

## Obesity and Motor Sequence Learning

Abdominal adiposity negatively associates with the rate of long-term sequential skill learning

Amira Millette<sup>a\*</sup>, Brigid Lynch<sup>a\*</sup>, Timothy Verstynen<sup>a,b</sup>

a. Department of Psychology

b. Center for the Neural Basis of Cognition, Carnegie Mellon University, Pittsburgh, PA, USA

\* These authors contributed equally to this work.

### **Corresponding Author:**

Timothy Verstynen

Carnegie Mellon University

Department of Psychology

340 U Baker Hall

Pittsburgh, PA 15213

412-533-AXN1 (office phone)

[timothyv@andrew.cmu.edu](mailto:timothyv@andrew.cmu.edu)

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Obesity is associated with functional and structural differences in the corticostriatal systems of the brain. These pathways are known to be critical for the acquisition of complex sensorimotor skills, such as the ability to learn a coordinated sequence of actions. Thus, individual differences in obesity should be associated with reduced efficiency of learning sequential skills. Here we measured long-term sequence learning across five days of training on the serial reaction time task in a cohort of neurologically healthy adults (N=30) with body types ranging from lean to obese. As expected, individuals with a greater degree of central adiposity, measured as central waist circumference, exhibited slower rates of learning, across all training days, than their leaner counterparts. This association between learning and central adiposity was restricted to response speeds, but not accuracy. These findings show that obesity is negatively associated with the efficiency of learning a long-term sequential skill, possibly due to previously observed associations between obesity and general basal ganglia function.

Keywords: sequence learning, obesity, serial-reaction time task (SRTT)

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### 1. Introduction

Over the last ten years, a small but growing body of research suggests that obesity may be variably linked to individual differences in cognitive function. For example, higher levels of obesity have been associated with reduced efficiency in a number of cognitive domains, including inhibitory control (Duchesne et al, 2010; Galioto et al., 2012; Gunstad et al., 2007; Hendrick et al., 2012; Nederkoorn et al., 2006a; Nederkoorn et al., 2006b) and general decision making (Boeka & Lokken, 2008; Cserjési et al., 2009; Davis et al., 2004; Davis et al., 2010; Lokken et al., 2009; Pignatti et al., 2006). Indeed, the cognitive associations with obesity appear to be fairly broad. For example, in a recent study by Galioto and colleagues, participants with morbid obesity showed reduced performance in executive function, memory, language, and attention tasks, relative to lean counterparts, even in the absence of a binge eating disorder diagnosis. However, it is worth noting that while reports of obesity-cognition associations are somewhat variable, they tend to be more consistent after accounting for individual differences in mood and affect (Volkow et al., 2008a).

At the neural level, obesity is consistently associated with individual differences in the neural substrates of decision making and reward processing, specifically within a set of pathways known as the cortico-basal ganglia system (Stice et al., 2008; Tomasi & Volkow, 2013; Volkow et al., 2011). For example, individuals with high obesity have been found to have decreased levels of dopaminergic D2 receptor availability in the striatum, a set of forebrain nuclei that serve as the primary input for the basal ganglia (de Weijer et al., 2011; Volkow et al., 2008b). Functional imaging studies also show that, compared to their lean counterparts, individuals with high adiposity have a hypo-

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responsive ventral striatal reward response that is thought to lead to overeating as a compensation for this blunted dopaminergic signal (Stice et al., 2008; Stice et al., 2010). These associations with striatal function are often discussed in the context of reward and hedonic overeating (Horstmann et al., 2011); however, the cortico-basal ganglia pathways also play critical roles in executive control and learning, suggesting that obesity may also be associated with non-reward related cognitive functions.

One cognitive function that relies critically on the integrity of cortico-basal ganglia pathways is sequential skill learning (Doyon et al., 2009; Lehericy et al., 2005). This is the cognitive ability to bind temporally independent items together into a unified sequence and is critical to many everyday behaviors, e.g., driving a vehicle with a manual transmission, learning a language, playing a new piano melody. Neuroimaging studies have shown that regions within the basal ganglia, particularly the striatal nuclei, are engaged during sequence learning and their activity is modulated over the course of training (Lehericy et al., 2005). Causal evidence for the role of striatal systems in motor sequence learning comes from studies of neurological patient populations with pathologies of the basal ganglia. For example, Parkinson's disease is a degenerative disorder of the dopaminergic projections from the substantia nigra pars compacta to the striatal nuclei. Parkinson's disease patients show significant deficits in motor sequence skill acquisition and consolidation when introduced to a novel motor sequence (Benecke et al., 1987; Dan et al., 2015). This patient evidence, combined with the neuroimaging evidence, highlights the critical role that striatal nuclei play in sequence acquisition (Doyon, 2008).

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Since obesity is associated with reduced striatal functioning and the striatum is critical to motor sequence learning, then it is possible that obesity is associated with the efficiency of learning a novel sequential sensorimotor skill; however, this association has yet to be tested. The current project aims to fill this gap by using a standard inventory of motor sequence learning, the serial reaction time task (Nissen & Bullemer, 1987), to measure the rate of long-term learning across five days of training in a sample of neurologically healthy participants with body types ranging from lean to obese. Specifically, we predict that individual differences in central adiposity, measured as waist circumference, would negatively correlate with the ability to learn a complex sequence of actions across multiple days of training.

## 2. Methods and Materials

### 2.1 Participants

Thirty-two right-handed volunteers were recruited from the local Pittsburgh community with a body-mass index range of 18.5kg/m<sup>2</sup> to 40.0kg/m<sup>2</sup>. While relatively small for biomedical and health psychology studies of obesity, our sample size is quite consistent with typical SRTT studies on both clinical and healthy populations (for example see Knopman & Nissen, 1991; Shin & Ivry, 2003). All participants reported no more than three years of musical experience in the last 10 years. Additional inclusion criteria included that participants reported current, unimpeded use of the right hand, had no history of carpal tunnel syndrome or similar disorders, and no familiarity with the Cyrillic alphabet. Each volunteer gave written, informed consent, and were financially compensated for their participation. Two participants failed to attend all five consecutive

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days of training and were therefore removed from the final data set. All procedures were approved by the Carnegie Mellon University Institutional Review Board (IRB) prior to testing.

### 2.2 Obesity measures

Body mass index was used as the primary measure of obesity for recruitment purposes. Height and weight measurements were taken from each participant prior to the start of the experimental task. Body mass index was calculated using the standard formula of weight in kilograms (kg) divided by the square of height in meters (m<sup>2</sup>). The standard ranges of body mass index were categorized as, lean (BMI of 18.5 - 24.9), overweight (BMI of 25.0 - 29.9), and obese (BMI greater than 30.0).

Waist circumference was used as a direct measure of central adiposity in the statistical analysis. The waist circumference measurement was taken from each participant prior to the start of the experimental task, using a plastic tape to measure around the participant's waist, just above the navel. Since there is no established definition of obesity based on waist circumference, we performed a median split on the waist circumference measure to create a categorical variable as the new waist circumference measure, with 36.0 inches as the median value. The lowest waist circumference value to 36.0 inches served as the "Low Adiposity" group (N=16), and 36.1 inches to the highest waist circumference value in the dataset served as the "High Adiposity" group (N=14). This categorization did not align perfectly with BMI categories, with 9 lean, 6 overweight, and 1 obese individuals in the Low Adiposity group and 1 lean, 4 overweight, and 9 obese individuals in the High Adiposity group.

## 2.3 Serial Reaction Time Task

### 2.3.1. Experimental Design and Setup

Participants were run in a standard version of the serial reaction time task for five consecutive days, with a one-hour training session on each day. All stimuli were presented on a 23" ASUS LED monitor with a resolution of 1920 x 1080 mp, using Matlab R2012a (MathWorks, Inc., Natick, MA). The stimuli were spatially centered on the computer screen in a black background, displayed in a white font color (Fig. 1). Participants were told to respond to a set of cued stimuli presented visually on the computer screen using the right index (1), middle (2), ring (3), and pinky (4) fingers consecutively, with each finger matched to one uniquely paired cue in this order: “Ж”, “Є”, “Н”, and “Л” (Fig. 1A). Each experimental session consisted of a total of six trial blocks. The experimental blocks were divided into types: Random blocks and Sequence blocks (see Fig. 2A-B). The Random blocks (trial blocks 1, 2, and 5) were comprised of 264 stimuli presented in a pseudorandom order, with a restriction to minimize repetition between any two contiguous stimuli. The Sequence blocks (trial blocks 3, 4, and 6) were comprised of twenty-two repetitions of stimuli from a 12-trial sequence [1, 3, 2, 1, 4, 3, 1, 4, 2, 3, 4, 2]. Each block began at a random part of the sequence so as to minimize immediate identification of the sequential pattern. The sequence pattern remained the same for all Sequence blocks and across the five training days. The experiment was self-paced such that participants were allowed to proceed to the next trial block when they were prepared for the following series.

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### 2.3.2. Task Instructions

Prior to the start of the experimental session, participants were informed that there was a 600ms response window and they were instructed to respond as quickly and as accurately as possible. Participants then were given a brief 12 trial practice session to familiarize themselves with the key and cue mappings. After this brief practice, the testing session began. Throughout the training session, participants were provided continuous visual feedback on their response accuracy; a correct key press resulted in the cue flashing green. Alternatively, an incorrect key response resulted in the cue flashing red. At the end of each trial block, participants were provided a feedback summary on their average response times and accuracies as a percent correct score for that block.

## 2.4 Data analysis

### 2.4.1. Analysis measures

The raw data was summarized for each block using a custom Matlab script. Mean response times (response time; in ms) and accuracies (% correct) were measured on each block to determine motor sequence learning in the task. These measures were used to compute the learning scores of each body type category, across the five experimental sessions.

### 2.4.2. Learning scores

Sequence specific learning was measured for response time by taking the mean value in the last two sequence probes (Block 4 and Block 6;  $\mu^4$ ,  $\mu^6$ ) and subtracting those from the same values from the last random probe (Block 5;  $\mu^5$ ). This measure provided



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information on sequence specific learning. Learning scores in response time were manually computed (eq. 1) by subtracting the mean response time in the random probe from the average of the mean response times of the sequence probes:

$$\delta_{RT} = \mu^5 - \frac{1}{2}(\mu^4 + \mu^6) \text{ (eq. 1)}$$

Likewise, learning scores in accuracy were manually computed (eq. 2) by taking the average of the accuracy of the random probes ( $\alpha^4, \alpha^6$ ) and subtracting the accuracy in the sequence probe ( $\alpha^5$ ):

$$\delta_{Acc} = \frac{1}{2}(\alpha^4 + \alpha^6) - \alpha^5 \text{ (eq. 2)}$$

Group differences in  $\delta_{RT}$  and  $\delta_{Acc}$  were determined using a two-way repeated measures ANOVA.

### 2.4.3. Learning slope

Finally, in order to quantify the linear rate of learning across training days, a learning slope was calculated (eq. 3) for each subject on sequence specific differences in response times and accuracies separately. We computed this by calculating the average between day difference in learning scores, for both response times and accuracies. This was computed as

$$\Delta = \frac{1}{4} \sum_{i=2}^5 \delta_i - \delta_{i-1} \text{ (eq. 3)}$$

where  $\delta_i$  is the learning score on day  $i$ . This score reflects the mean change in learning, per day across the entire experiment. This value was correlated against anthropometric measures of obesity using a Spearman's rank order correlation coefficient.

### 3. Results

#### 3.1. Response Time and Accuracy

Mean response times and accuracies were recorded for each block of trials for all days. Figure 2A shows the block-wise response times averaged across all subjects for the five training days. There is a noticeable increase in response speeds during the sequence probes (Blocks 4 and 6), compared to the random probe (Block 5). Across most blocks there is also a saturation of the accuracy after Training Day 1 and this was particularly strong in the sequence blocks (Fig. 2B). The last random block provides a “learning probe” that allows for us to measure sequence-specific learning at the end of each day. We calculated learning scores based off of these probe blocks for each subject and each day (see Methods).

#### 3.2. Learning Score

In order to look for group differences in learning scores for response time and accuracy, we performed a median split on our main obesity variable of interest, waist circumference, and categorized subjects into Low (N=16) and High (N=14) adiposity groups. A repeated-measures ANOVA found a significant main effect of training day on response time learning scores (Fig. 2C;  $F(4, 116) = 17.55$ ;  $p < 0.001$ ), as well as a significant group by day interaction ( $F(4, 116) = 2.51$ ;  $p = 0.045$ ). In general, the Low Adiposity group had a greater rate of learning across training than the High Adiposity group. This group effect is driven by across day learning, as 2-sample t-tests did not find a significant group difference on each individual training day (all  $p$ 's  $> 0.10$ , all  $t$ 's  $<$

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1.68). This association between sequence learning and abdominal adiposity group appears to be specific for movement speeds. The learning scores based on accuracy performance did not show a training day by group interaction (Fig. 2D;  $F(4, 116) < 1$ ;  $p = 0.565$ ). It is noteworthy that this effect of body type on long-term learning is not significant when BMI group is used as the group category as there was not a significant interaction between response time learning score and body-mass index ( $F(2, 116) = 0.327$ ;  $p = 0.540$ ). This is consistent with previous results showing that waist circumference is as a more reliable and direct measure of obesity than BMI (Gómez-Ambrosi, et al. 2012).

### 3.3. Learning Slope

To better understand the relationship between central adiposity and response time learning, we used a linear slope analysis to estimate the rate of across day learning for each subject (see Methods). Using a non-parametric Spearman's rank correlation test ( $\rho_S$ ), we found a significant negative correlation between learning slope of response times and waist circumference (Table 2;  $\rho_S = -0.401$ ,  $p < 0.05$ ). Consistent with our hypothesis, as central adiposity increased, the rate of motor sequence learning across days decreased (Fig. 3). Within each day, we saw the emergence of an association between central adiposity and sequence specific response time learning, becoming significant on the last day of training (Day 1:  $\rho_S = 0.13$ ,  $p = 0.40$ ; Day 2:  $\rho_S = -0.14$ ,  $p = 0.07$ ; Day 3:  $\rho_S = -0.04$ ,  $p = 0.23$ ; Day 4:  $\rho_S = -0.12$ ,  $p = 0.09$ ; Day 5:  $\rho_S = -0.25$ ,  $p = 0.03$ ). There was a similarly negative correlation between learning slope of accuracies and BMI but it did not reach statistical significance ( $\rho_S = -0.230$ ,  $p = 0.221$ ). As with response time learning, an association between central adiposity and sequence specific

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accuracy learning emerged on each day, with a significant association on the last day of training (Day 1:  $\rho_S = 0.21$ ,  $p = 0.22$ ; Day 2:  $\rho_S = -0.03$ ,  $p = 0.35$ ; Day 3:  $\rho_S = 0.29$ ,  $p = 0.10$ ; Day 4:  $\rho_S = 0.35$ ,  $p = 0.05$ ; Day 5:  $\rho_S = 0.38$ ,  $p = 0.04$ ).

### 4. Discussion

For the first time we have shown that a measure of obesity, central adiposity, is associated with a decrease in the efficiency of long-term sequential skill learning. Participants with a higher waist circumference acquired a sensorimotor sequence at a slower rate than lean counterparts across five days of training on the serial reaction time task. This association with central adiposity was limited to response speeds, but not accuracy, consistent with the idea that these two performance measures may be learned independently (see also Verstynen et al., 2012).

Given the critical role of basal ganglia networks in long term skill learning (Doyon, 2008), these findings fit with the growing body of research that obesity is related to the integrity and efficiency of basal ganglia circuits. Much of this analysis has focused on the relationship between obesity and reactivity of striatal reward pathways (Tomasi & Volkow, 2013; Wang et al., 2001). For example, Stice and colleagues found a negative association between dorsal striatal reactivity in response to a high value food stimulus and BMI. Importantly, this was moderated by the presence of the dopamine allele of the TaqIA polymorphism. In addition, individuals with high obesity also exhibit reduced dopamine D2 receptor availability throughout the striatum when compared to the lean counterparts (de Weijer et al., 2011; Volkow et al., 2008). Our finding that obesity is associated with reduced efficiency of a striatal-dependent form of learning, suggests

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these striatal associations with obesity may relate to global functioning of basal ganglia pathways, rather than just processing the saliency of rewarding stimuli. Specifically, reward prediction errors are coded by phasic dopaminergic signals into the striatum and these reward prediction errors are crucial for reinforcement learning (Frank & Badre, 2012). Blunted dopamine reactivity in the striatum of individuals with obesity would reduce the sensitivity of this learning signal over time, thereby slowing the rate of learning. Thus, individual differences in dopamine may be the primary mechanism impacting the rate of skill learning reported here. Future work should focus on neural measures of reward saliency and how they relate to learning within the context of obesity.

Our findings, considered in the context of previous striatum-obesity associations (Horstmann et al., 2010; Nummernmaa et al., 2012; Stice et al., 2008; Tomasi & Volkow, 2013), suggests that obesity may reflect an inherent concern of basal ganglia function. Although there is some heterogeneity in reports of obesity-cognition links (Fitzpatrick et al., 2013), the most reliable cognitive associations with obesity tend to be those processes (e.g., inhibitory control, reward saliency, decision making) that also rely on healthy cortico-basal ganglia pathway function. This observation highlights a system, cortico-basal ganglia networks, that could better explain the specific behavioral patterns that lead to increased obesity.

While our results suggest that obesity itself may associate with long-term procedural learning, many other factors correlate with obesity that may also contribute to the rate of motor learning. For example, obesity is correlated with reduced cardiorespiratory fitness (Ross & Katzmarzyk, 2003; Wong et al., 2004). Accumulating

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evidence suggests that cardiorespiratory fitness impacts cognitive function (Szabo et al., 2011). Since we did not measure cardiorespiratory fitness in this study, we cannot preclude this possibility here. Beyond cardiorespiratory fitness, many physiological (e.g., inflammation) and metabolic (e.g., insulin) systems associated with elevated adiposity have also been associated with variability in cognitive function (Rosano et al., 2012). Understanding how these physiological and metabolic factors may moderate or mediate the association between adiposity and skill learning should be a focus of future studies. Testing this requires replicating the current study with a much larger sample size that includes additional measurements of health related systems.

Of course, the current association between central adiposity and skill learning could be explained by secondary factors not related to basal ganglia function per se. For example, participants with higher central adiposity may also fatigue sooner than their lean counterparts, thus arousal levels may also account for efficiency of motor learning. Follow-up work should quantify levels of fatigue across groups as a control for this possibility. Finally, obesity has been shown to be comorbid with depression and anxiety disorders, which may impact attention and, consequently, learning (Strine et al., 2008). Administering a standardized battery to quantify mood and affect will aid in controlling for these additional extrinsic factors. Follow-up work should also confirm that the striatum is mediating the relationship between obesity and long-term motor sequence skill learning by looking at striatal activity during this form of long-term learning across groups. Neuroimaging tools, such as fMRI, can provide valuable information to the particular regions involved in this motor learning task, and with this, we can confirm the striatal link to obesity to motor sequence skill learning.

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Regardless of these mechanistic limitations, our results show, for the first time, that individual differences in obesity levels negatively associate with long-term skill learning. This extends our understanding of obesity and cognition links beyond reward processing and implies that obesity may associate with general basal ganglia function. This has wide-ranging implications on the role of obesity in complex cognitive functions, like sensorimotor skill learning, and opens new avenues of research into the effects of physical fitness on the brain beyond reward processing.

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### Figures Captions

*Figure 1:* Block-wise mean a) response times (RT) and b) accuracies across experimental cohort. All error bars are standard error of the mean.

*Figure 2:* Learning across training days. Mean blockwise scores for a) response time and b) accuracies across all subjects and days of training. Sequence specific learning scores ( $\delta$ ) on each day of training (see main text for details) for c) response time and d) accuracy, separated by adiposity group. All error bars are standard error of the mean.

*Figure 3:* Individual differences in learning score slope for response time ( $\delta_{RT}$  Slope) and waist circumference.

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	Lean (n = 10)	Overweight (n = 10)	Obese (n = 10)
<b>Sex</b>			
Male	4	8	5
Female	6	2	5
<b>Age (in years)</b>			
Mean	21.1	22.8	25.4
Median	20.5	21.5	23.5
St. Dev.	1.91	5.37	8.25
Minimum	19	18	19
Maximum	25	36	46
<b>BMI (kg/m<sup>2</sup>)</b>			
Mean	21.91	27.22	32.52
Median	22.9	27.4	31.55
St. Dev.	2.23	1.53	2.66
Minimum	18.1	25.0	30.4
Maximum	24.4	29.0	34.1
<b>Waist Circumference (in inches)</b>			
Mean	31.1	38.3	43.7
Median	30.5	35.5	44.0
St. Dev.	4.79	6.46	4.67
Minimum	25.0	31.0	35.0
Maximum	41.0	54.0	53.0

*Table 1:* Participant demographics.

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	Sex	Age	BMI	WC	$\delta_{RT}$ Slope
Age	- 0.035	-	-	-	-
BMI	- 0.054	0.257	-	-	-
WC	- 0.327	0.357	0.740**	-	-
$\delta_{RT}$ Slope	.0307	- 0.236	-0.230	-0.401*	-
$\delta_{Acc}$ Slope	- 0.023	- 0.178	0.103	0.191	-0.115

\* Significance at alpha < 0.01

\*\* Significance at alpha < 0.05

*Table 2:* Spearman's non-parametric correlation coefficient between each variable and covariate. Body mass index, BMI; Waist circumference; WC; Learning score,  $\delta$ ; Response time, RT; Accuracy, Acc.





