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Apathy and Brain Atrophy During the First Year of Moderate-Severe Traumatic Brain Injury: A Longitudinal Study

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APATHY AND BRAIN ATROPHY DURING THE FIRST YEAR OF MODERATE-SEVERE TRAUMATIC BRAIN INJURY: A LONGITUDINAL STUDY

by

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ABSTRACT

Apathy and Brain Atrophy During the First Year of Moderate-Severe Traumatic Brain Injury: A longitudinal study

by

Gulnaz Kudoiarova

Advisor: Junghoon J. Kim, Ph.D.

Apathy, defined as disinterest and loss of motivation, is a common complication after moderate-severe traumatic brain injury (msTBI). The existing body of research in various neurological and neurodegenerative disorders suggests that apathetic symptoms may be associated with variation in the volume of the brain regions such as dorsal anterior cingulate cortex and ventral striatum. However, the longitudinal pattern of TBI-induced atrophy in these key regions and its relationship with apathy symptoms remain to be demonstrated. The current study aimed to describe the atrophy pattern in the anterior cingulate gyrus (ACG) and the nucleus accumbens (NAc; part of ventral striatum) after msTBI and examine the brain-behavior relationship between the degree of atrophy in these regions and apathetic symptoms during the first year after msTBI. To this end, 30 patients with msTBI were assessed at 3, 6, and 12 months post-injury for neuroimaging and behavioral evaluations. Thirty-five matched healthy volunteers were evaluated once as a control group. At all time points, a significant group difference was found between patients and controls in terms of apathy measured by the apathy subscale of the Frontal Systems Behavior Scale, indicating that apathetic symptoms after msTBI persist throughout the first year post-injury. Similarly, the group difference in cortical thickness of ACG was significant at all three time points. In contrast, the group difference in NAc volume was

significant only at 12 months post-injury, suggesting a delayed onset of progressive neurodegeneration in NAc. Cortical thickness in ACG, but not NAc volume, showed an expected inverse relationship with apathy scores at all time points—that is, larger degree of atrophy associated with higher apathy score (Spearman's rho ranging from -.26 to -.39). However, the statistical significance of this relationship did not survive multiple comparison correction. A potentially critical role of ACG in post-traumatic apathy in msTBI is discussed.

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I would also like to thank Daniel Brennan, a Ph.D. student in Dr. Kim's lab, who offered indispensable knowledge and help in implementing ANTs cortical thickness pipeline. Additionally, I am grateful for the feedback provided by Naomi Gaggi, another Ph.D. student in the lab. Working on this research has been an immense learning experience and I am very grateful for all your help.

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

1. Introduction

1.1. Apathy: Definition and prevalence across disorders

The term "apathy" is used to indicate decreases in behavior, specifically decreases in purposeful or goal-directed behavior (Marin, 1996). There is general agreement in the previous literature on a triadic dimensionality of the apathetic symptom. That is, apathy is conceptualized in terms of lack of initiative, lack of interest, and emotional blunting (Marin, 1991). Lack of initiative specifies loss of concern for routine and new events, lack of interest describes diminished self-initiated or environment-stimulated behavior, and emotional blunting corresponds to the loss of spontaneous emotional responsiveness to positive or negative stimuli and events.

Apathy occurs across a range of neurological and psychiatric conditions such as traumatic brain injury (TBI; Lane-Brown & Tate, 2009), disorders involving basal ganglia (Stuss et al., 2000; Parkinson's disease: Pluck & Brown 2002; Aarsland et al., 2009; Huntington's disease: Thompson et al., 2012), Alzheimer's disease (Fernandez-Martinez et al., 2008; Mega et al., 1996), neurodegenerative diseases of frontal and subcortical brain regions (Litvan et al., 1996; Litvan et al., 1998), schizophrenia (Chue & Lalonde, 2014; Faerden et al., 2009), HIV (McIntosh et al., 2015), and cerebrovascular accidents (Caeiro et al., 2013; Jorge et al., 2010).

Defined as part of negative symptomatology, apathy constitutes one of the most common long-term clinical consequences of TBI. The average estimated prevalence in the TBI population is reported to range between 45-50% (Arnould et al., 2013). However, several other studies report a prevalence close to 70% (Kant et al., 1998; Lane-Brown & Tate, 2009). The symptom has been associated with a range of cognitive, functional, and health issues. Specifically, apathy has been associated with poor recovery and rehabilitation outcomes (Gray et al., 1994; Hama et

al., 2007; Brett et al., 2017), daily functioning problems (Zahodne et al., 2013), loss of social autonomy (Prigatano, 1992; Mazaux et al., 1997), risk of cognitive decline (Dujardin et al., 2007; Robert et al., 2006), poor social reintegration (Mazaux et al., 1997), difficulties of post-injury psychosocial reintegration (Arnould et al., 2015), and caregiver distress (Marsh et al., 1998; Willer et al., 2001; Bayen et al., 2012).

1.2. Functional anatomy of apathy across disorders

1.2.1. TBI

Several magnetic resonance imaging studies have observed volumetric changes associated with apathy in patients with TBI, especially in moderate-severe TBI (msTBI). More specifically, the results of a long-term study of the neural basis of apathy specific to penetrating msTBI revealed that increased apathy symptoms were associated with brain damage of the left middle, superior, and inferior frontal regions, insula, supplementary motor area, anterior cingulate cortex (ACC), as well as lesions to white matter tracts in the corona radiata and the corpus callosum (Raymont et al., 2011; Knuston et al., 2013).

Some authors have emphasized the role of the subcortical areas, the basal ganglia, in particular (Grunsfeld & Login, 2006; Spalletta et al., 2012). Several studies suggest that hemorrhagic lesions of the basal ganglia are a frequent complication among TBI patients (Xu et al., 2007; Shah et al., 2012). In line with this are the previous findings reported by Finset and Andersson (2000). The authors emphasize that the most severe cases of apathy were present in TBI patients with subcortical lesions. Furthermore, Grunsfeld and Login (2006) reported an interesting case study of abulia in a patient who suffered a penetrating brain injury during endoscopic sinus surgery, inflicting the basal ganglia damage. After the surgery, the patient was present with apathetic manifestations, lack of motivation and initiative. The researchers

hypothesized that the decreases in behavior were the consequences of the disruption of fronto-subcortical circuits at the level of basal ganglia. Particularly the anterior cingulate circuit, as its role has been reported to be essential for the initiation of behavior, motivation, and goal-directed orientation.

Concluding this section, it is important to emphasize that despite the growing interest in the field, there still has been very little research carried out on the neuroanatomical basis of apathy in msTBI. More recent evidence in the literature on the anatomy of apathy (Le Heron et al., 2018) suggests that considering the clinical phenotype of apathy, specifically, its remarkable similarity across disorders, there is a possibility that there are also common brain system alterations across diseases with very disparate underlying pathologies. In the following sections, neuroimaging studies in various neurodegenerative and neuropsychiatric conditions that reported volumetric changes of cortico-basal brain regions associated with apathy are reviewed in hope to define a more comprehensive view of the brain regions commonly implicated in apathetic manifestations.

1.2.2. Parkinson's disease

Specific to the structural changes associated with apathy in Parkinson's disease, investigators found that patients present with apathy had greater atrophy within the nucleus accumbens (NAc) and dorsolateral head of caudate (Carriere et al., 2014). However, mixed results have been reported regarding the possible associations with cortical thinning. Of these, Carriere et al. (2014) and Baggio et al. (2015) found no association between cortical thickness and apathy status. Alternatively, an earlier study by Reijnders et al. (2010) reported a significant correlation between increasing apathy severity and reduced gray matter (GM) volume in anterior and posterior cingulate gyri, insula, and lateral inferior frontoparietal region.

1.2.3. Huntington's disease

Huntington's disease (HD) is an inheritable neurodegenerative disease that predominantly affects striatum. Apathy was described as an intrinsic feature of HD as the symptom is indicated to closely follow the disease progression (Thompson et al., 2012). A study by Scahill et al. (2011) specific to pre-symptomatic individuals and individuals with the early disease did not find any associations between apathy and reduced GM volume. In contrast, another study found a negative correlation between the bilateral rectus gyrus white matter (WM) of HD patients and apathy (Delmaire et al., 2013). This region was shown to contain fibers that connect the orbitofrontal cortex (OFC) and subcortical structures, including the ventral striatum (VS).

1.2.4. Alzheimer's disease

The neuroimaging studies presented on the structural changes of the brain, specific to apathetic patients with Alzheimer's disease (AD), also reflect variability in the results, which, in part, may reflect differing inclusion criteria, analysis techniques, and image acquisition. AD is the most common neurodegenerative disease, typically affecting elderly individuals. The disease starts with memory impairment and progresses to other neurocognitive domains. The pattern of deterioration corresponds with neuropathology of AD; the neurodegeneration usually emerges in the medial entorhinal cortex and hippocampus, in time spreading to other brain regions. Apathy is one of the most prevalent behavioral and psychological symptoms in AD and is associated with higher severity of the disease (Mega et al., 1996).

Two well-designed studies identified that atrophy within the ACC, dorsolateral prefrontal cortex (dlPFC), putamen, and caudate nucleus was associated with apathy in patients with AD (Bruen et al., 2008; Tunnard et al., 2011). However, two other investigations (Kim et al., 2011;

Starkstein et al., 2009) found the opposite results, suggesting no association between apathy and GM volume.

1.2.5. Frontotemporal dementia, progressive supranuclear palsy, and corticobasal syndrome

Apathy was found to be present among the neurodegenerative disorders that affect frontal and subcortical brain regions (Litvan et al., 1996; Litvan et al., 1998). Frontotemporal dementia (FTD) is a term used to describe a cluster of neurocognitive disorders that include progressive dysfunction in executive functioning, language, and behavior. Progressive supranuclear palsy (PSP), and corticobasal syndrome (CBS) collectively refer to atypical parkinsonian syndromes which are characterized with a more rapid deterioration.

A large study that combined patients with FTD, PSP, and CBS reported that the presence of apathy in those cohorts correlated with reduced GM volume in ACC, OFC, middle frontal gyrus, anterior insula, and caudate (Rosen et al. 2005). Furthermore, reduced GM volume in dorsal anterior cingulate cortex (dACC) and insula was found in apathetic patients with progressive supranuclear palsy (Stanton et al., 2013).

1.2.6. Schizophrenia

Apathy has been widely associated with behavioral impairments present in the negative symptomatology of schizophrenia. Schizophrenia is a major psychiatric disorder which affects patient's thoughts, perception, and behavior. Findings of the neuroimaging study (Takayanagi et al., 2013) investigating the association between brain morphometry and apathy in schizophrenic patients suggest a higher volume loss in the ACC of the patients present with apathy compared with nonapathetic patients and healthy control subjects. Furthermore, the morphometric observations specific to the volume of the VS highlight that greater self-reported apathy severity was associated with a smaller volume of the right VS (Roth et al., 2016).

1.2.7. Human immunodeficiency virus

Apathy has been recognized as a significant symptom of the human immunodeficiency virus (HIV). While the etiology of apathy associated with HIV has not been determined, several studies suggest that the symptom may develop secondary to direct effects of the virus on cerebral function. Specifically, McIntosh et al. (2015) suggest that apathy indeed arises from the direct result of viral infection, which was found to aggregate in the basal ganglia (Nath, 2002; Clements et al., 2002). Furthermore, McIntosh et al. (2015) indicate a significant association between apathy and NAc atrophy in HIV. Additionally, several studies report disruption of frontal WM tracts in apathetic individuals with HIV. Two studies have demonstrated the association of apathy with reduced fractional anisotropy within the genu of the corpus callosum, anterior thalamic radiations, and superior corona radiata – tracts connecting medial frontal cortex and subcortical regions (Hoare et al., 2010; Kamat et al., 2014).

1.2.8. Stroke

Nearly one-third of patients recovering from a hemorrhagic or ischemic stroke present with apathy (Caeiro et al., 2013). Studies with stroke patients are particularly important because they allow examination of the relationship between lesion site and function, although with less precision than in animal. Thus, studies of stroke patients provide a primary opportunity for understanding the neurobiology underlining apathy.

Many studies have been published on apathy's association with lesions in the basal ganglia (Bhatia & Marsden, 1994; Gerace et al., 2013; Maeda et al., 2012; Phillips et al., 1987). Specifically, lesions affecting the caudate nucleus and NAc were found to correlate with the development and progression of the symptom significantly. Severe cases of apathy were also observed following lesions to the globus pallidus zona interna (GPi), a crucial output component

of the basal ganglia (Adam et al., 2013). Many studies report apathy following thalamic injury, specifically, paramedian or anterior regions (Engelborghs et al., 2000; Ghika-Schmid & Bogousslavsky, 2000; Krolak-Salmon et al., 2000; Nishio et al., 2011; Perren et al., 2005).

Alterations in frontostriatal circuits were closely associated with post-stroke apathy. Specifically, Siegel and colleagues (2014) provide an in-depth case study of a single patient who developed apathy after multiple small embolic infarcts. The authors report that the structural imaging did not reveal any damage specific to ACC. However, the patient had reduced functional connectivity within the cingulo-opercular network, leading to the conclusion that the occurrence of apathy could be associated with frontal network dysfunction at a distance (Siegel et al., 2014). Moreover, one study found that, compared to healthy controls, apathetic patients had reduced blood flow within the basal ganglia, irrespective of stroke location (Onoda et al., 2011)

1.2.9. Summary of the functional neuroanatomy of apathy across disorders

Taken together, the comprehensive review of the neuroimaging studies investigating neural correlates of apathy across disorders, despite the variations in design, converge on a consistent pattern. Specifically, this pattern indicates that two structures are linked to apathy most frequently: the dACC and VS. That is, across the disorders, apathy is associated with consistent changes in the frontostriatal circuit, which constitutes a strong anatomical basis for the disrupted goal-directed behavior that defines the apathetic syndrome. The frontostriatal circuits are defined as neural pathways connecting frontal lobe regions with the striatum. These circuits constitute a part of the executive functions. The ventromedial prefrontal cortex and its connections to ventral striatum and amygdala suggested to play a critical role in affective-

emotional processing (Guimaraes et al., 2008). Specifically, they were found to be important for elaboration of the plan of actions needed for goal-directed behavior.

1.3. Longitudinal course of apathy

Another critical aspect of apathy is the evolution of the symptom. A literature review (Arnould et al., 2013) suggests that, for the most part, the existing body of research on the continuity of apathy in TBI is cross-sectional in nature (Starkstein & Tranel, 2012). However, no studies to date specifically conducted longitudinal assessment of the symptom progression in a well-defined TBI cohort over the early chronic phase of recovery.

Several studies highlight that apathy remains prolonged after injury. More specifically, Lane-Brown and Tate (2009) report that apathy was estimated at a 72% prevalence rate following 5-6 years after the injury. Analogous findings were reported on the period between 2 - 4 years and 5 - 8 years (Monsalve et al., 2012), estimating the prevalence of apathy at 50%. Furthermore, findings of the same study suggest that patients between 5 and 8 years after their injury were present with a more severe apathy than those in the 2 - 4 years group (Monsalve et al., 2012).

Given that the existing literature on apathy beyond the early phase of post-TBI recovery suggests that the symptom remains prevalent, and in some cases, tends to increase, observations focused on the progression of apathy during the early chronic phase are much needed. These observations could enhance our knowledge of the potential interventions devoted to the processes involved in the progression and continuance of the symptom. Thus, a longitudinal assessment with little variation between the evaluation points across patients is advantageous to assess the trajectory of apathy evolution.

1.4. Current study

The first aim of the current study was to examine the group differences in apathetic symptoms and atrophy between moderate-severe TBI (msTBI) patients and healthy controls for the two regions of interest known to be relevant to apathy—that is, ACC and VS. It was hypothesized that patients with TBI would show atrophy in these regions compared to demographically matched healthy control participants. We also tentatively hypothesized that the two regions would display the same pattern of atrophy over the course of one year post-injury. The second aim was to explore the brain-behavior relationship between morphology and apathy score. It was hypothesized that apathy scores would correlate with increased atrophy in the regions of interest. The third aim of the study was to describe the longitudinal course of apathy symptoms during the first year after msTBI with multiple assessment points at 3, 6, and 12 months post-injury. It was hypothesized that the apathy scores would substantially improve over time as other cognitive functions typically do during the first year post-msTBI.

2. Methods

2.1. Participants and procedure

Data used in this study were obtained during a longitudinal multimodal neuroimaging research project investigating neural correlates of functional recovery following moderate-severe diffuse TBI (PI: Junghoon J. Kim). Initially, 42 TBI patients between the ages of 18 and 64 were recruited from the rehabilitation unit on a medical campus. Each patient was diagnosed with a non-penetrating TBI of at least a moderate severity defined by one of the following: a Glasgow Coma Scale (GCS) not related to sedation, paralysis, or intoxication of less than 13 while in the emergency department; 12 or more hours of loss of consciousness, or post-traumatic amnesia (PTA) lasting 24 hours or longer.

The initial assessment (referred to as Time 1), took place at 3 months (M = 101.47, SD = 18.97 days) after injury. Time 2 follow-up occurred at 6 months (M = 184.3, SD = 17.64 days) post-injury. Assessment at Time 3 took place at 12 months (M = 366.23, SD = 21.52 days) after the injury. The data collection intervals with an allowable window between 2 to 3 weeks provided a homogenous subject pool with relatively little variation in the scanning intervals. If patients did not participate in all three sessions, they were excluded from the study. The final subject pool of 30 patients was matched by 35 neurologically intact healthy controls.
The control group underwent a single data collection session.

Exclusion criteria for all subjects included a history of prior TBI, history of premorbid CNS disease, significant psychiatric history, substance abuse, pregnancy, inability to complete MRI scanning due to implants, claustrophobia or restlessness, and lack of English proficiency. The study was approved by the institutional review board, and written informed consent was granted by all participants.

2.2. Assessment of apathy

The assessment of apathy was conducted using the apathy subscale of the Frontal System Behavior Scale (FrSBe), which has previously shown a good reliability and validity in a variety of clinical groups and settings (Grace and Malloy, 2001). The subscale consisted of 14 items, each rated on a 5-point scale. The evaluation of apathy was performed by the patients and their caregivers.

Previous literature on apathy reports suggests that the use of scale completed by informants could lead to a misestimate of the behavioral disorder because the problematic behaviors associated with apathy may sometimes occur without the caregiver's knowledge

(Rochat et al., 2011). Within the framework of this criterion, we decided to conduct the statistical analysis, including the apathy subscale completed by the patients only.

2.3. MRI acquisition

All participants underwent brain MRI on the same 3T Siemens Trio scanner using an 8 channel head coil. Structural images were obtained using a three-dimensional T1-weighted magnetization-prepared rapid acquisition gradient-echo protocol with the following parameters: voxel size=1x1x1 mm, TE=3,08, TR=1620ms, flip angle = 15°. All images were manually reviewed by an expert for quality, and lesions, if present, were identified and saved as lesion masks for subsequent analysis.

2.4. Image processing

The image processing for the quantitative morphometric analysis of the brain was performed using the longitudinal version of Advanced Normalization Tools (ANTs, https://github.com/ANTsX/ANTs). A volumetric cortical thickness map was calculated for each subject for each timepoint; this involved bias correction (Tustison et al., 2010), brain extraction (Avants et al., 2010), n-tissue segmentation (Avants et al., 2011), template building (Avants et al., 2010), and spatial normalization (Avants et al., 2011). Because ANTs utilize tissue priors for estimating volumetric cortical thickness in the target image, it also requires a template image (anatomical reference) and associated tissue priors, inducing potential biases by these prior images that must be minimized. In order to address this issue, we implemented an iterative method of template building and tissue prior estimation that created custom prior images for each subject so that cortical thickness for each timepoint was estimated via a subject-specific prior.

We began by creating a group template (anatomical image), averaging a subset of the overall sample together. After that, using publicly available tissue priors from a manually labeled

dataset (the OASIS dataset; https://www.oasis-brains.org/), we estimated tissue probabilities for the group template and used them as unbiased tissue priors for the entire sample. Subsequently, a similar procedure was done at the subject level. First, the multiple images for a given subject were combined to an unbiased average of the multiple timepoints creating a subject-specific template. Second, the group-level tissue priors created in the previous step were used to estimate the subject-specific tissue probabilities for the associated subject-specific templates. Third, these subject-specific tissue probabilities were used as the priors for estimating volumetric cortical thickness at each timepoint for a given subject. Finally, we used the joint label fusion method to label individual timepoints anatomically. The anatomic labels were taken from the commonly used BrainCOLOR atlas labeling system (Wang et al., 2013). This method wrapped multiple anatomical images and their associated manually labeled region of interest (ROI) labels to the target image.

From the processing of the pipeline described above, we obtained cortical thickness and gross volume from our ROIs. Because the labels for dACC and VS do not exist in the BrainCOLOR atlas, we used the anterior cingulate gyrus (ACG) and nucleus accumbens (NAc) labels as the closest approximation. The left and right parts of the anterior cingulate gyrus (ACG) are represented in Figure 1. In the subsequent statistical analyses, we used the summation values of the left and right brain structures. Similarly, ventral striatum (VS) was approximated by the nucleus accumbens (NAc) label (Figure 2). The olfactory tubercle, a second component of the ventral striatum was not included in the approximation because it is difficult to automatically segment due to the lack of contrast in its vicinity and is not yet available as a separate label. Again, in the subsequent analyses, we used the total volume of the left and right parts of the nucleus accumbens.

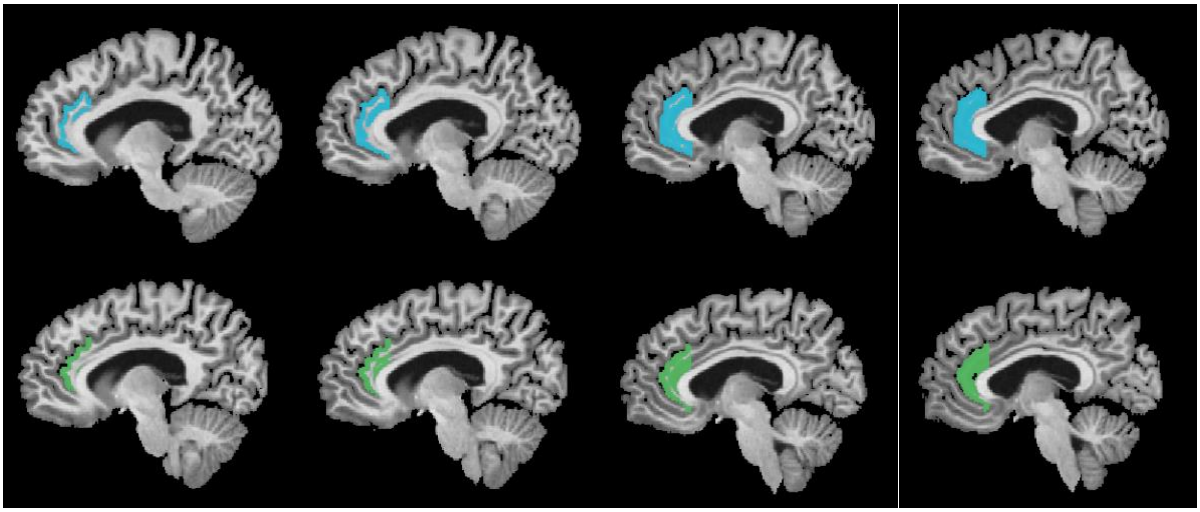

Figure 1. Left and right anterior cingulate gyrus segmentation. Segmentation of the left (top in blue) and right (bottom in green) ACG for one subject randomly selected from the dataset. Slices are shown from lateral (left) to medial (right)

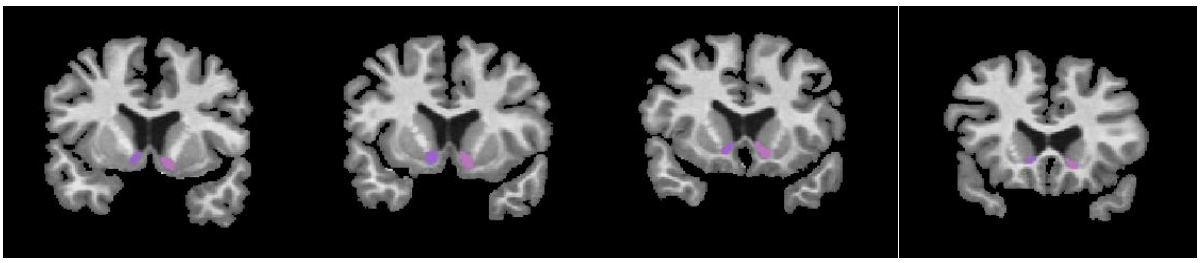

Figure 2. Left and right nucleus accumbens segmentation. Segmentation of NAc for one subject randomly selected from the dataset. Slices are shown from anterior (left) to posterior (right)

2.5. Statistical analyses

Data were analyzed using Python (https://www.python.org/). The initial part of the analysis was specific to the assessment of apathy. First, exploratory analyses of each variable were conducted to examine the distribution of the data. Second, a series of Mann-Whitney U tests were performed to evaluate the statistical difference of apathetic manifestations between

TBI patients and control participants. Third, Friedman's test was used to analyze whether patients had experienced significant changes in apathy during the post-TBI recovery phase of one year. Longitudinal alteration was calculated to estimate a percent wise comparison of the directionality of apathy change. To this end, a delta for each phase was calculated by subtracting Time 2 from Time 1, Time 3 from Time 2, and Time 3 from Time 1.

Analogously, the assessment of atrophy began with the exploratory analyses of each variable, followed by a series of Mann-Whitney U tests comparing the cortical thickness of ACG and the volume of NAc of the patients at Time 1, Time 2, and Time 3 to control participants. Bivariate partial correlations with post-hoc tests were calculated using the Spearman's rho to examine the relationships between the regional thickness/volume and apathy scores at each time points. Gender, age, and total intracranial volume (ICV) were included as covariates for the assessment of the correlation specific to the subcortical volume. Gender and age were included for the analysis of the cortical thickness. All analyses were designed two-tailed with the alpha level set to 0.05.

3. Results

3.1. Demographic characteristics

Demographic characteristics are summarized in Table 1. As seen from the table, the participants between the two groups were well matched for demographic variables. Between-group differences on demographic characteristics were evaluated by means of independent sample t-test for continuous variables, and chi-square test for the categorical variable.

Table 1. Demographic characteristics of TBI and control groups

Group	N	Age (years)			Gender			Education (years)		
		Mean	SD	*P-val*	Male	Female	*P-val*	Mean	SD	*P-val*
TBI	30	32.67	13.32	0.39	20	10	0.50	13.57	2.47	0.23
Control	35	34.97	10.32		26	9		12.88	1.86	

SD = standard deviation.

3.2. Preliminary analyses

Examining the distribution of each variable using Shapiro-Wilk test revealed that, for the most part, the variables were not normally distributed; ACG (p_{time1} = .04, p_{time2} = .12, p_{time3} = .02), NAc (p_{time1} = .02, p_{time2} = .03, p_{time3} = .04), FrSBe - Apathy (p_{time1} = .02, p_{time2} = .02, p_{time3} = .39). Therefore, non-parametric statistics were used for subsequent analyses.

3.3. Group comparison of apathy symptoms

A series of Mann-Whitney U tests were conducted comparing TBI participants' apathy scores at Time 1, Time 2, and Time 3 to control participants. At all three time points, patients' scores were significantly higher (i.e., more apathetic) when compared to control participants ($p_{time\ 1} < .001$, $p_{time\ 2} < .001$, $p_{time\ 3} < .001$) (Figure 3). At the individual level, over the first phase of post-traumatic recovery, that is 3 to 6 months, 3 patients (10%) displayed no change in their apathetic symptoms, 11 patients (37%) showed worsening symptoms, and 16 patients (53%) showed improving symptoms. For the second phase (during the period between 6 and 12 months), 3 patients (10%) displayed no change, 10 patients (33%) showed worsening symptoms, and 17 patients (57%) showed improving symptoms. The overall assessment of the post-TBI recovery phase between 3 and 12 months revealed that a total of 2 patients (7%) displayed no

change in their apathetic symptoms, 10 patients (33%) showed worsening symptoms, and 18 patients (60%) showed improving symptoms.

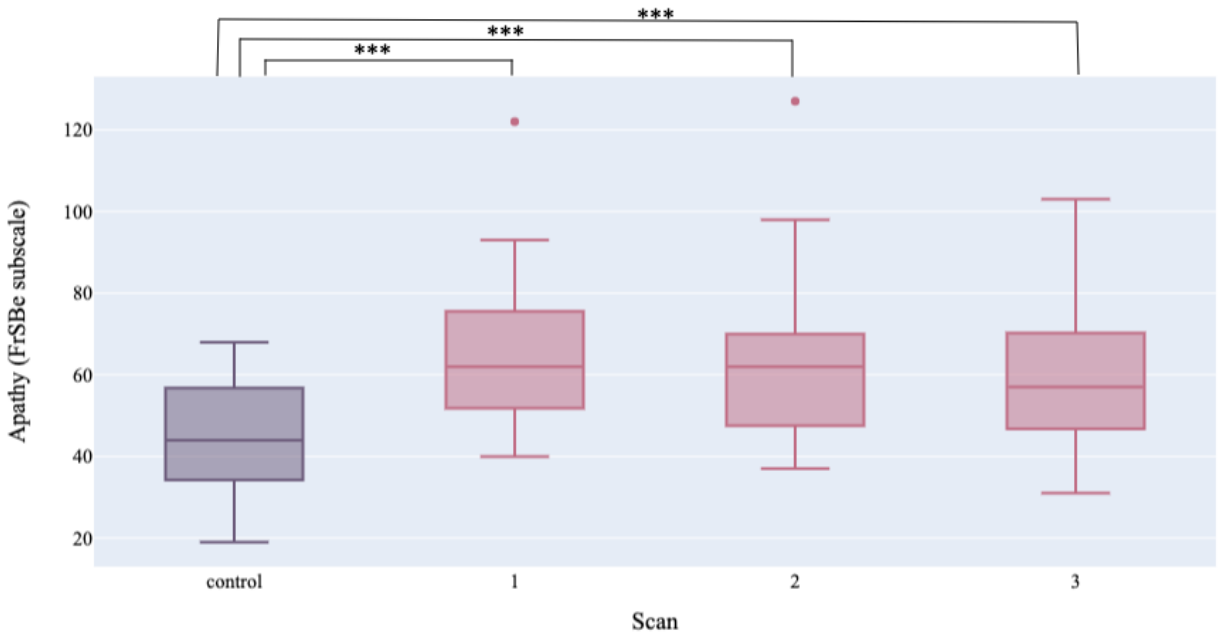

Figure 3. Apathy scores in TBI group and healthy controls. Labels 1 – 3 specify the assessment of apathy in TBI group at Time 1 – Time 3 respectively. *** $p < .001$

3.4. Group comparisons of atrophy in ACG and NAc

A series of Mann-Whitney U tests were conducted comparing TBI participants' cortical thickness and subcortical volume at Time 1, Time 2, and Time 3 to control participants. For cortical thickness, the results revealed significant group differences at each time point. More specifically, compared with control participants, TBI patients showed significant cortical thinning in the ACG ($U_{time\ 1} = 143$, $p_{time\ 1} < .001$; $U_{time\ 2} = 173$, $p_{time\ 2} < .001$; $U_{time\ 3} = 217$, $p_{time\ 3} < .001$). For the assessment of the subcortical volume of NAc, the results did not reveal significant group differences at 3 and 6 months post-injury. However, significant volume

reduction of NAc in patients was detected at 12 months post-injury ($U_{time\ 1}$ = 414.5, $p_{time\ 1}$ = .11; $U_{time\ 2}$ = 402.5, $p_{time\ 2}$ = .08; $U_{time\ 3}$ = 384, $p_{time\ 3}$ = .05).

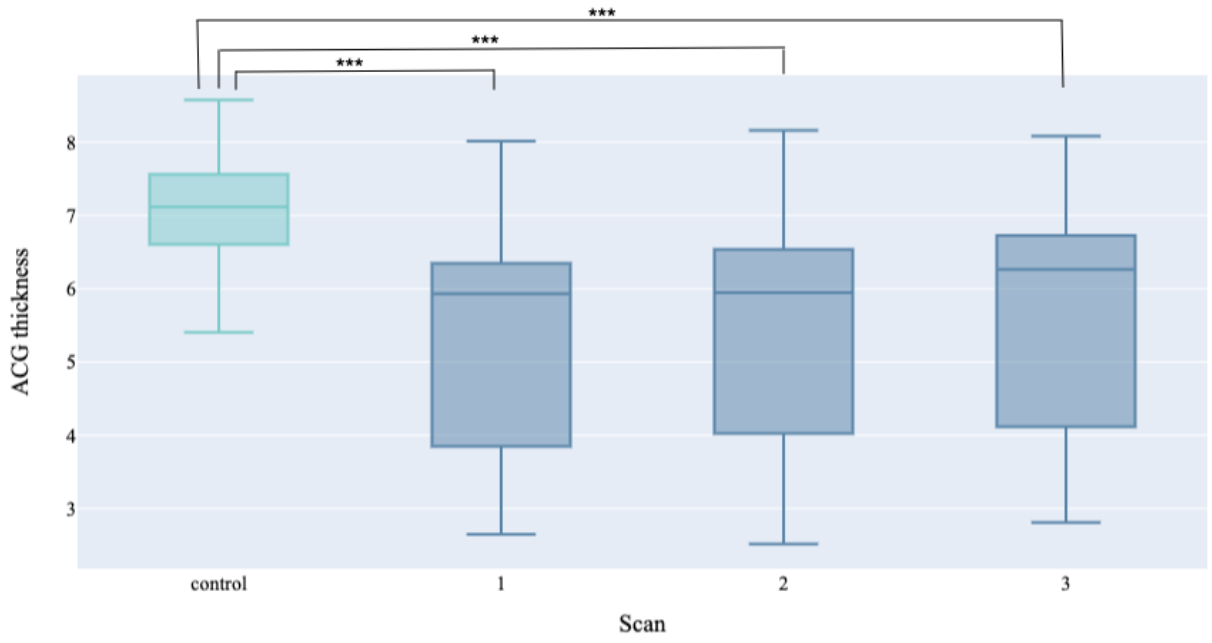

Figure 4. Cortical thickness of ACG in patients with TBI and healthy controls. Comparison of cortical thickness (mm) of the patients at 3, 6, and 12 months (from left to right) to control group. Labels 1 – 3 specify the assessment of apathy in TBI group at Time 1 – Time 3 respectively. *** p < .001

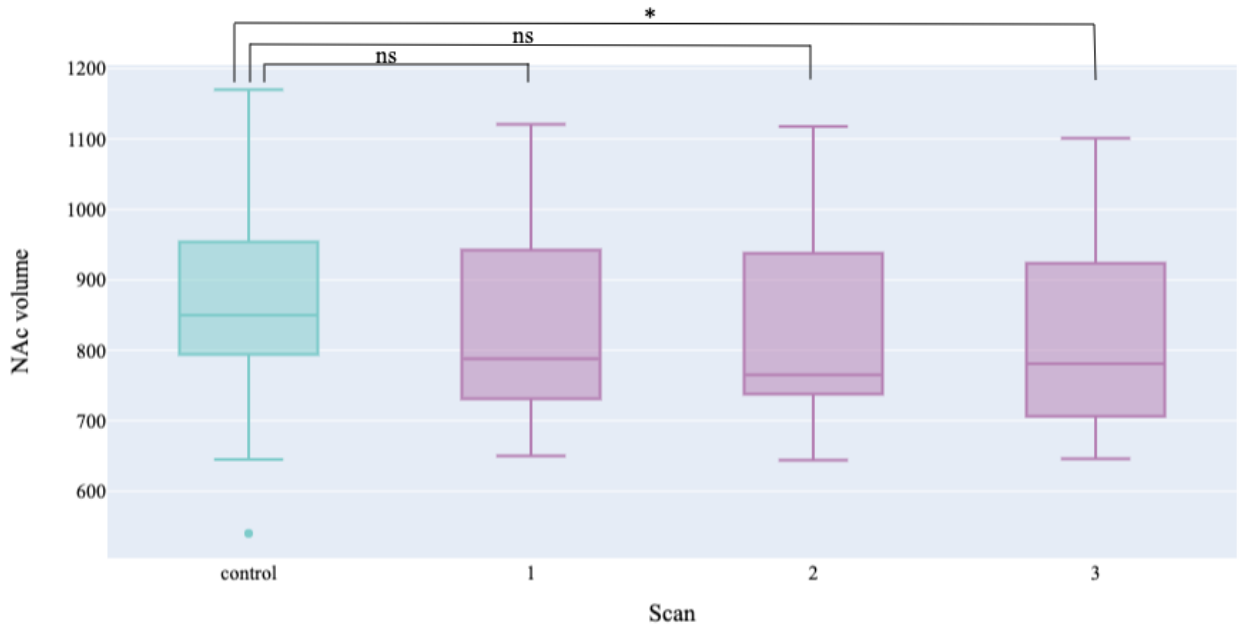

Figure 5. NAc volume in patients with TBI and healthy controls. Comparison of NAc volume (mm2) of the patients at 3, 6, and 12 months (from left to right) to control group. Labels 1 – 3 specify the assessment of apathy in TBI group at Time 1 – Time 3 respectively. * $p < .05$

3.5. Correlation analyses of atrophy and apathy scores

Partial correlations of Spearman's rho were computed in the TBI group to examine the relationship between the thickness/volume of the two ROIs and apathy scores assessed by FrSBe apathy subscale. Correlation coefficients (Spearman's rho) are summarized in Table 2. The correlation between ACG and apathy score at Time 2 was significant ($p = 0.037$), only prior to multiple comparison correction. Considering the small sample size and the risk of Type II error, we reported the p-values of the correlations without multiple comparison correction (Table 2).

Table 2. Correlation between apathy and morphometry metrics for the two regions of interest

	FrSBe – Apathy		
ROIs	Time 1	Time 2	Time 3
ACG	-0.26	-0.39*	-0.34
NAc	0.23	0.14	0.08

* $p < .05$

4. Discussion

The main objectives of the study were to 1) examine the group differences between TBI patients and control participants in terms of apathetic symptoms and brain morphology (ACG and NAc) during the first year after moderate-severe TBI (msTBI) and 2) evaluate possible associations between the morphological metrics from the two regions and apathy symptoms. The main findings and their implications are summarized in the following paragraphs.

Regarding apathetic symptoms, our findings revealed that the patient group's mean scores for the apathy subscale in FrSBe were significantly higher when compared to the control group at all time points. This pattern of results indicates the persistent nature of apathetic symptoms during the first year after msTBI. These findings are congruent with those obtained by Brands and colleagues (2015) and Goverover and colleagues (2017). Their research in TBI patients who were living in the community suggested that those individuals exhibited a significant reduction in activity participation and a decline in achieving life goals.

The results from the individual level analysis, however, revealed a different aspect of the data. Assessment of the overall change between 3 and 12 months identified that 18 patients (60%) had improvement in their symptoms, 10 patients (33%) reported worsening symptoms, and 2 patients (7%) showed no change. These findings suggest that the majority of the patients

reported improvement of their condition, despite the group-level statistics not detecting this longitudinal change.

Of particular interest were the distinct patterns of neurodegeneration observed in ACG and NAc. Specifically, significant atrophy was found to be present in ACG at all three time points of assessment, suggesting that the atrophy occurs early following the injury and remains prolonged. Our findings are congruent with studies of MRI brain morphometry in patients with TBI describing cerebral atrophy (Bendlin et al., 2008; Sidaros et al., 2009; Farbota et al., 2012, Green et al., 2014) and reflect progressive neurodegeneration following TBI. However, our report is among the first that describe the longitudinal aspect of atrophy in the regions related to apathy.

In contrast, our findings indicate a different temporal trajectory regarding the atrophy of the NAc. More specifically, our observations indicate that, unlike the ACG, NAc does not show immediate atrophy starting at Time 1 (3 months post-injury) but rather displays a delayed neurodegenerative process. This may be causing the atrophy to become detectable after a certain period of time. In our case, it was 12 months, but the possibility remains that the atrophy continues beyond one year post-injury. Our findings align with the previous work suggesting NAc atrophy following TBI (Tate et al., 2017). Furthermore, our study is one of the first to describe the temporal characteristic of atrophy specific to this region of interest. As reported by Monsalve and colleagues (2012), a more severe apathy was identified among patients between 5 – 8 years after the injury. Considering a delayed onset of neurodegeneration in NAc, it is plausible that a more severe apathy during the late phase of recovery is, in part, inflicted by the neurodegenerative processes of NAc. Our study timeline was limited to the evaluation of TBI patients during the first year of injury. Future studies of morphometric assessment of NAc in a

more chronic phase of msTBI may provide further insight into the possible association with apathy.

In terms of brain-behavior relationship, our results hinted at an intriguing trend of a relationship between apathy scores and ACG atrophy at all time points (see Table 2). The consistently negative correlations with reasonably large effect sizes suggest a potential inverse relationship–that is, a greater apathy score accompanying more severe atrophy in ACG. However, these correlations did not survive multiple comparison correction.

The involvement of ACC in motivated behavior has been confirmed by many neuroimaging studies (Le Heron et al., 2018). It is argued that the ACC supports the selection and maintenance of goal-directed behaviors through its contribution to cognitive control and reinforcement (Holroyd & Yeung, 2012). Specifically, the ACC has been described to play a crucial role in assessing and motivating choices that will lead to effort and sustain the motivation required to continue the behavior until attaining a goal (Le Heron et al., 2018). Consequently, any disturbance in the circuitry of ACC induced by TBI-induced neurodegeneration may lead to altered responses within ACC, causing a lack of motivation and, therefore, apathy. Considering our findings, it seems plausible that ACC plays one of the key roles, orchestrating apathy during the early chronic phase post-msTBI.

This study has a number of strengths. First, while many previous longitudinal morphometry studies in msTBI suffer from variable time post-injury across participants, we followed up the same cohort at pre-defined time intervals, rendering time post-injury across subjects less variable. Second, we explicitly dealt with focal lesions during registration and segmentation processes during our morphometry analysis in order to minimize the confounding effects of focal encephalomalacia on the estimation of cortical thickness and subcortical regional

volume. Third, the two groups analyzed in this study were well matched for demographic variables, eliminating potential confounds from mismatched groups.

This study also has a number of limitations. First, the sample size of participants was relatively small and may have obscured potentially meaningful findings. Therefore, the results should only be generalized with caution. Second, a more comprehensive and in-depth assessment of apathy could provide a more appropriate assessment for multiple aspects of apathy. Third, due to the limited availability of the atlas labels, we could only obtain the thickness of ACG, which was used as an approximation for the dACC. Future studies with a larger patient sample and additional measurements for different aspects of apathy may provide a better understanding of the relationship between structural brain changes and apathetic symptoms, eventually facilitating the development of a definite model of neural correlates of apathy. Additionally, more sophisticated automatic segmentation tools that can isolate the dACC area need to be used in the future studies.

5. Conclusion

Apathy is a common symptom of many disorders of the brain. In the field of neurological and neurodegenerative diseases, apathetic manifestations have been associated with a number of adverse outcomes for patient's recovery, including decreased response to treatment, reduced functional level, and chronicity. The current study reported that apathetic symptoms after msTBI persisted throughout the first year post-injury and that the key brain structures involved in apathy underwent different temporal dynamics of atrophy. We also found an intriguing trend of a relationship between apathy scores and cortical thinning in the anterior cingulate gyrus. Our results will inform future definitive studies that will eventually help researchers and clinicians identify the optimal targets and time window for neurorehabilitation of TBI-induced apathy.

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