RELATIONSHIPS BETWEEN STRIATAL GRAY MATTER INTEGRITY AND IMPLICIT ASSOCIATIVE LEARNING

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Abstract

Previous studies have implicated striatal structures (i.e., caudate, putamen) in implicit associative learning (IAL), or the learning of associations between events without conscious awareness that subserves language and habit learning. While previous neuroimaging studies have examined IAL in relation to striatal function and the integrity of white matter tracts emanating from the striatum, none have examined the relationship between striatal gray matter integrity and IAL. Gray matter integrity can provide valuable information about microstructural properties of caudate and putamen (e.g., degree of neuronal density) that may complement previous examinations of the neural substrates of implicit learning. In this study, 25 young adults (21.33 ± 2.20 years old) underwent diffusion tensor imaging and completed the Triplets Learning Task, which requires the acquisition of associations between two cues (location of red circles) with a target (location of green circle). Task performance (IAL scores) correlated with measures of bilateral caudate gray matter integrity (e.g., axial diffusivity [AD], mean diffusivity [MD], radial diffusivity [RD]). That is, better IAL scores were significantly related to lower bilateral caudate AD. Additionally, better IAL scores exhibited a marginally significant correlation with lower left putamen MD and RD and right putamen MD. These results for striatal gray matter integrity are consistent with previous neuroimaging studies demonstrating involvement of striatum in IAL. Moreover, they support the notion that gray matter integrity is sensitive to individual differences in cognition, even among healthy younger adults.

Introduction

Implicit associative learning (IAL) is the learning of relationships between events in one's environment without explicit awareness (Stillman, Howard, & Howard, 2016). This type of learning is crucial in acquiring language during childhood and in picking up important cues from one's environment or during social interactions (Stillman, Howard, & Howard, 2016; Kuhl, 2004; Foerde & Shohamy, 2011; Lieberman, 2000). IAL is different from other types of learning, particularly declarative learning, in that it occurs below the level of conscious awareness and has different neurological bases (Foerde & Shohamy, 2011).

The Triplet Learning Task (TLT) is one measure of IAL that has been used extensively in behavioral, functional, and structural studies (Simon, Howard, & Howard, 2010; Stillman et al., 2013; Forman-Alberti, Seaman, Howard, & Howard, 2014; Howard, Howard, Dennis, & Kelly, 2008). During each trial of the TLT, participants must respond to the location of a target in sequential three-stimuli events (cue 1, cue 2, target), also termed "triplets". Unbeknownst to participants, cue locations predict the target location on more frequently presented trials (high frequency [HF] triplets) while they do not predict the target location on less frequently presented trials (low frequency [LF] triplets). IAL is measured as the difference in participant reaction times on predictive HF versus non-predictive LF triplets, with larger HF-LF reaction time differences and faster HF reaction times indicating implicit associative learning. The TLT has a reduced motor component relative to other IAL tasks, including the alternating serial reaction time task (ASRT) and the serial reaction time task (SRTT) that require a motor response to each stimulus, making it a better task design for neuroimaging techniques that are sensitive to response-related motion.

The striatum, a group of subcortical gray matter structures including the caudate and the putamen, has previously been implicated as a neural correlate of IAL. In functional magnetic resonance imaging (fMRI) studies of young adults, individual differences in bilateral caudate activation (HF triplets > LF triplets) were associated with individual differences in late stage implicit learning (Simon, Vaidya, Howard, & Howard, 2012). Similarly, another fMRI study utilizing a serial reaction time task (implicit learning vs. baseline conditions) found significant right caudate and right inferior putamen activation for the implicit learning vs. baseline contrast (Rauch et al., 1997). Further analyses revealed that among the individuals who exhibited better learning (reaction time in learning condition < reaction time in baseline condition), increased putamen activation was positively correlated with greater reaction time advantage (Rauch et al., 1997). Additionally, another study found that increased positive functional resting state connectivity between dorsal caudate and a cluster extending from the right parahippocampal gyrus into the right hippocampus was correlated with faster HF compared to LF reaction times, or better implicit learning performance (Stillman et al., 2013). Consistent with these fMRI finding, studies using diffusion tensor imaging (DTI) have shown that better integrity of white matter tracts emanating from the caudate, specifically the left caudate-dorsolateral prefrontal cortex (DLPFC) tract, was related to better implicit learning performance (Bennett, Madden, Vaidya, Howard, & Howard, 2011). Genotyping studies have also shown that the presence of a dopamine transporter gene, which allows for greater synaptic dopamine expression in the striatum, is related to better implicit sequence learning (Simon et al., 2011). Finally, a PET study using a dopamine receptor ligand found that dopamine transmission in bilateral caudate and left dorsomedial putamen is associated with faster reaction times on a test condition measuring implicit sequence learning compared to a non-learning control condition (Badgaiyan, Fischman, & Alpert, 2007). However, although numerous methods have been utilized to implicate striatal involvement in IAL, the integrity of these gray matter structures has not been examined in relation to learning.

One way to assess gray matter integrity is using diffusion tensor imaging (DTI) (Soares, Marques, Alves, & Sousa, 2013). DTI measures the diffusion (or movement) of water molecules within three-dimensional units that comprise brain scan images, termed voxels. Rates of diffusion, which are sampled from many directions, can be summarized as a diffusion tensor with three axes or eigenvalues ($\lambda 1$, $\lambda 2$, and $\lambda 3$) from which multiple "integrity" metrics can be calculated. Fractional anisotropy (FA) measures the coherence of orientation of diffusion. Higher FA, or greater anisotropic diffusion, indicates the restriction of diffusion in one direction, while lower FA, which is an indicator of greater isotropic diffusion, indicates less restricted diffusion. Mean diffusivity (MD), in contrast, measures the average diffusion of water along the three axes within a given voxel, with lower mean diffusivity indicating less diffusion. Other measures of diffusion, including axial diffusivity (AD) and radial diffusivity (RD), measure the rate of diffusion along the main axis ($\lambda 1$) and transverse axes ($\lambda 2 + \lambda 3 / 2$), respectively.

Although DTI has traditionally been used to examine the integrity of white matter tracts as assessed through diffusion, it might reveal important information about gray matter microstructure. While the particulars of what is being measured by these integrity metrics is widely debated, explanations for better white matter integrity metrics (higher FA and lower MD, AD, and RD) include more or thicker myelination, increased fiber packing density, intact axonal membranes, and reduced extracellular water (Chad, Pasternak, Salat, & Chen, 2018). Extending these DTI metrics to the microstructure of gray matter, some scholars have suggested that better gray matter integrity (lower FA, MD, AD, and RD) may be linked to increased neurogenesis, decreased neurodegeneration, increased synaptogenesis, increased dendritic (de)arborization, and changes in gray matter morphology (Zatorre, Fields, & Johansen-Berg, 2012). One healthy aging study examining striatal integrity among young, middle-aged, and older adults found significant positive relations concerning putamen (FA, MD, AD, RD) and caudate (MD, AD) diffusion metrics with age, signifying that less striatal gray matter diffusion is found among young adults compared to older adults (Gong et al., 2014). This study posited axonal disintegration, cell loss, and iron deposition as potential contributors to age-related diffusion increases and integrity degradation in striatal regions, indicating that neuron and neurite density may also be important for striatal integrity in healthy young adults (Gong et al., 2014). This study aims to establish if these gray matter integrity metrics may provide explanations concerning individual differences in IAL performance tied to brain microstructure.

To examine whether the study of individual differences in gray matter integrity could yield valuable information about IAL, this study pursued one aim, composed of two sub-aims. The primary aim was to analyze whether striatal gray matter integrity was correlated with implicit associative learning among a healthy young adult sample. Subaim one was to determine whether bilateral caudate integrity was related to IAL, while subaim two was to determine if bilateral putamen integrity was related to IAL. That caudate and putamen have been implicated as neural substrates of IAL functionally and structurally provides good indication that they would correlate significantly with IAL.

Methods

Participants

Thirty-two undergraduate students (21.33 ± 2.20 years old) from the subject pool at the University of California, Riverside, were recruited. All participants gave informed consent and received course credit for participation. Participants were screened to ensure they could enter the scanner safely (e.g. pregnancy, claustrophobia, having metal inside the body) and for neurological (e.g. depression) conditions which could influence responses using Initial MRI and Participant Screening Forms. Participants were also screened for cognitive (e.g. cued recall, visuospatial ability) conditions using the Montreal Cognitive Assessment (MoCA). Seven participants were excluded from the final analyses due to poor behavioral performance on the TLT (1 participant, ACC < 60.75%), incomplete data (4 participants), DTI pre-processing errors (1 participant), and classification as an outlier on the learning score measure (1 participant) (N = 25).

Procedure

Participants completed two separate testing sessions approximately one week apart. During the first session (1 hr. 15 min.), a high-resolution structural scan was acquired. During the second session (1 hr. 15 min.), participants performed eight sessions of the TLT during acquisition of both functional scans (session 1-3 and 6-8; only the behavioral data will be reported here) and diffusion scans (sessions 4-5). Once finished, participants were given a TLT recognition task and a post-test interview.

Triplet Learning Task

The Triplet Learning Task (TLT) is a probabilistic sequence learning task that involves the acquisition of associations between events. During the TLT, participants are presented with four empty circles lined horizontally on a screen visible from inside the scanner. On each trial or “triplet”, three circles fill in consecutively in a red, red, green sequence (cue 1, cue 2, target). Each red cue was presented for 150 ms, while the green target remained for 800 ms, with two 150 ms inter-stimulus-intervals between the two cues and target and a 600 ms inter-trial-interval between triplets (2,000 ms/triplet). Participants passively viewed the presentation of the red cues and were asked to quickly and accurately respond to the position of the green target using two MR-compatible button boxes. Each button box had two buttons, totaling four buttons which correspond to each of the four circle positions. Accuracy and response times (RT) were collected for all target responses.

Unbeknownst to participants, some triplets occurred with greater frequency (high-frequency, HF) than others (low-frequency, LF). To optimize learning, HF triplets involved both first-order (the location of the second red cue predicted the location of the green target) and second-order (the location of the first cue predicted the location of the target) structure.

Participants completed eight sessions, each composed of four blocks of 32 triplets (1,024 triplets total). For each block, 4 unique HF triplets were presented 6 times, totaling 24 HF triplets per block. Eight unique LF triplets were also presented in each block, forming a 3:1 ratio of HF (75% frequency) to LF (25% frequency) triplets. Triplets were counterbalanced to ensure that cues and targets occurred in each location equally often. Trials in every block were randomized, as well. Within a session, each block was separated by a 10,000 ms break, during which black text stating “rest now” was presented on the screen. Sessions were separated by a break during which researchers manually restarted the task. Every session lasted approximately 5 minutes, making for a total test time of approximately 40 minutes.

Recognition Tests

Participants completed a recognition test outside of the scanner once they finished the TLT. Similar to the TLT, participants viewed triplets and responded whether they occurred frequently, infrequently, or not at all during the learning phase using one of three button presses. The four unique HF triplets, eight unique LF triplets, and eight triplets that were not a part of the main study (no frequency, NF) were presented. NF triplets included trills (e.g. 232, 434; where the numbers refer to the location of the first cue, second cue, and target of a given triplet, with 1 indicating the farthest left circle and 4 the farthest right circle) and repetitions (e.g. 333, 444).

After the recognition task, participants completed an interview acquired verbatim from Howard, Howard, Dennis and Kelly (2008) to further ascertain explicit awareness. Interview questions probed to see if participants could recall any patterns observed during the learning phase, starting generally about performance strategies before delving into specifics about patterns or relationships participants might have noticed. The questions utilized were the following: (1) What strategy did you use to improve your speed and accuracy in the experiment?, (2) Did you notice any relationship between either of the first two lights and the third light?, (3) Did all the lights turn on equally often, or did some lights come on more often than others?, and (4) In fact, there was a relationship between the first two lights and the third. What do you think it was for the first light? What about the second light?

Calculating IAL Scores

All behavioral data was manually cleaned up for MRI acquisition artifacts, which biased target responses on certain trials in sessions one to three and sessions six to eight, prior to being analyzed using the Statistical Package for the Social Sciences (SPSS). Mean accuracy was acquired separately for HF and LF triplets for every block then averaged across sessions for every participant. Median reaction times on correct trials were calculated separately for both HF and LF triplets in each of the 32 blocks for each individual. Median RTs for every block were then averaged across sessions to acquire mean of median HF and LF session RTs for every participant. IAL scores, used to measure the extent of implicit associative learning, were calculated as the difference in reaction time between HF and LF triplets summed across sessions one to eight, excluding sessions 4-5 due to the MRI acquisition artifact, for every participant.

Larger positive scores indicate better learning.

MRI Scanning Protocol

Participants were scanned using a 3T Siemens Prisma magnetic resonance imaging (MRI) scanner fitted with a 32-channel head coil. A mirror attached to the head coil allowed participants to view the stimuli presented on a screen behind the MRI during the scan. To minimize head movements, fitted padding was utilized.

Two diffusion-weighted echo-planar imaging sequences were acquired in opposing acquisition order with the following parameters: time repetition (TR)/time echo (TE) = 3500/102 ms, field of view (FOV) = 218×218 mm, 72 axial slices, and 1.7 mm3 spatial resolution. For each sequence, gradients (b = 1500 and 3000 s/mm2) were applied in 64 orthogonal directions, with six images having no diffusion weighting (b=0).

A single high-resolution structural image (magnetization-prepared rapid gradient-echo sequence, MPRAGE) was also acquired with the following parameters: TR/TE = 2400/2.72 ms, FOV = 256×256 mm, 208 axial slices, and 0.8 mm3 spatial resolution.

Pre-processing

For each participant, diffusion data were pre-processed using the FMRIB Software Library (FSL) and the Analysis of Functional Neuro Images (AFNI) suite (Jenkinson et al., 2012; Smith et al., 2004; Cox & Hyde, 1997). FSL's topup was used to correct for echo-planar imaging (EPI) distortions. AFNI's 3D skull strip was used to remove non-brain tissue and generate a whole brain mask. FSL's EDDY correction was used for susceptibility artifact and gross motion correction. FSL's DTIFIT estimated a single diffusion tensor at each voxel using the whole brain mask to limit analyses to brain tissue. The output included voxel-wise images for FA, MD, AD, and RD.

Integrity Metrics

Striatal structures (caudate, putamen) were automatically segmented on each participant's high-resolution structural image using FSL's FIRST. FSL's flirt was used to align the MPRAGE to the DTI b0 image and the same transformation was used to get each participant's segmented striatal structures into diffusion space. Aligned segmented striatal structures were visually checked to ensure accurate region capture.

Results

Behavioral Results

To assess IAL, separate repeated measures Session (1-8) x Triplet Type (HF, LF) ANOVAs were conducted for mean accuracy and mean of median RTs. One participant was dropped from this analysis due to missing data ($N = 24$).

For mean accuracy, there was a significant main effect of Session (F (7, 161) = 6.057, $p <$ 0.001). Post hoc t-tests revealed that sessions 4 and 5 had significantly higher accuracy compared to the other sessions ($ps < 0.05$). The main effect of Triplet Type and the interaction between Triplet Type and Session did not attain significance ($ps > 0.40$).

For reaction time, there was a significant main effect of Triplet Type (F (1, 23) = 76.968, $p < 0.001$) with participants being faster on HF (447.36 ± 11.07) compared to LF (468.39 ± 10.65) triplets. A significant main effect of Session was also exhibited (F (7, 161) = 7.260, $p <$ 0.001), which revealed faster RTs over time. Pairwise comparisons revealed a general trend wherein RTs early in learning (Session 1 and 2) were significantly different from RTs later in learning (Sessions 3 through 8). Specifically, RTs in session one were significantly different from RTs in sessions three ($p = 0.047$), four ($p < 0.001$), five ($p = 0.006$), six ($p = 0.014$), seven ($p = 0.009$), and eight ($p < 0.001$), but they did not significantly differ from RTs in session two

($p > 0.05$). RTs in session two were also significantly different from RTs in sessions four ($p = 0.001$), five ($p = 0.021$), seven ($p = 0.030$), and eight ($p < 0.001$), but they did not significantly differ from RTs in sessions one, three, and six (*ps* > 0.05). RTs in session three were significantly different from RTs in sessions one ($p = 0.047$), four ($p = 0.009$), and eight ($p = 0.001$), but did not significantly differ from RTs in sessions two, five, six, and seven (*ps* > 0.05). RTs in session four were significantly different from RTs in sessions one ($p < 0.001$), two ($p = 0.001$), and three ($p = 0.009$), but did not significantly differ from RTs in sessions five, six, seven, and eight (*ps* > 0.05). RTs in session five were significantly different from RTs in sessions one ($p = 0.006$) and two ($p = 0.021$), but did not significantly differ from RTs in sessions three, four, six, seven, and eight (*ps* > 0.05). RTs in session six were significantly different from RTs in sessions one ($p = 0.014$) and eight ($p = 0.008$), but did not significantly differ from RTs in sessions two, three, four, five, and seven ($p > 0.05$). RTs in session seven were significantly different from RTs in sessions one ($p = 0.009$) and two ($p = 0.030$), but did not significantly differ from RTs in sessions three, four, five, six, and eight (*ps* > 0.05). Lastly, RTs in session eight were significantly different from RTs in sessions one ($p < 0.001$), two ($p < 0.001$), three ($p = 0.001$), and six ($p = 0.008$), but did not significantly differ from RTs in sessions four, five, and seven (*ps* > 0.05). The Session x Triplet Type interaction did not reach significance ($p > 0.254$).

Correlations Between Implicit Associative Learning and Integrity

To assess relationships between learning and striatal integrity, IAL scores were separately correlated with integrity of bilateral caudate and putamen (FA, MD, AD, and RD). Significant effects were Bonferroni corrected for four comparisons per region of interest ($p < 0.0125$).

Results revealed a significant negative correlation between IAL and left caudate AD (r =

-0.546, $p = 0.005$) and right caudate AD ($r = -0.503$, $p = 0.010$). IAL scores showed a trend for negative correlations with left putamen MD ($r = -0.437$, $p = 0.029$) and RD ($r = -0.405$, $p = 0.045$), as well as right putamen MD ($r = -0.398$, $p = 0.049$). For all correlations, better implicit learning was related to better striatal integrity (i.e., lower diffusion).

Median Split

A median split of IAL performance, which separated participants into High ($N = 13$; IAL score ≥ 126.6 ms) versus Low ($N = 12$; IAL score < 126.6 ms) Learners, was also conducted to examine differences in striatal integrity between these two groups. Independent samples t-tests revealed significant differences between High and Low Learners concerning left caudate AD ($t(23) = -2.449$, $p = 0.022$) and right caudate MD ($t(23) = -2.776$, $p = 0.011$), AD ($t(23) = -3.477$, $p = 0.002$), and RD ($t(23) = -2.294$, $p = 0.031$), with lower MD, AD, and RD in caudate for High versus Low Learners. Significant differences between High and Low Learners were also exhibited concerning left putamen MD ($t(15.269) = -2.460$, $p = 0.026$) and AD ($t(15.668) = -2.537$, $p = 0.022$), as well as right putamen AD ($t(18.015) = -2.436$, $p = 0.025$); High Learners also had lower MD, AD, and RD in putamen compared to Low Learners. Marginally significant differences between High and Low Learners were also observed for left putamen RD ($t(15.677) = -1.956$, $p = 0.069$) and right putamen MD ($t(23) = -1.847$, $p = 0.078$). These results indicate that High Learners tend to have lower diffusion metrics, or better bilateral caudate and putamen integrity, than Low Learners.

Explicit Awareness

To test for explicit knowledge, a repeated measures Triplet Type (HF, LF) x Response Type (‘frequently’, ‘infrequently’) ANOVA was performed on frequencies of responses on the recognition test. NF triplets and the ‘not at all’ response type were not included in the ANOVA because explicit awareness depends on whether participants can distinguish HF from LF triplets. Importantly, results revealed no main effect of Triplet Type (F (1, 23) = 0.793, p = 0.382), indicating that participants could not accurately distinguish which triplets occurred frequently or infrequently. There was a significant main effect of Response Type (F (1, 23) = 83.198, $p <$ 0.001), indicating that participants have a tendency toward 'frequent' responses than 'infrequent' responses across HF and LF triplets. The interaction between Triplet Type and Response Type was not significant (F (1, 23) = 1.221, p = 0.281).

Additionally, during the interview, no participants revealed any knowledge of specific triplet sequences or observable probabilistic patterns from the triplet task.

Discussion

This study was the first to examine relations between IAL and striatal gray matter integrity using traditional DTI metrics. Our results reveal two main findings in line with initial predictions. First, we found significant negative correlations between IAL and bilateral caudate diffusion metrics, indicating that better implicit learning relates to better integrity in this region; the results of the median split, which found that High Learners had significantly better bilateral caudate integrity than Low Learners, also indicates that better learning is related to better integrity. Second, negative marginal correlations between IAL and bilateral putamen integrity were found, though the median split found that High Learners had significantly better bilateral putamen integrity than Low Learners. These results indicate that individual differences in striatal gray matter microstructure predict implicit learning among young adults, signifying that examining gray matter integrity may reveal important relations between gray matter structure and IAL, as well as behavior more broadly.

As hypothesized, the current study found that striatal integrity was significantly related to

IAL. This finding is consistent with previous studies showing that better implicit learning is correlated with increased bilateral caudate activation, greater white matter integrity in tracts emanating from the caudate, and greater dopaminergic expression in the striatum (Simon, Vaidya, Howard, & Howard, 2012; Bennett, Madden, Vaidya, Howard, & Howard, 2011; Simon et al., 2011). These results are also consistent with the literature that implicates putamen in the motor aspects of implicit learning, given that learning scores are derived from RT data (Bennett, Madden, Vaidya, Howard, & Howard, 2011; Doyon, 2009; Seger, 2006). Together these findings support the conclusion that the striatum is a critical structure for learning associations.

Interestingly, the striatal integrity-IAL relationships were only seen for the MD, AD, and RD diffusion metrics, not the FA measure. Because the tissue within gray matter is less organized than white matter, FA may not be a sensitive measure of striatal integrity. However, finding significant relationships between IAL and AD, and to a lesser extent MD and RD, suggests that these diffusion metrics may be capturing some aspects of gray matter structure which may be crucial for learning, including gray matter microstructural properties like the degree of neuronal and neurite density within a region of interest, the presence of other neuronal bodies like glia cells, or a combination of these factors.

Greater neuronal and neurite density would mean greater diffusion restriction in gray matter areas which could optimize cognition related to regions of interest. In this case, better striatal integrity relates to less diffusion and better learning, perhaps indicating that greater neuronal and neurite density in bilateral caudate and putamen optimizes or predicts better implicit learning. Synaptogenesis, which can be assumed to relate to synapse or neurite density, has previously been claimed as an important factor in associative learning and memory, with the various processes related to synapse formation and maturation, including BDNF expression and protein synthesis, implicated as essential for associative processes (Nelson & Alkon, 2015). One may assume that synapse presence thus relates to associative learning in general, and that neurite density could factor into why individuals with greater integrity, and thus greater potential neuronal and neurite density, exhibit better IAL. Similarly, the presence of glial cells would also influence integrity metrics as they inhibit diffusion within given spaces. Further study is needed to ascertain if this is indeed what diffusion metrics are measuring when applied to gray matter or to determine if other variables are involved.

Modified TLT Captures Implicit Learning

Though this TLT was modified to control for first- and second-order biases among individuals, participants still exhibited IAL on this task, indicating that this unique triplet design is able to capture implicit learning (Stillman, Howard, & Howard, 2016; Simon, Vaidya, Howard, & Howard, 2012). Participants performed accurately on this task, and RT trends revealed implicit learning, as participants responded significantly faster to HF than LF triplets, and general skill learning, as participants became significantly faster over time. Though the Session x Triplet Type interaction was not significant, this is consistent with some of the existing literature on the TLT (Simon, Vaidya, Howard, & Howard, 2012). The lack of a significant interaction may also be due to the unique design of this TLT, which might make HF triplets more salient to participants, thus allowing them to respond significantly faster to HF triplets earlier in the task than in previous TLT studies. Of course, the associations still remained implicit despite potentially more salient predictive qualities, given that participants showed no explicit awareness both on the recognition task and the explicit awareness interview.

Potential Limitations and Future Directions

While the results of this study indicate promising relationships between striatal integrity and implicit learning, they must be understood within the constraints of some limitations. One limitation is the acquisition error that occurred during sessions 4 and 5 of the MRI TLT, which has limited our ability to examine participant performance during the middle of the task. Even though most IAL studies, including this one, are mainly interested in comparing early and/or late learning and do not require analysis of sessions presented in the middle of learning, other researchers may be interested in these sections if they would like to examine the particularities of implicit learning in young adults over time. Another limitation of this study is its relatively small sample size, which might have limited the power of the analyses. Future studies should consider the recruitment of a larger number of participants.

A more complex limitation is the usage of traditional DTI metrics to examine gray matter integrity given that these metrics are typically understood within the context of white matter. It is difficult to interpret why some measures which provide information on the coherence of orientation of diffusion would be significant within the context of gray matter. One explanation is that the striatum is more structured than other gray matter regions, and DTI metrics could be partially influenced by striated connections between the caudate and putamen. Traditional DTI metrics also do not provide enough information about what aspects of microstructure are being measured within a given region. As such, future studies may consider analyzing gray matter integrity through the usage of neurite orientation dispersion and density imaging (NODDI), which may provide more information about the microstructure of gray matter regions as this model can account for free water contamination and intra- and extracellular diffusion components. They may also consider the usage of animal models to examine the complexities of gray matter microstructure.

To expand gray matter integrity and cognition research, future studies should consider incorporating aging populations in their analyses. Examining differences in gray matter integrity between younger and older individuals or studying gray matter integrity across a certain timespan could expand our understanding of the relationships between gray matter microstructure and learning across the lifespan or across given timepoints. This information would allow us to understand how processes like neurogenesis, neurodegeneration, synaptogenesis, and dendritic (de)arborization affect the integrity of gray matter regions, and how these processes relate to learning as one ages.

Conclusion

This study is the first to show significant relationships between striatal gray matter integrity as measured through traditional DTI metrics and implicit associative learning. Individual differences in the integrity of striatal subregions (e.g. bilateral caudate and putamen) were correlated with IAL among a healthy young adult sample. Further analyses also found that individuals designated as High Learners had significantly better integrity, or lower diffusion, in striatal subregions than individuals designated as Low Learners. In conjunction, these results further support striatal involvement in IAL and indicate that striatal microstructure predicts implicit learning. These results also suggest that examining gray matter integrity may reveal important relationships between gray matter microstructure and IAL, or cognition more broadly. Future studies should expand on these results by incorporating a larger sample size, utilizing more precise diffusion measures like NODDI, or studying gray matter integrity in animal models. Future studies should also adopt these methods for consideration in lifespan gray matter integrity research.

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