, we conducted an independent component analysis using the Group ICA of fMRI Toolbox (GIFT) (Calhoun & Adali, 2012; Calhoun et al., 2001). To obtain loading coefficients for components, we regressed
each component’s timecourse for each individual, onto the timecourse of the task. The loading coefficient for each individual is a measure of how much that individual’s component related to the timecourse of the task. For example, a higher positive loading coefficient indicates that activation within that component was higher, and coupled with the task conditions. A high negative loading coefficient indicates that a component was related to the task, but had decreased activation during the task conditions. Using the t-test utility in GIFT, we compared component time course to the time course of the task conditions. The caudate component was the only component that was significantly related to the task during the task condition Sync. Other components were not significantly related to that task conditions, and this is most likely because the task correlation values for each component had positive and negative correlation values, driving the means for the loading coefficient scores close to zero. Statistics for task components are included in table

We identified components that contain the regions of interest for our analyses including a caudate component, a putamen component, a supplementary motor and pre-supplementary motor area component, a middle temporal DMN component, and a precuneus DMN component. We then regressed the component timecourses onto the task time course to obtain a loading coefficient for each component for each participant. Figures 4 through 8 depict our ICA maps of our chosen components.
Figure 4 Putamen Component

Figure 5 Precuneus/ middle temporal default mode
Figure 6 Middle temporal component

Figure 7 Caudate Component
2.3 Analyses

2.3.1 Quality Assurance

2.3.1.1 Clustering dataset

A small portion of our the variables from our dataset were significant for Levene’s test, and exhibited non-normal distribution, which could be attributed to our large sample size. After normalizing the data, our results were not significantly different between data sets, so all of the data presented are a result of the non-transformed data. As it is often difficult to determine what is a normal range for psychiatric and functional measures, we did not exclude any outliers for the initial clustering analyses.
2.3.1.2 fMRI dataset

Mean framewise displacement (MFWD) is included as a covariate in many fMRI analyses as one method, in a series of steps, to correct for head motion. MFWD is defined as “the sum of the absolute values of the differentiated realignment estimates at every timepoint” (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). Regressing out MFWD can sometimes remove variability between groups, and we wanted to ensure that including MFWD as a covariate would not remove effects of interest, and would not explain any differences we see between apathy and depression in the fMRI dataset. Because motion often covaries with group or variables of interest, we conducted a preliminary analysis to compare MFWD with apathy and depression scores (Power et al., 2014). Both apathy and depression were significantly related to mean framewise displacement, but both had similar positive correlation values. If depression and apathy were related to MFWD at different levels, regressing out MFWD might affect the interpretation of our results. However, because correlation values were similar, we included MFWD as a covariate in our analyses.

2.3.2 Aim 1

Using R, we constructed 3 linear mixed models using the lme4 package. Consistent with previous papers published with this dataset, site was modeled as a random effect (Jane S Paulsen, Smith, Long, & PREDICT HD investigators and coordinators of the Huntington Study Group, 2013; Verbeke & Molenberghs, 2000). Gender was dummy coded, and included as a fixed factor. Apathy, depression, CAP score, and years of education were modeled as continuous independent variables. The outcome variables were the cluster scores of interest (language and memory, cognitive control, and motor symptoms).
2.3.3 Aim 2

Using SPSS version 23, we created one multivariate model with our ICA loading coefficients as outcome variables, depression, apathy, CAP score, and mean framewise displacement were the covariates, and gender was the fixed factor.

3 Results

3.1 Aim 1

We found a significant relationship between apathy and cognitive control and motor symptom cluster scores. Apathy scores were significantly negatively related to cognitive control cluster scores ($B = -0.02, t(714) = -3.32, p<.001$) and motor symptom cluster scores ($B = 0.01, t(774) = 2.91, p<.001$). Results are displayed in tables 4 and 5, and displayed in figures 9 and 10.

Depression was not significantly related to any cluster scores of interest.
We did not find a significant multivariate effect of apathy or depression on the ICA loading coefficients. However, when we further probed the relationship to individual component coefficients, we found that apathy is significantly positively related to SMA/pSMA loading coefficients during the Cont condition only ($B = .006, F(5,23)=5.19, p=.03$). Depression was not related to any loading coefficients during the Sync condition, but was positively related to putamen loading coefficients during the Cont condition($B = .001, F(5,23)=8.31, p=.01$). Partial plots for these results are depicted in figures 11 and 12.
Figure 11 Partial plot for depression scores against putamen loading coefficients.

Figure 11 Partial plot for depression scores against putamen loading coefficients.
4 Discussion

The purpose of this study was to determine whether or not apathy and depression are distinct mood symptoms within prodromal Huntington’s disease. We compared apathy and depression in relation to cognition as well as neural activity. Within the diagnosed population, there is a clear distinction between a depressed mood, and apathy independent of depression. The cognitive results support the distinction between these two mood symptoms, but the task related fMRI data, is more challenging to interpret.

4.1 Cognitive cluster scores

4.1.1 Motor Symptoms

Apathy, but not depression was significantly related to motor symptom severity. As apathy scores increase, motor symptom cluster scores also increased. This is consistent with our hypothesis and suggests that motor symptoms and apathy are related to the same brain regions. Motor symptoms, although not severe enough to reach clinical diagnosis, are present in this population (Siemers et al., 1996; Stout et al., 2011). Caudate degeneration is one of the earliest detectable regions of atrophy, and posited to be the primary cause of these early motor symptoms (Papp et al., 2011). Because apathy is often related to caudate atrophy, it follows that these two constructs would be related in the prodromal population (Levy & Czernicki, 2006; Mendez et al., 1989).
4.1.2 Cognitive Control

Apathy, but not depression, appears to be related to cognitive control in this population. In accordance with previous literature, apathy in prHD seems to be related to distinct neurological correlates and related cognitive control and motor impairment. Similar to the distinction in the diagnosed HD literature, in the prodromal population, increased apathy appears to be related lower executive function, while depression is not. A possible explanation of this relationship is that more apathetic individuals have less intention to engage in the task at hand, and therefore would perform worse on tasks requiring the execution of cognitive control. It is also likely that the apathy exhibited by this population is caused by the atrophy of the caudate and putamen. This is in keeping with previous literature regarding prodromal HD, “cognitive apathy” and related dysexecutive syndromes (Levy & Dubois, 2006; Martinez-Horta et al., 2016). This further supports the distinction between apathy and depression in this population.

4.1.3 Language, Memory, & Perception

In this population, neither apathy nor depression was related to language and memory scores. Our hypothesis about the relationship between language and memory and apathy was not supported. This cluster was one of the largest clusters, made up of a variety of different measures ranging from reading to perception tests. Our lack of results could be explained by the heterogeneity of the cluster itself, or lack of variability within the scores themselves. In this study, we combined all individuals across the prodromal HD spectrum. Other studies have only identified impairment in the tasks within the language and memory cluster very close to disease onset (Paulsen et al., 2014; Paulsen et al., 2013). These tests may not be sensitive to changes in the “far from diagnosis” stage. Because apathy is exhibited in the earliest phases of prodromal
HD, and language and memory task scores only change closer to disease onset, apathy and language and memory performance may be unrelated.

### 4.1.4 Summary

The clustering results support an apathy and depression distinction within the prodromal population. If apathy were merely an aspect of depressive symptoms, we would expect to see similar relationships between apathy scores and depression scores. We would anticipate that apathy would be related to some if not all of the cognitive clusters to which depression is related.

Although this analysis cannot reveal whether increased apathy is the cause of poorer performance, or whether both cognition and apathetic mood states are related to the same underlying brain regions, it does suggest that apathy may be an important disease related marker that could signify other, more widespread changes. It is not likely that individuals will be able to recognize a decline in executive function, but an increase in apathy is certainly easier to recognize, and could indicate disease progression. As methods for early intervention for prodromal HD develop, initial onset of an apathetic mood may be a helpful indicator, to individuals with prHD and caretakers, of impairment in functioning and related brain regions.

### 4.2 fMRI Motor Tapping Task

Apathy was related to activation in the supplementary motor area. Consistent with our hypotheses, as apathy scores increase, the supplementary motor area becomes more synced with the task time course. The SMA is often involved in rhythmic tapping tasks (Lang, Obrig, Lindinger, Cheyne, & Deecke, 1990; Wildgruber, Erb, Klose, & Grodd, 1997). In our prHD sample, apathy was related to increased correlation between self paced timing and the preSMA/SMA. Consistent with other apathy literature, the SMA and preSMA must work harder to compensate for the lack of functioning in the caudate and putamen (Bonnelle et al., 2015). In
these apathetic individuals, other brain regions may need to compensate for lack of caudate and putamen activation that is crucial to the process of internal time keeping (Meck & Benson, 2002). Although not referring specifically to the SMA, neural compensation has been observed in previous fMRI studies within prHD (Klöppel et al., 2015).

We did not identify a relationship between apathy and basal ganglia components. We anticipated that apathy would be related to decreased task synchrony in the caudate nucleus, but our results did not support our hypothesis. Apathy as a result of lesions to the caudate is primarily exhibited as an inability to self-initiate. It is possible that our task did not provide a valid paradigm for self-initiation. All cues were external, and during the continue phase of the task, participants were maintaining activity that was previously initiated. In order to further probe the relationship between self-initiation and the caudate activation, future research could include the use of an experimental design that requires self-initiation. Examples include tasks that allow participants to choose when to begin a task, or one that involves participants choosing a direction on which to move a joystick. Such paradigms lend themselves easily to fMRI research, and would be feasible to conduct with this sample.

In the initial analysis published on this fMRI dataset, individuals close to diagnosis exhibited decreased neural activation in the preSMA and SMA compared to controls (Zimbelman et al., 2007). Our results do not necessarily conflict with those previously published. In the original analysis, they did not consider or report any mood related variables, and they stratified their dataset by close and far from disease onset. In our analysis, we included all stages of the prodromal phase of HD and investigated differences between conditions instead of across the various task conditions.
Depression was related to activation in the putamen during the continue condition, meaning that as depression scores increase, putamen component time courses became more correlated with the time course of the self-paced tapping portion of the task. We did not anticipate a relationship between putamen task synchrony and depression scores. There is evidence that putamen volumes are related to depression within major depressive disorder (Husain et al., 1991). Although the Husain study looked at the putamen volumes and not activation, our results fall in line with their results. However, because this relationship has not been investigated across a variety of studies, the relationship between depression and putamen activation warrants further investigation. Although these results are not supported in previous prHD literature, it could be that because the putamen is involved in self-paced tapping, increased task synchrony indicates more effort. Individuals with greater levels of depression may have to exert more effort during the task than non-depressed individuals, especially because the regions of the putamen identified by ICA were primarily motor nuclei (Haber, 2016). This could lead to increased synchrony during the continue condition.

We anticipated that higher depression scores would be related to higher activation in the DMN regions during the task, and thus higher positive loading coefficients. We did not identify this relationship within our results. While it does support a distinction between apathy and depression, as depression and apathy were related to activation in separate brain regions, we did not find the anticipated correlation with the default mode network regions. A possible explanation for our lack of results between precuneus regions of the DMN and depression scores could be that the task was not difficult or engaging enough to bring out the changes related to depression. As cognitive load increases, default mode activation generally decreases. If the task was not challenging enough to initiate down regulation of the default mode network within
precuneal regions, any relationship with depression would not be identified. The default mode network changes may not be robust in this population to identify using fMRI. Changes in the default mode related to depression are detectable within major depressive disorder. The depression reported in this population may not be a result of the same mechanisms as in MDD and may not exhibit the same neural patterns.

4.3 Limitations

This study did have a number of limitations, thus results should be evaluated in context of these shortcomings. We did have a large sample size for the clustering analysis, and the results from that analysis support our hypothesis. However, an additional explanation for these findings could lie in the measures used to quantify the mood symptoms. Both apathy and depression scores were taken as subscales from larger inventories. However, the apathy measures were taken from the Frontal Systems Behavioral Scale, which is a scale developed specifically to measure aspects of frontal functions, of which apathy is given great attention. Depression is measured by the symptom checklist-90, which measures the presence of a wide variety of psychiatric symptoms ranging from obsessive-compulsive tendencies, irritability, global symptoms severity, etc. The SLC-90 scale may not capture the nuances of depression, which the FrSBe captures with apathy. This may lead to an underreporting of depressive symptoms, and may affect the relationships to cognition and neural activity.

In the fMRI dataset it is possible that the task chosen for the fMRI analysis was not appropriate to produce the distinction between motor planning networks and the default mode network. This task does not require a high degree of cognitive control, and may not have had sufficient rest periods necessary to initiate up and down regulation of the default mode network. Further studies with resting states analyses within this population are warranted to evaluate
resting state networks as there is a wealth of literature available to compare results, and the data itself is easier and more reliable to collect than task based scans.

4.4 Future considerations

In many movement disorders, apathy and depression are considered to be distinct constructs, with different neurological correlates. While they are correlated, higher apathy may be more indicative of disease progression rather than a facet of depression. Within the prodromal HD population, individuals report symptoms of apathy as well as depression. The literature pertaining to prodromal HD does not make as clear of a distinction between apathy and depression. The lack of delineation may seem purely theoretical, but it has a practical application within prHD. Individuals who exhibit symptoms of apathy may be mischaracterized as experiencing depression, which may lead to an attempt to treat symptoms with ineffective methods.

Future research with this population may lead to a symptom inventories that distinguish apathy and depression. This may lead to better symptom management, and earlier recognition of symptoms. Because there is still a wealth of evidence that indicates depression is related to neurological changes, it may be fruitful to perform a similar analysis within a more reliable dataset with a larger number of individuals. The lack of results within the task-based literature may indicate that a resting state study would be more appropriate.

The concept of “cognitive apathy” and its relation to striatum deterioration warrants further investigation. Although many studies have identified the caudate and putamen as the first regions to atrophy, investigation into the specific regions and nuclei within the striatum may reveal which functions (cognitive, psychiatric, motor) are most related to which nuclei. This can aid in treatment of symptoms and early intervention, when therapies develop, and provide the
scientific community with a better understanding of regional function of the striatum. This information will be helpful when developing early intervention strategies and treatments for the prodromal HD population.
REFERENCES


Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject
https://doi.org/10.1016/j.neuroimage.2011.10.018

https://doi.org/10.1016/j.neuroimage.2013.08.048


https://doi.org/10.1136/jnnp.2006.112565


https://doi.org/10.1073/pnas.0812686106


https://doi.org/http://dx.doi.org/10.1016/j.neulet.2012.02.095


https://doi.org/10.1016/j.pscychresns.2012.01.002


https://doi.org/10.1007/s00415-010-5768-0


