THE BASAL GANGLIA'S RELATIONSHIP WITH AUTISTIC REPETITIVE MOTOR BEHAVIORS AND SEX ASSIGNED AT BIRTH

by

Dan G. Kingsley

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of
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Committee:

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Date: __________________________________ Spring Semester 2023
George Mason University
Fairfax, VA

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Bachelor of Arts
University of Northern Colorado, 2022

Director: Allison Jack, Assistant Professor
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Dedication

I dedicate this work to all of the genderqueer, nonbinary, transgender, AFAB, neurodivergent people, who listened to me infodump about my thesis, looked at me with joy and said, “you’re changing the world for me.”

Acknowledgements

I wish to thank my advisor, Dr. Jack, for her guidance and support throughout this process. I also want to thank the members of my committee for their invaluable input and infinite patience: Dr. James Thompson and Dr. Martin Weiner.

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List of Abbreviations

Basal Ganglia	BG
Assigned Female at Birth	AFAB
Assigned Male at Birth	AMAB
Caudate Nucleus	CN
Nucleus Accumbens	Nac
Repetitive Movement Behaviors	RMB
Self-Injurious Behavior	SIB
Sex Assigned at Birth	SAB
Stereotyped Behavior	SB
Ventromedial Prefrontal Cortex	vmPFC

Abstract

THE BASAL GANGLIA'S RELATIONSHIP WITH AUTISTIC REPETITIVE MOTOR BEHAVIORS AND SEX ASSIGNED AT BIRTH

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George Mason University, 2023

Thesis Director: Dr. Allison Jack

This project aimed to investigate the relationship between the volume of the caudate nucleus (CN) and repetitive motor behaviors (RMB) in an autistic sample, and whether sex assigned at birth moderates this relationship. Additionally, we explored the potential interactions of the ventromedial prefrontal cortex (vmPFC) with the caudate and RMB. We used structural MRI data and the Repetitive Behavior Scale-Revised (RBS-R) to measure CN volume and RMB, respectively. Our analysis revealed that only scan age and estimated full-scale IQ were significantly related to CN volume, while RMB and sex assigned at birth did not have a significant relationship. We also found a significant negative correlation between CN volume and estimated full-scale IQ. The independent samples t-tests revealed no significant difference between AFAB and AMAB groups in terms of RMB, but there was a difference in all normalized structural volumes, with a greater mean for the AMAB group. However, after controlling for confounding factors, sex assigned at birth was not significantly related to CN volume. Age was significantly

correlated with RMB, with reported RMB decreasing as age increased; this relationship was further affected by sex assigned at birth. Our findings suggest that CN volume is related to estimated full-scale IQ in autistic individuals, but not to RMB or sex assigned at birth.

Introduction

"Stimming" (self-stimulatory) behaviors in autism are behaviors in which the individual repeats physical movements, sounds, lines up specific objects repeatedly, or seeks sensory input in a controlled and repetitive manner. "Stims" vary widely and may include, for example, watching the same video clip over and over, hand flapping, or nail biting. Autistic people report that they engage in stimming as a self-regulatory mechanism, typically in response to an overwhelming environment, sensory overload, noisy thoughts, or an uncontainable emotion, and that stimming may serve a calming feedback loop (Kapp et al., 2019). Typically, these behaviors have been perceived by non-autistic individuals as "negative" or "wrong." Behavioral interventions delivered by therapists, clinicians, educators, or even parents, may often focus on identifying stimming and redirecting an autistic person to stop that behavior (Shenoy et al., 2017; DeVita-Raeburn 2016). Even outside of intervention contexts, neurotypical individuals may target "awkward" behaviors and unknowingly make ableist comments to autistic people (*Socially Inappropriate)*. This can have long-term adverse effects on autistic people's mental health; it can cause them to camouflage or mask in harmful ways, or even make an autistic person feel ashamed to react to their emotions and environments in natural ways through stimming (Bascom, 2011). Research on stimming has historically focused on reducing or redirecting repetitive motor behaviors (RMB). However, research into the potential *benefits* of stimming is key. It is important that autistic people get to see themselves centered in research about their own neurotype.

There has been limited research on the potential positive aspects of stimming, and most of this research has mostly been qualitative, with little to no focus on the neurobiological bases of stimming and autism (*Stimming in autism — Autistic people who stim deserve acceptance*). Further, previous research has suggested that autistic individuals may differ in their expressions of certain types of repetitive behaviors depending on their sex assigned at birth (Harrop et al., 2015); however, sex differences in the underlying neural mechanisms of RMB are understudied. This project aims to study the relationship between stimming, brain structures associated with mood/reward processes in autistic individuals, and sex assigned at birth. Additionally, previous research has suggested that assigned male at birth (AMAB) autistic individuals versus assigned female at birth (AFAB) individuals may differ in expressions of certain types of repetitive behaviors; however, sex differences in the underlying neural mechanisms are understudied (Di Martino et al., 2011; Hollander et al., 2005; Langen et al., 2007, 2014).

Thesis

Abstract

This study aimed to investigate the relationship between the volume of the caudate nucleus (CN) and repetitive motor behaviors (RMB) in an autistic sample, and whether sex assigned at birth moderates this relationship. Additionally, we explored the potential role of the ventromedial prefrontal cortex (vmPFC) in camouflaging, and its potential relationship with the caudate. We used structural MRI data and the Repetitive Behavior Scale-Revised (RBS-R) to measure CN volume and RMB, respectively. Our analysis revealed that only scan age and estimated full-scale IQ were significantly related to CN volume, while RMB and sex assigned at birth did not have a significant relationship. We also found a significant negative correlation between CN volume and estimated full-scale IQ. The independent samples t-tests revealed no significant difference between AFAB and AMAB groups in terms of RMB, but there was a difference in all normalized structural volumes, with a greater mean for the AMAB group. However, after controlling for confounding factors, sex assigned at birth was not significantly related to CN volume. Age was significantly correlated with RMB, with reported RMB decreasing as age increased, and this relationship was further affected by sex assigned at birth. Our findings suggest that CN volume is related to estimated full-scale IQ in autistic individuals, but not to RMB or sex assigned at birth.

Autism

About 1 in 44 children are diagnosed with an autism spectrum condition (ASC) in the United States. The DSM-5 outlines two significant symptom domains that contribute to an autism diagnosis: social communication and interaction, and restricted, repetitive behaviors and interests (RRBI). RRBIs can be divided into four subcategories: stereotyped or repetitive motor behaviors (RMB); insistence on sameness; intense, fixated interests; and hyper- or hyposensitivity to sensory stimuli (American Psychiatric Association, 2013). The focus of this project is on restricted, repetitive behaviors, most specifically on repetitive motor behaviors. This paper will first cover “autistic” behaviors, including repetitive motor behaviors, camouflaging, and executive functioning. Then it will move on to specific behaviors and their neuronal bases; it will also cover how sex assigned at birth can affect these things. Finally, it will detail what the basal ganglia and other structures are associated with in human behavior and related disorders to ASC.

The CDC estimates the sex ratio of assigned male to assigned female ASC prevalence to be about 4:1 (Maenner et al., 2020). Loomes et al. estimates the ratio to be closer to 3:1, after comparing the ratio reported by studies that used active vs. passive case ascertainment (2017). There are multiple factors that may be involved in this sex disparity, such as the female protective effect, a hypothesis suggesting that certain aspects of female biology might protect against certain genetic mutations that males are not protected against (Walsh et al., 2021). Another factor at play is the scarcity of research on AFAB autism.

RMB and factors potentially associated with RMB expression

Stimming and RMB. The goal of this project is to focus on one category of stims: repetitive motor behaviors. RMB are intentional, repeated physical movements. These behaviors are seen in any demographic (for neurotypical individuals it is often called fidgeting; common examples are bouncing or shaking a knee or a leg, tapping a pen, or pacing). However, they occur more often in autistic people (APA, 2013).

Stims are usually reported as a natural response to feelings (similar to a neurotypical person laughing when amused or smiling when they see something they like). Autistic people stim for many reasons; some people report that it soothes them when they are stressed or anxious, or that when they are happy the most natural thing to them is to stim (Kapp et al. 2019). Association learning is the process by which specific stimuli or thoughts are associated with certain actions (Haruno and Kawato 2006). Stimming may develop from a process of association learning. For example, the stimulus might be the feeling of excitement or joy and the action might be hand flapping. Over time hand flapping (an RMB) will become associated with excitement, leading to it occurring more frequently. Association learning has been linked to the caudate nucleus in the striatum. The striatum, specifically the putamen and caudate nucleus, have been implicated in ASC research, for their behavioral implications and reward associations (Hollander et al., 2005; Langen et al., 2007; Schuetze et al., 2016).

The Repetitive Behavior Scale - Revised (RBS-R) is a commonly used caregiver-report measure of RRBIs in ASC. The RBS-R assesses various repetitive behaviors, from lining toys up repeatedly to hand flapping. AFAB autistic individuals typically have a lower RBS-R score than AMAB autistic people (Supekar et al., 2016). However, the RBS-R does not fully capture the spectrum of possible repetitive motor behaviors, especially those that AFAB people may be more likely to engage in (Wiskerke et al. 2018). Therefore, AFAB autistic people may still be engaging in repetitive motor behaviors not assessed in the RBS-R (such as crocheting or sewing). More research on neural systems associated with RMB may provide insight into AFAB stimming and how the expression of stimming behaviors may be related to camouflaging.

Camouflaging and executive functioning. Camouflaging is the social set of compensatory skills used by autistic people to disguise their social difficulties. On average, AFAB autistic individuals use more camouflaging skills than assigned male at birth (AMAB) autistic individuals (Dean et al., 2016). Camouflaging may be a factor in why AFAB autistic individuals are regularly reported to have fewer RMB than AMAB autistic people. One of the brain structures potentially implicated in camouflaging is the ventromedial prefrontal cortex (vmPFC; Lai et al. 2019).

The vmPFC is a key region for executive functioning (EF) abilities, another set of skills autistic people often struggle with. Executive functioning refers to the group of skills that enable individuals to mentally plan multiple steps, complete goals, control impulses, follow multiple-step directions, and focus with distractions around (Leung et al., 2016). One study suggested that social symptoms of ASC may be associated with a specific set of executive functions (Leung et al., 2016). Murphy et al. found that autistic participants on average showed decreased activation in the vmPFC, which has been implicated with immediate reward choices (2017). They used a temporal discounting task to assess EF; the autistic group performed worse on average. A temporal discounting task is designed to assess how much a subjective value of the reward is reduced when the reward is received is delayed; a classic example is the marshmallow test. A person is presented with a single marshmallow and then told if they do not eat the marshmallow for a certain amount of time, they will receive two marshmallows after the time has passed.

Sex assigned at birth and autism

On average AFAB autistic people are reported to have less RRBI than AMAB individuals (both RMB and circumscribed interests). Harrop et al. (2018) executed a visual attention eye-tracking study on a large group of both AFAB and AMAB individuals. The participants were shown a variety of possible circumscribed interest objects; these objects were "gender-typical," that is, they included toys that are usually preferred or played with by female children as well as objects that are preferred by male children. The results suggested that interests were less in common overall for the autistic group and were more similar to each typically developing gender group. This study demonstrates how male-dominated research in autism may affect results for non-male autistic people. If researchers operate under the assumption that all autistic children are similar, or have similar interests (i.e., that "autism" is an overpowering factor compared to gender or sex assigned at birth), and assume that most autistic individuals are male, their results may not be as salient for non-male autistic people. This assumption may affect what we infer about RRBIs and specifically RMB because at this moment RRBI measurements and RMB measurements do not differentiate or account for differing expressions depending on sex assigned at birth. If AFAB autistic individuals have alternative or camouflaged RMB (such as crocheting), but the current measurements do not assess for these camouflaged RMB, then on average AFAB RMB will be reported as less common than AMAB RMB.

Neuronal structures potentially associated with RMB and their expression

The basal ganglia (BG) are separated into these structures: the striatum (made of the caudate nucleus, the putamen, and the nucleus accumbens), the globus pallidus, the subthalamic nucleus, and the substantia nigra (comprised of the pars compacta and the pars reticulata) (Kandel et al., 2014). BG is associated with reward learning, habit formation, voluntary motor behaviors, emotions, motivation, and some aspects of cognitive function (Subramanian et al. 2017).

The Striatum

The striatum, also called the corpus striatum, is the largest section of the basal ganglia, formed by the caudate nucleus, the putamen, and the nucleus accumbens. Its functions include motor and action planning, motivation, reinforcement and reinforcement learning, and reward learning (Subramanian et al. 2017). The striatum's function and dysfunction have been observed in Parkinson's disease (and other movement disorders,) depression, obsessive-compulsive disorder, and autism spectrum condition (Kandel et al., 2014).

The striatum has often been implicated in autism. Qiu et al. (2010) found a correlation between striatum shape differences and motor difficulties (measured using the Physical and Neurological Examination of Subtle Signs for Children) in an autistic all-male sample (aged 8-12 years). It has also been suggested that repetitive behaviors are associated with striatal hyperconnectivity (Abbott et al., 2018). Langen et al. (2014) reported an increased growth rate pattern in the striatum for autistic individuals (5AFAB:44AMAB) that was not seen in the typically developing control group. They also noted that faster striatum growth was correlated with higher rates of repetitive behavior in their preschool age group. In a previous study, Langen et al. discovered a significant increase in caudate volume in an autistic group compared to a typically developing group (2007).

The caudate nucleus (CN) is highly involved in voluntary motor behaviors, several types of learning (such as association and procedural learning), and inhibitions of actions. It is also a key part of the brain's reward system. The reward system is comprised of neural structures in charge of the sensation of "desire" or "wanting," association learning (specifically positive reinforcement and classical conditioning), and positive emotions such as euphoria, joy, and pleasure (Nusslock and Alloy, 2019). One of the essential neurochemicals involved in the reward system is dopamine (Chakravarthy et al., 2010). Dysregulation of reward processing can lead to executive dysfunction (Kriete and Noelle, 2015).

Due to the caudate nucleus' role in both voluntary motor behaviors and the reward system, it is likely that it is involved in autistic repetitive motor behaviors. I theorize that, for an autistic person, voluntary motor behaviors may be repeated over and over, releasing dopamine; over time they become associated with the feeling of pleasure or rewards, leading to stimming becoming the natural response to self-soothe when anxious, or react when joyful. In 2005 Hollander et al. found that right caudate volume (controlling for total brain volume) was significantly greater in an autistic group compared to a typically developing group. Right caudate volume was also positively correlated with ADI-C domain repetitive behavior scores, especially with obsessive-compulsive behaviors (Hollander et al., 2005). Another study found that an autistic group had a greater reward response in the caudate nucleus to non-social circumscribed interest rewards (such as video games) than to social rewards (Kohls et al. 2018). It is important to note that these studies did not include many AFAB autistic individuals, and some were AMAB-exclusive studies.

The putamen, combined with caudate nucleus, forms the striatum; it is involved in voluntary movement regulation and several types of learning. Conditions often associated with putamen involvement are Parkinson's disease, OCD (obsessive compulsive disorder), ADHD, ASC, and Tourette's syndrome (Kandel et al., 2014). In 2005 one study reported that greater putamen volume in autistic individuals was positively correlated with repetitive behaviors in adults (Hollander et al). In another study, Schuetze et al. found that the putamen growth pattern for AMAB autistic individuals was different than AMAB typically developing growth patterns (2016). One study found that RRBs (reported using the RRB domain of the ADI-R) were correlated with gray matter morphometry of the right putamen in AMAB autistic children, but not for AFAB autistic children (Supekar et al., 2016). Contrarily, a 2020 twin study found that correlations between RRBIs and brain structures were only significantly observed in AFAB twins, not in AMAB twins (van't Westeinde et al., 2020).

The nucleus accumbens (NAc) is associated with motivation, reward-related behavior, pleasure, and reinforcement learning (Kandel et al., 2014). NAc differences have been implicated as a factor of lack of social reward response, or at least lessened, in autistic individuals, partially accounting for autistic differences in social behavior (Scott-Van Zeeland 2010). Another study found that an autistic group on average had less NAc activity when instructed to think positively about human faces, compared to a typically developing group (Richey et al., 2015). These studies did not have equal sex assigned at birth *n*'s (Scott-Van Zeeland et al. was an AMAB-exclusive study).

The Prefrontal Cortex

The prefrontal cortex is associated with many processes, including immediate reward choices, executive functioning, social behavior, some aspects of personality, and specific components of speech and language (Gabrieli et al., 1998)**.** It has also been implicated in autistic camouflaging (Lai et al. 2019). This study found that enhanced camouflaging was positively correlated with greater vmPFC neural self-representation response in AFAB but not AMAB autistic individuals (neural self-representation is neural activity that may represent a person's reflection or concept of themselves).

One study found that increased prefrontal cortex connectivity with the salience network (SN; the brain network thought to be responsible for directing attention to important and relevant environmental stimuli) was positively correlated with higher sensory over-responsivity (SOR) only in the AFAB ASC group. In the AMAB group higher SOR was associated with SN connectivity and sensory processing regions (Cummings et al. 2020). This study points out how the same autistic characteristics can be associated with two different neural processes based on the sex assigned at birth. Cummings suggested that this study might demonstrate some ways that autistic sensory experiences (in this case, sensory over-responsivity), which is related to RMBs (Repetitive Motor Behaviors) are related to autistic social characteristics.

Hypotheses

The first hypothesis of this project is that the **volume of the caudate nucleus, which is involved in voluntary motor behaviors, will be positively correlated with the degree of RMB** (as measured by the Repetitive Behavior Scale-Revised [RBS-R] Stereotyped Behavior Subscale score as well as the Self Injurious Subscale [SIB]) **in an autistic sample.**

Additionally, AFAB autistic individuals have regularly been reported to have lower RBS-R scores compared to AMAB individuals; however, the RBS-R does not fully capture the spectrum of possible RMB, especially those that AFAB people may be more likely to engage in (Wiskerke et al., 2018). Therefore, AFAB autistic people may still be engaging in repetitive motor behaviors not assessed in the RBS-R (such as crocheting or sewing). Due to this lack of measurement sensitivity the existing literature may not accurately reflect the true prevalence of RMB in AFAB. **If AFAB autistic people are engaging in RMB not assessed by RBS-R, the correlation between caudate volume, and RBS-R Stereotyped and SIB scores may be weaker for AFAB than AMAB.**

Further, if the measurement is flawed but the BG (CN, NAc) have increased activity in ASC folk in relation to RMB I would expect to see the two groups' caudate volume average (respective to their total intracranial volume) to be similar, but the RBS-R Stereo and SIB scores would be significantly different between the two groups. This would then presumably indicate there might be something missing from the RBS-R. If there is a biological difference between AMAB and AFAB autism in caudate volume, there should be an observed difference in the volume of caudate.

According to Kapp et al., stimming can soothe anxiety and/or produce feelings of pleasure (2019); I theorize that these feelings become linked to RMB through a process of association learning. Consequently, **I hypothesize that structural covariance analysis will reveal that the volume of the caudate (responsible for voluntary motor**

movements) and the NAc (responsible for rewards and positive reinforcement) have a positive relationship in autistic individuals.

AFAB autistic individuals are reported to have fewer restrictive and repetitive behaviors (including repetitive motor behaviors), but they are also reported to have higher levels of autistic camouflaging (Lai et al., 2017). The ventromedial prefrontal cortex (vmPFC) is often indicated as one of the structures involved in camouflaging (Lai et al., 2019). **I hypothesize that if AFAB autistic folk display less stereotyped behaviors that are codable on a common measure of RRBIs, specifically because they are camouflaging more often than AMAB autistic individuals, then the volume of vmPFC and the caudate may have an inverse relationship.** A larger vmPFC may be typically seen with a smaller caudate. Lai et al. did not see a relationship between vmPFC activity and camouflaging in an AMAB group, therefore I also do not expect to see a relationship in this analysis (2019).

Methods

Participants

This analysis relies on data from Wave 1 of the GENDAAR Project (Gender Exploration of Neurogenetics and Development to Advance Autism Research; NIMH Data Archive Data Collection #2021). Data was collected from the following sites: Yale University, Harvard University/Boston Children's Hospital, University of California Los Angeles, and the University of Washington/Seattle Children's Research Institute.

Participants were between the ages of 7-18 years, and their autism diagnoses were confirmed by expert clinicians with the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2; Lord et al., 2012), and the Autism Diagnostic Interview-Revised (ADI-R; Lord et al., 1994) using DSM-5 criteria. Participants were excluded if the clinician had any suspicion that they were not autistic regardless of their score on the ADOS or ADI. Restricted, repetitive, behaviors and interests were recorded using the Repetitive Behavior Scale-Revised (RBS-R). Participants were included if they scored ≥70 on any IQ metric as estimated via the Differential Ability Scales, Second Edition (DAS-II; Verbal, Nonverbal, Spatial, Special Nonverbal Composite, or General Conceptual Ability Standard Score; Elliot., 2007). See Jack et al., 2021, for full details of cohort characterization and inclusion/exclusion criteria.

Individuals taking anti-epileptic medication or who reported having had a seizure a year before the neuroimaging took place were excluded from the initial scan. For full medication exclusion criteria see Jack et al., 2021 Supplementary material. Due to the evidence that neuroleptic medications, also known as anti-psychotic medications, can affect basal ganglia volume, individuals taking any neuroleptic medication were excluded from this analysis (Langen et al., 2007).

This project analysis only included participants from Wave 1 who were autistic and had complete, usable structural MRI (sMRI) and RBS-R data from this timepoint. 9 participants were excluded from this analysis due to missing RBS-R scores. Visual inspection for artifacts was used to determine if sMRI scans were usable. Three participants were excluded for one of the following reasons: white matter injury, had <70 on all DAS-II subscale standard scores, or did not meet diagnostic criteria for ADOS-2 or ADI-R. The final sample had total *N*=128; AFAB: 61, AMAB: 67.

Table 1

Independent sample t tests between AFAB and AMAB groups

	AFAB n=61	AMAB n=67		2-tailed
	M(*SD*)	*M*(*SD*)	*t*	*p*
Mean scan age (months)	156.67(32.02)	155.43(35.79)	0.21	.837
FSIQ (DAS-2 GCA)	103.75(21.18)	101.43(20.51)	0.63	.530
ADOS CSS	6.3(1.73)	6.85(2.17)	-1.57	.119
ADI-R: A (Social)	18.73(6.42)	19.88(4.97)	-1.13	.263
ADI-R: B (Communication)	15.67(4.63)	17.11(4.55)	-1.76	.081
ADI-R: C (Behavior)	5.7(2.59)	6.52(2.67)	-1.74	.085
RBS-R (SB)	3.03(3.17)	3.1(3.14)	-0.19	.851
RBS-R (SIB)	1.54(1.77)	2.16(3.35)	-1.40	.164
RBS-R SB+SIB	4.49(4.27)	5.27(5.52)	-0.92	.36
Caudate vol (left)* mm^3	3923.26(447.03)	4119.21(533.32)	-2.24	.027
Caudate vol (right)* mm^3	4043.92(467.82)	4277.9(530.66)	-2.64	.009
NAc vol (left)* mm^3	610.83(108.7)	660.76(108.13)	-2.60	.010
NAc vol (right)* mm^3	640.39(100.93)	673.62(116.19)	-1.72	.088

(normalized) NAc vol (right) mm^3	.00(.00)	.00(.00)	4.20	<.001
(normalized) NAc vol (left) mm^3	.00(.00)	.00(.00)	2.77	<.001
vmPFC (left) mm^3	14611.03(1613.61)	15590.72(1666.39)	-3.38	<.001
VmPFC (right) mm	1413.23(1623.89)	15758.34(1738.54)	-3.17	<.001
(normalized) vmPFC (left) mm^3	.01(.00)	.01(.00)	4.39	<.001
(normalized) vmPFC (right)	.01(.00)	.01(.00)	4.33	<.001

Note: FSIQ (DAS-2 GCA): Differential Ability Scales-II (DAS-II), General Conceptual Ability Standard Score, ADOS CSS: Autism Diagnostic Observation Schedule - Calibrated Severity Score (CSS), observational measure, ADI-R (Social) Autism Diagnostic Interview Revised, Social Total, parent interview, ADI-R (Communication): Autism Diagnostic Interview Revised, Communication Total, parent interview, ADI-R (Behavior): Autism Diagnostic Interview Revised, Behavioral Total, parent interview, RBS-R (SB): Stereotyped Behavior Total, Repetitive Behavior Scale Revised, Parent-report, RBS-R (SIB): Self-Injurious Behavior, Repetitive Behavior Scale Revised (RBS-R), Parent-report.

These structures have been normalized for total intracranial volume using the proportion method.

*These structures have not been normalized by either total intracranial or total brain volume.

Measurements

The *Repetitive Behavior Scale-Revised (RBS-R)* assesses repetitive motor behaviors and interests and contains 6 subscales: stereotyped behavior, self-injurious behavior, compulsive behavior, ritualistic behavior, sameness behavior, and restricted behavior. There are a total of 43 items, reported on a 4-point Likert scale; 0 = “behavior does not occur”, 1 = “behavior occurs and is a mild problem” 2 = “behavior occurs and is a moderate problem”, and 3 = “behavior occurs and is a severe problem”. The Stereotyped Behavior subscale has 6 items, and the Self-injurious Behavior scale has 8 items.

The *Differential Ability Scales Second Edition General Conceptual Ability Score* measures a group of cognitive abilities including verbal and visual working memory, immediate and delayed recall, visual recognition and matching, processing, and naming speed, phonological processing, as well as an understanding of basic number concepts (DAS-II; Elliot, 2007).

MRI Acquisition

All four sites began data collection using a Siemens 3 T Tim Trio magnet with 12 channel head coil. Two sites upgraded to a Siemens 3 T Prisma Fit with 20 channel headcoil partway through data collection. Scan site (n = 6; site of data collection + scanner type) is included in all analyses as a nuisance regressor.

Quality assurance of raw MRI scans. Before processing via FreeSurfer, raw MRI scans were rated by a team of trained research assistants. Specifically, scans were visually inspected and rated for motion-related and other artifacts, including ringing and phase wrapping. To ensure standardization across raters, training included rating a set of 20 scans that was assigned to all raters. After training on these 20 scans, raters were assigned batches of unprocessed MRI scans. Each scan was rated by at least two independent raters. Scans were rated on a scale from 0 to 2 as follows: 0 = "unusable scan," 1= "usable but not high quality" and 2 = "usable." "Unusable scans" designated those scans with severe motion and/or other artifacts that made them unsuitable for use in FreeSurfer. Scans rated as "usable but not high quality" were scans that showed, for example, some evidence of motion artifacts but not severe artifacts that would render them unusable for processing and analyses. Differences between ratings and scans rated as "1" (i.e., "usable but not high quality") were discussed during group meetings to determine the final set of scans submitted to FreeSurfer.

For the 140 autistic participants otherwise meeting inclusionary criteria in the current study, a total of 137 participants had usable sMRI data.

MRI Processing

The project used Freesurfer's automatic segmentation of the left and right caudate and left and right putamen; FSL's FIRST and Freesurfer demonstrate high levels of agreement in segmentation of the subcortical structures. (Hibar et al. 2015, Lidauer et al., 2022, Perlaki et al. 2017). The Desikan-Killiany Atlas was used for parcellation. sMRI data will be processed following a standardized protocol; see Stein et al., 2012, Nature Genetics. The nucleus accumbens (NAc) has been shown to be difficult to accurately segment automatically (Lidauer et al., 2022). Thus, the NAc was first automatically segmented with Freesurfer, and afterward, the mask was manually adjusted for each individual (Birbilis et al. 2021).

The ventromedial prefrontal cortex (vmPFC) has been implicated in camouflaging (Lai et al., 2019) and was a region of interest (ROI) in this project. Freesurfer defines the vmPFC as the sum of the left and right medial orbitofrontal and lateral orbitofrontal cortices (Morey et al., 2015). The Desikan-Killany Atlas was used for this project.

Analysis

All statistical analyses were conducted using SPSS 28.0 (SPSS Inc., Chicago, Illinois). The design used was a multiple linear regression with sex assigned at birth, RBS-R SIB and SB sub-scores summed (RMB measure), and the interaction between sex assigned at birth and RMB measure as predictor variables, and the region of interest (left or right caudate volume) as the outcome. Estimated FSIQ, scan site, and scan age were added as covariates Volumetric data were normalized for estimated total intracranial volume using the proportion method (O'Brien et al., 2011); the ROI volume was divided by the eTIV (generated by Freesurfer) and used as the new ROI variable. Age, IQ, and the RMB measure scores were grand mean centered.

Two multiple linear regression models were run; one for the left caudate nucleus and one for the right caudate nucleus (Eisenberg et al., 2015). Multiple studies have found asymmetrical development and volume of the left and right caudate in autistic populations, hence why the caudate were not summed across hemispheres (Hollander et al., 2005).

Independent samples t-tests were used to examine group differences in scan age, FSIQ, ADOS, ADI-R; modules A, B, and C, RBS-R; SB and SIB subscales, as well as ROI volume (CN, NAc, putamen, and vmPFC), RBS-R; SB and SIB subscales.

An a priori power analysis was conducted using G*Power version 3.1.9.7 (Faul et al., 2007) to determine the minimum sample size required to test the study hypothesis. Results indicated the required sample size to achieve 80% power for detecting a medium effect, at a significance criterion of $\alpha = .05$, was N = 55 for linear multiple regression. Thus, the obtained sample size of N = 128 is sufficient to test the study hypothesis.

Structural Covariance

The design was a seed-based structural covariance analysis using Freesurfer, using the following ROIs (region of interest): the left and right caudate, the left and right nucleus accumbens, and the left and right vmPFC. Detailed definitions of the ROIs can be found in "MRI Processing;" to summarize, FreeSurfer (version 7) was used to automatically segment the volume of subcortical structures. For the seed-based covariance, the volume in each of the seed regions (CN, NAc, and the vmPFC) was correlated with the morphology of another seed region (Alexander-Bloch et al., 2013). The two structural covariances run were the caudate nucleus (voluntary motor movements) and the nucleus accumbens (pleasure), and then of the caudate and the ventromedial prefrontal cortex. The RBS-R SB and SIB subscales (summed) were related to the CN volume for both analyses. To examine structural covariance between ROIs, Spearman's rho was used. Partial correlations were used to control for age, FSIQ, and estimated total intracranial volume.

To examine the associations of the RBS-R (SB and SIB subscales) with structural covariance between the CN and NAc, for each ROI z-scores were computed (e.g., z-score for volume of the left caudate, z-score for volume of right NAc) after normalization for eTIV using the proportion method. A product of the z-scores for each pair of ROIs was calculated (e.g., the product of the z-score for the left caudate and right NAc). This product was then correlated with the behavioral metric using Spearman's rho and partial correlations controlling for age, and estimated FSIQ, (e.g., product of the left caudate and right vmPFC z-scores correlated with RBS-R SB+SIB metric) (Eisenberg et al., 2015). Freesurfer's automated intracranial volume estimate was used to exclude variation in overall brain size from explaining volume covariances between ROIs.

CN, NAc, and RBS-R SB and SIB subscales

For this project, RMB were defined as the sum of the RBS-R subscales SB+SIB. Associations between the measure, CN, and NAc were assessed using Spearman's rho to protect against extreme or skewed RBS-R (SB and SIB) scores (Eisenberg et al., 2015).

CN and the vmPFC

Data about camouflaging skills and traits were not collected during the initial wave of the GENDAAR project, therefore the vmPFC cannot be directly correlated with measured camouflaging behaviors. However, due to the implications of the vmPFC and its role in camouflaging behaviors, it is relevant to examine the structural relationship of the CN and the vmPFC.

Results

Descriptives

The independent samples t tests demonstrated a significant volumetric difference in the CN, nucleus accumbens, and vmPFC between the AFAB and AMAB groups (see Table 1) Specifically, the AMAB group had a significantly higher mean score on all ROI volumes (except for the right nucleus accumbens) than the AFAB group.

A Pearson's correlation was conducted to assess the relationship between all variables. There were several significant negative correlations; scan age and the RMB measure, scan age and the RMB and SAB interaction, and estimated FSIQ and the RMB measure (see Tables 2 and 3).

Both the left and right CN volumes were significantly negatively correlated with estimated FSIQ. The right CN was also negatively correlated with scan age (see Tables 2 and 3).

Table 2

Means, SDs, and Pearson Correlations amount the left CN volume and IVs							
Variable	M	SD	1	2	3	4	5
1. L CN vol (mm3)	.00	501.88	-	-.16	-.20*	-.03	-.10
2. Scan Age	.00	1.37		-	.08	-.30*	-.30*
3. FSIQ	.00	20.78			-	-.26*	-.17
4. RBS-R (SB+SIB)	.00	1.16				-	.62*
*p<0.05 2 tailed							

Table 3

Means, SDs, and Pearson Correlations amount the right CN volume and IVs							
Variable	M	SD	1	2	3	4	5
1. R CN vol (mm3)	.00	513.32	-	-.20*	-.22*	-.04	-.05
2. Scan Age	.00	1.37		-	.08	-.30*	-.30*
3. FSIQ	.00	20.78			-	-.26*	-.17
4. RBS-R (SB+SIB)	.00	1.17				-	.62*
*p<0.05 2 tailed							

Hypothesis 1

Multiple Regression

$$LeftCN = RMB + SAB + ScanAge + FSIQ + SAB \cdot RMB$$
$$RightCN = RMB + SAB + ScanAge + FSIQ + SAB \cdot RMB$$

The first model (left caudate nucleus) had an adjusted R^2 value of .09; $F(10, 117) = 2.24$, $p < .020$. The second model (the right caudate nucleus) had an adjusted R square (.11); $F(9, 118) = 2.58$, $p < .007$. The model revealed that the only significant predictors of left and right CN volume were estimated FSIQ and scan age (see Table 2 and 3). The RMB measure, and the interaction of SAB by RMB measure, were not statistically related to the left or right caudate nucleus volume. The Harvard scan site was also a significant predictor of right CN volume (β = -.21).

Table 4

Regression Coefficients for Predicting left CN volume in ASC group

Variable	B	STD Error	95% CI	β	t	p
Constant	.003	.000	[.000, .000]		41.39	<.001*
Sex (F=1)	9.603E-5	.000	[.000, .000]	.14	1.67	.097
Scan Age (months)	-1.913E-6	.000	[.000, .000]	-.20	-2.22	.028*
FSIQ	-3.774E-6	.000	[.000, .000]	-.24	-2.64	.009*
RBS-R (SB+SIB)	-5.464E-6	.000	[.000, .000]	-.08	-.66	.511
Sex*RBS-R	-8.144E-6	.000	[.000, .000]	-.07	-.63	.527

Note: Adjusted R^2 = .09 (N = 128, p =.020). CI = confidence interval for B.

Table 5

Regression Coefficients for Predicting right CN volume in ASC group

Variable	B	STD Error	95% CI	β	t	p
Constant	-2483.98	.000	[.000, .000]		-7.41	<.001*
Sex (F=1)	-314.93	.000	[.000, .000]	-.15	1.71	.089
Scan Age (months)	-2.111E-6	.000	[.000, .000]	-.22	-2.50	.014*
FSIQ	-3.624E-6	.000	[.000, .000]	-.23	-2.59	.011*
RBS-R (SB+SIB)	-3.175E-7	.000	[.000, .000]	-.01	-.04	.969

Sex*RBS-R	-8.918E-6	.000	[.000, .000]	-.08	-.71	.480
Note: R^2adj = .11 (N = 128, p =.007). CI = confidence interval for B.						

Due to the significance of the Harvard scan site, estimated FSIQ, and age, we wanted to further investigate the data from the Harvard scan site. Table 6 shows a bow and whisker plot of scan sites and the GCASS DAS. This table shows two cases from the Harvard scan site were extreme outliers.

Scan Site and estimated FSIQ Plot

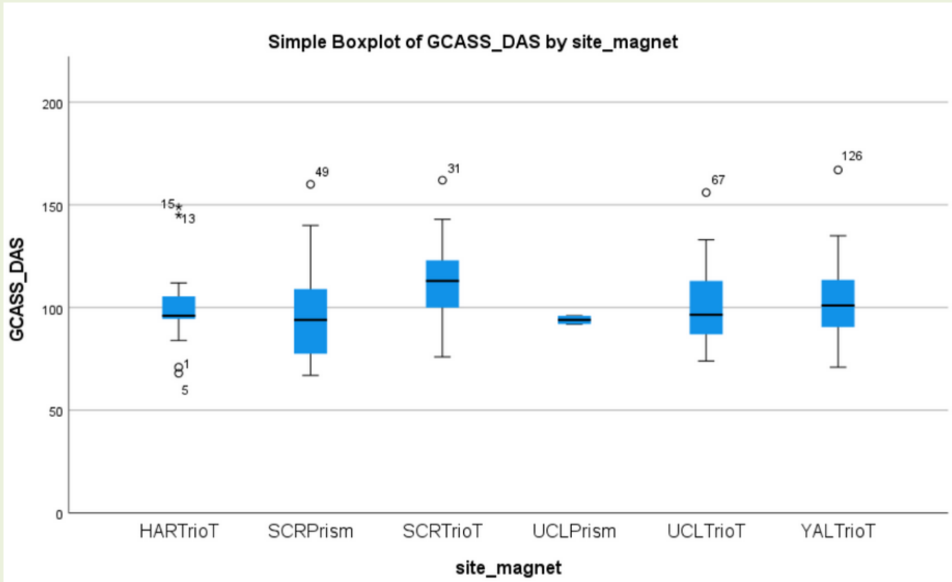

Figure 1

Table 7 shows RMB by scan age, and differentiated by SAB. Both groups' RMB decreased as age increased, and the AFAB group decreased more than the AMAB group.

RMB by age by SAB

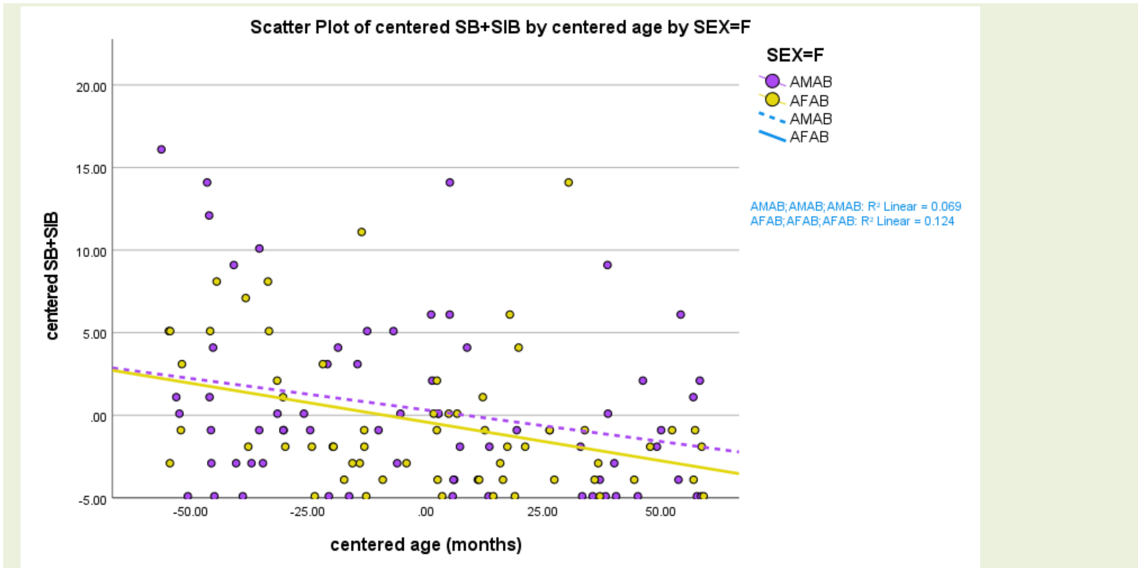

Figure 2

Hypothesis 2

A partial correlation was run to control for estimated FSIQ and scan age,with the variables of RBS-R SB+SIB (centered) and z score products (left CN*right NAc, left CN*left NAc, right CN*right NAc, right*right NAc; all centered). No significant relationships were found.

Table 6

Partial Correlations of ROIs and RBS-R SB+SIB		
ROI Z Score Products	*Partial Correlation*	*p*
Left CN*Left Nac	.08	.405
Left CN*Right Nac	.06	.544
Right CN*Left Nac	.08	.398
Right CN*Right Nac	.06	.490

Hypothesis 3

No significant relationship was found in the partial correlation of the RBS-R SB+SIB and ROIs (CN and vmPFC).

Table 7

Partial Correlations of ROIs and RBS-R SB+SIB		
ROI Z Score Products	*Partial Correlation*	*p*
Left CN*Left vmPFC	.09	.330
Left CN*Right vmPFC	.06	.498
Right CN*Left vmPFC	.08	398
Right CN*Right vmPFC	.06	.490

Discussion

We had predicted that the **volume of the caudate nucleus, which is involved in voluntary motor behaviors, would be positively correlated with the degree of RMB** (as measured by the Repetitive Behavior Scale-Revised [RBS-R] Stereotyped Behavior

[SB] Subscale score and the Self Injurious Subscale [SIB]) **in an autistic sample,** and that sex assigned at birth would moderate this relationship. However, this analysis revealed that only scan age and estimated FSIQ were significantly related to CN volume. The RBS-R SB+SIB was not significantly related to volume, and the interaction of RMB and sex assigned at birth also were not related to volume.

Multiple studies have found a significant positive relationship between CN volume and varying estimated FSIQ measures in neurotypical groups (Grazioplene et al, 2015, MacDonald et al., 2013). In this analysis the left and right caudate nucleus volume had significant negative correlations with estimated FSIQ and predicted a negative progression in CN volume. Sandman et al. found that increased volume of the basal ganglia (specifically the putamen) in preadolescent children (mean age = 90 months) was associated with impaired cognitive performance (2014).

The independent samples t tests showed no significant difference between the AFAB and AMAB SB+SIB scores, but it did show a difference in all normalized structural volumes (caudate nucleus, nucleus accumbens, putamen, and ventromedial prefrontal cortex), with a greater mean for the AMAB group. However, after controlling for age, estimated FSIQ, and scan site, our analysis did not find a significant relationship between sex assigned at birth and CN volume.

The ratio method of normalizing for intracranial volume was used, although, some research has suggested that a residual method is better at capturing differences when sex assigned at birth is a factor (Barnes et al., 2010, Dhamala et al., 2022).

Age was a significant predictor in our analysis. Multiple studies have found growth patterns of the CN associated with repetitive behaviors (Langen et al., 2014, Qiu et al, 2016). Rather than look at caudate volume related to RMB, it may have been more prevalent to look at volume over time related to RMB.

Moving on to age-related findings, age was significantly correlated to RMB. As age increased, reported RMB decreased. Additionally, the relationship between age and RMB was further affected by sex assigned at birth. As age increased in the AFAB group, their reported RMBs decreased more than the AMAB group.

One explanation for this relationship is camouflaging. Camouflaging skills fluctuate with age, due to a variety of influences such as social environment, cognitive changes, and experiences (Cook et al.) Therefore, it may be that as AFAB Autistic individuals age and strengthen their camouflaging skills, their levels of RMB decrease. This analysis did show that age impacted RMB, which may be due to camouflaging and deserves further studies.

The second analysis was a structural covariance, set up to investigate the relationship between RMB and the volume of the CN and the NAc. We were not able to determine a statistically significant relationship between either of these structures in relation to RMB. These findings suggest that structural covariance between these brain regions may not play a significant role in the levels of RMB in autistic individuals, and that RMB are not significantly linked to association learning in the NAc.

The third analysis was another structural covariance; we proposed to see an inverse relationship between the CN and the vmPFC in the AFAB group. No significant relationship was found in any of this structural analysis. As stated previously, the large age range may have obscured more sensitive effects in the structural covariances.

Limitations

Eisenberg et al. pointed out that the range of RMB might be too broad to appropriately map onto neuroanatomy, and we have previously discussed how the full range of RMB might not be captured by the RBS-R particularly for AFAB individuals.

As stated before, many studies have found abnormal growth patterns in the striatum for autistic individuals. To accurately assess the relationship of RMB and striatum, a longitudinal study may be more appropriate to account for any unusual growth patterns.

The understanding of AFAB RMB is still limited, so the measurements used to assess RMB levels may not be sensitive to that group. Research on the interaction between camouflaging and RMB is also limited and was not applied to this analysis.

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Biography

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