Exploring the Relationship Between Obesity and Long-term Motor Sequence Skill Learning

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Abstract

Mastering motor sequences is essential for many daily life activities, such as typing on a keyboard or playing a piano. This form of learning relies on the striatal nuclei (Doyon, 2008; Doyon et al., 2009) that form the principal inputs to a group of subcortical regions known as the basal ganglia. Previous research has shown that central obesity is associated with compromised striatal functioning, particularly when processing reward signals (Stice et al, 2008). Thus, it is possible that increased physical obesity may be linked to reduced skill learning in a sequential motor task. Using an indirectly-cued serial reaction time task (SRTT), long-term motor sequence learning was assessed in a cohort of thirty participants, with body types ranging from lean, to overweight, to obese. As expected, individuals with a greater degree of central adiposity, measured as central waist circumference, had slower rates of learning across training days compared to leaner counterparts. This association between learning and central adiposity was restricted to response speeds, but not accuracy. These findings confirm the association between physical obesity and the efficiency of long-term motor sequence learning, suggesting that obesity is a general basal ganglia concern, not just for reward processing, but also motor skill learning.

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

Introduction

In the early stages of motor learning, the novice pianist will experience difficulties in executing the precise sequence of notes to create a musical melody. She will produce serial actions slowly and with frequent errors. Thus, the finger movements to create the melody will be executed in a disjoined fashion, with each movement appearing to be independently planned from the previous action. But with days or weeks of practice, temporally adjacent movements will become more fluid, faster, and more accurate. Consequently, with long-term practice, the novice player can play a melody with greater ease, and proceed to learn more complex melodies.

This form of motor sequence learning has been well studied over the past thirty years, yet many aspects of it remain poorly understood. We know that motor sequence learning engages the act of integrating discrete, temporally independent movements into one concatenated sequence of actions (Verwey, 2001; Wymbs et al., 2012). Much like the novice pianist, with continued practice, the motor parameters will become optimized and the entire sequence will be successfully performed (for review see Penhune & Steele, 2011). For this type of learning to occur the individual must undergo an early, fast learning stage, an intermediate stage where basic patterns are learned but not learned efficiently, and a late learning stage where sequence knowledge is crystallized (see reviews Doyon, Penhune, and Ungerleider, 2003; Doyon et al. 2009).

The process of learning a motor sequence relies on the recruitment of distributed neural networks (Bassett et al., 2011). In particular, the basal ganglia, a series of subcortical nuclei that rests deep within the forebrain, have been strongly associated with long-term motor sequence learning (Lehericy et al., 2005; Reiss et al., 2005;

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Kawashima et al., 2011). The precise role that the basal ganglia play in skill learning remains elusive because this subcortical network is associated with many different cognitive functions, including reward processing (Tomasi & Volkow, 2013), executive control (Volkow et al., 2008; Penhune & Steele, 2011), and motor functions, such as basic motor gating (see reviews for Kaji, 2001; Turner & Desmurget, 2010), planning and execution (see review for Graybiel, 1998; Korchounov et al, 2010). Therefore it is a challenge to fully capture the mechanisms by which the basal ganglia contribute to sequential skill learning. Nonetheless, it is well established that damage or dysfunction of these nuclei impairs sequence acquisition (see review for Doyon, 2008).

Previous neuroimaging and animal studies have identified the striatal nuclei, the primary input regions of the basal ganglia, as particularly crucial for long-term sequential skill learning (see review for Doyon et al., 2009; Yin et al., 2009; Jouen et al., 2013). In particular, distinct long-term changes to both the cortico-striatal circuits (Hikosaka et al., 2002; see review for Doyon et al., 2003; Lehericy et al., 2005; Yin et al., 2009; see review for Penhune & Steele, 2011) and the cortico-cerebellar circuits have been linked to the acquisition of a new motor sequence pattern (Hikosaka et al., 2002; Doyon et al., 2003, see review for Penhune and Steele, 2011) throughout the many stages of motor learning. The cortico-striatal circuits are revealed to be active in the early, fast learning stages of motor sequence learning (Doyon et al., 2003), during the greater chunk of the learning process. With additional practice and mastery, the levels of activation in the striatal nuclei increase, and the when a motor sequence is fully automated, the levels of activation in the cortico-striatal circuits diminish (see review for Doyon et al., 2009).

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 (PD) is a degenerative disorder of the dopaminergic projections from the substantia nigra pars compacta to the striatal nuclei (Wichmann & DeLong, 1996; Blandini et al., 2000). PD patients show significant deficits in motor sequence skill acquisition and consolidation when introduced to a novel sequence, such that they display reduced reaction time-based and sequence-specific performance in a variety of motor tasks (Pendt et al., 2011; see review for Doyon, 2008; Gobel et al., 2013). Also, in comparing PD patients to mild cognitive impairment patients, a recent study has found that motor learning tasks require essential contributions from the basal ganglia regions, rather than the medial temporal regions, i.e. hippocampus (Gobel et al., 2013). This suggests that motor sequence execution in a serial reaction time task especially recruits the basal ganglia nuclei.

General, non-pathological, health factors such as physical obesity, have also been associated with reduced or impaired striatal functioning (Stice et al., 2008; Wang et al., 2009). Decreased levels of dopaminergic D2 receptor availability in the striatal nuclei are found to be associated with increased levels of obesity (Volkow et al., 2008; de Weijer et al, 2011; review Reinholz et al., 2008). Functional imaging studies also show that obese individuals, compared to their lean counterparts, have a hypofunctioning ventral striatal reward circuit that is thought to lead to overeating to compensate for this malfunctioning dopaminergic system (Stice et al., 2008; Stice et al., 2010; Burger & Stice, 2012). In a recent study by Rotermund and colleagues (2014)

diet-induced obesity and was found to be a predictor the development of Parkinson's via an aggregated protein called alpha-synuclein that contributes to PD.

Since obesity is associated with reduced striatal functioning and the striatum is critical to motor sequence learning, then it is possible that obesity may also be associated with the efficiency of sequential motor skill learning. However, to date, this association has yet to be tested. The current project aims to fill this gap in the literature. Specifically, given the directional associations between obesity and striatal function, we increased physical obesity should contribute to an overall reduction in the efficiency of learning a novel sensorimotor sequence over long timescales of training. We used an indirectly cued serial reaction time task (SRTT) (Nissen & Bullemer, 1987) to assess motor learning over the course of one week.

Methods and Materials

Participants: Thirty-two right-handed volunteers were recruited from the local Pittsburgh community with a body-mass index range of $18.5kg/m^2$ to $40.0kg/m^2$. 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, no history of carpal tunnel syndrome or similar disorders, and unfamiliarity 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 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.

Body Mass Index (BMI): Body mass index was used as the primary measure of obesity. 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^2). 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: Waist circumference was used as a direct measure of central adiposity. The waist circumference measurement was taken from each participant prior to the start of the experimental task, by wrapping a plastic tape measure around the participant's waist, just above the navel. We performed a median split on the waist circumference 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 waist circumference" group (N=16), and 36.1 inches to the highest waist circumference value in the dataset served as the "high waist circumference" group (N=14).

Task: Participants were run in an indirect cued version of the SRTT 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. 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", "Њ", 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 (Fig. 2). The Random blocks (trial blocks 1, 2, and 5) were comprised of twenty-two repetitions 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 experimental block when they were prepared for the following series.

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-key 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 (Fig. 1b). 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.

Data analysis: Raw data were summarized for each block using a custom Matlab script. Average response times and accuracies in each block and the mean response times for individual keys and cues were computed. Mean response times (ms) and accuracies (% correct) were measured 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.

Sequence specific learning was measured by taking the mean accuracy and response times in the last two sequence probes (Block 4 and Block 6) and subtracting out the same values from the last random probe (Block 5). This measure provided 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:

$$Learning\ score\ RT\ =\ Block\ 5_{RT}\ -\ \left((Block\ 6_{RT}\ +\ Block\ 4_{RT})\ \div\ 2\right) \text{ (eq. 1)}$$

Likewise, learning scores in accuracy were manually computed (eq. 2) by subtracting the average of the mean accuracy of the sequence probes from the mean accuracy in the random probe:

$$Learning\ score\ Acc\ =\ \left((Block\ 6_{Acc}\ +\ Block\ 4_{Acc})\ \div\ 2\right)\ -\ Block\ 5_{Acc} \text{ (eq. 2)}$$

Learning slopes for response times and accuracies were calculated to estimate the average day-to-day change in performance across training. We computed this by fitting a linear model to the difference in each day's learning score, for both response times and accuracies, from the previous day. This reflects the rate of learning across the entire experiment.

In order to compare the means of each of the measures computed, we ran a linear regression on waist circumference and learning slopes, as well as repeated-measures ANOVA tests with the training day and group as factors.

Results

Mean response times and accuracies were recorded for each block of trials for all days. *Figure 3* shows the block-wise response times averaged across all subjects for the five training days. There is a noticeable increase in response speeds (Fig. 3a) during the sequence probes (Blocks 4 and 6), compared to the random probe (Block 5). There is also a noticeable saturation of the accuracy after Training Day 1, across most blocks, but particularly, the sequence blocks (Fig. 3b). The last random block provides a "learning probe" that allows for us to measure sequence-specific learning at the end of the day. We estimated learning scores based off of these probe blocks for each subject and each day (see Methods).

In order to estimate the rate of sequence learning across days, we calculated the slope of the learning scores for response times and accuracies for each subject using a linear model estimate (see Methods). Using a non-parametric Spearman's rank

correlation test, we next estimated the association between subject-specific factors and the rate of sequence learning across days. Table 2 shows these pairwise correlations. There was a significant negative correlation between learning slope of response times and waist circumference (Spearman's ρ = -.401, p < .05). Consistent with our hypothesis, as central adiposity increased, the rate of motor sequence learning across days decreased. There was a similarly negative, but weaker correlation between learning slope of response times and BMI (Spearman's ρ = -.230, p = .221), but this did not reach the level of statistical significance. Finally, we revealed a significant correlation between waist circumference and body mass index (Spearman's ρ = .740, p < .001).

In order to better understand the relationship between central adiposity and motor sequence learning across days, we used a median split to categorize subjects into low (N=16) and high (N=14) central adiposity groups. A repeated-measures ANOVA found a significant main effect of training day on response time learning scores (Fig. 4a; F (1, 28) = 28.041; p < .001), as well as a significant interaction between training day and the central adiposity group (F (1, 28 = 4.233; p < .05). In general, the low central adiposity group had a greater rate of learning across training than the high central adiposity group. It is noteworthy that this effect of body type on long-term learning is not significant when BMI is used as the group category; there was not a significant interaction between response time learning score and body-mass index (F (2, 27) = .630; p =.540). This is consistent with previous results showing that waist circumference is as a more reliable and direct measure of obesity than BMI (Li et al., 2007).

The association between sequence learning and central 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 ($F_{(1, 28)}$ = 2.402; p = .132) (Fig. 4b). Similar to the response time learning, we also did not see the day by body-mass index interaction in learning score accuracy performance ($F_{(1, 26)}$ = 1.009; p = .587). This suggests that the response time learning is most sensitive to differences in central adiposity.

Discussion

Here, we show that a measure of obesity, central adiposity, is associated with a decrease in long-term sequential motor learning. Participants with a higher waist circumference learned at a slower rate than lean counterparts in our five-day serial-reaction time task. Specifically, this association with central adiposity was limited to response speeds, but not accuracy, consistent with the idea that these two performance measures are independent (Verstynen et al. 2012a). Given that motor sequence learning is mediated by the striatum (Doyon et al., 2003), and obesity is linked to striatal function (Stice et al., 2008), these results supports the growing body of evidence that obesity may impact striatal-dependent cognitive functions.

Our findings provide a novel direction for exploring the impacts that increased obesity may have on striatal function. Many studies have confirmed that striatal dopamine systems, and related neural substrates, are critical for motor sequence learning (Doyon et al, 2003; Doyon et al, 2009; Yin et al, 2009; Lehericy et al, 2011; Penhune & Steele, 2012; Kawashima et al, 2012). The striatal nuclei are preferentially

engaged during the early consolidation of motor sequence skills (Doyon et al, 2003; Doyon et al, 2009; Yin et al, 2009; Lehericy et al, 2011; Penhune & Steele, 2012). Parkinson's disease, and similar basal ganglia patients show characteristic impairments in motor sequence skill learning tasks, due to the diminishing dopaminergic projections in the system (see review for Doyon et al., 2009; Pendt et al., 2011; Gobel et al., 2013)

Over the past fifteen years, it has become well-established that obesity is associated with differences in striatal functioning. Much of this evidence focuses on the relationship between obesity on the reward pathways of the brain, particularly those in the striatum itself (Stice et al., 2008; Stice et al., 2010; Burger & Stice, 2012; Marques-Iturria et al., 2015). Stice and colleagues (2008) found that blunted striatal responsivity in obese individuals was moderated with the presence of the dopamine allele of the TaqIA polymorphism when experiencing a high value food reward, compared to lean counterparts or obese individuals without the allele. In addition, many studies have found a reduced dopamine D2 receptor availability in obese individuals, compared to the lean counterparts (Wang et al .2001; Volkow et al., 2008; Stice et al., 2008; de Weijer et al., 2011). Given that dopamine reward signals are critical for striatal-dependent learning, this highlights a plausible mechanism for why central adiposity is associated with long-term skill learning in our study.

While our results suggest that obesity itself may impact striatal-dependent motor learning, many other factors correlated with obesity may also contribute to the rate of motor learning. For example, obesity is correlated with reduced cardiorespiratory fitness (Ross & Katzarzyk, 2003; Wong et al., 2004). Recent evidence suggests that cardiorespiratory fitness can impact cognitive function (Erickson et al. 2011), particularly
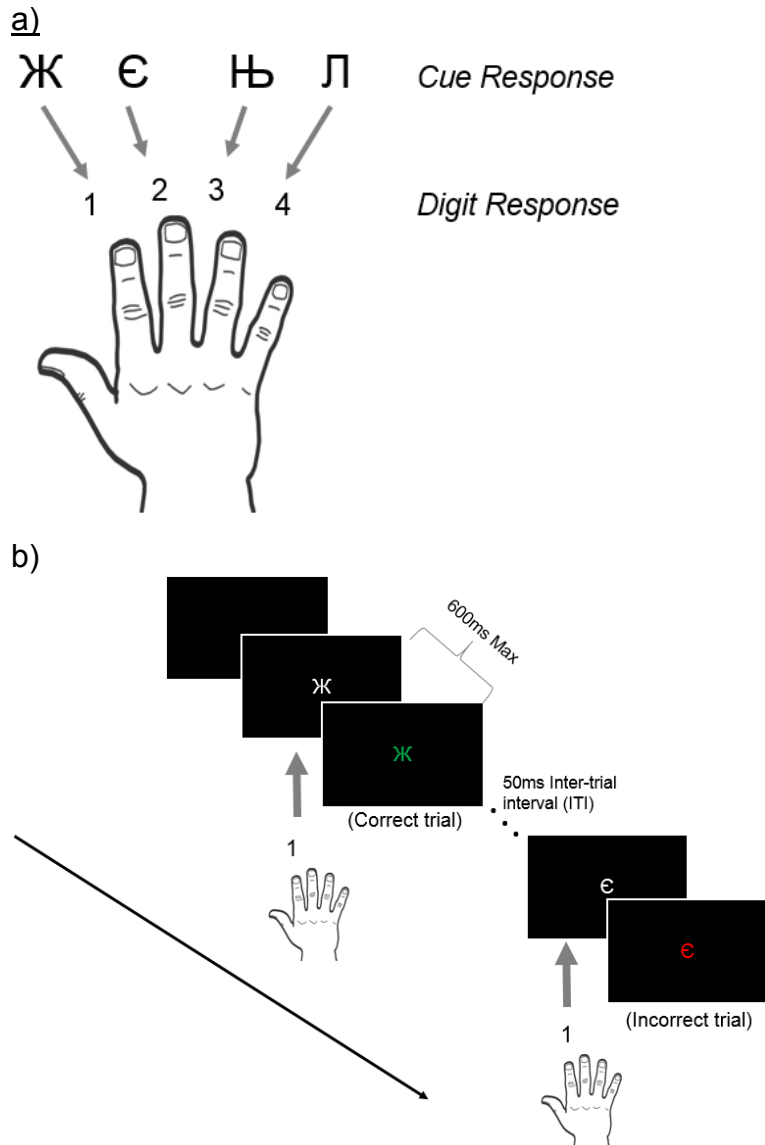
striatal-dependent cognitive functions like task switching (Verstynen et al. 2012b). Since we did not measure cardiorespiratory fitness, we cannot preclude this possibility here. Participants in the higher central adiposity group may also fatigue sooner than their lean counterparts, thus arousal levels 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 (Pagato et al., 2009, Rosen-Reynoso et al., 2011). Administering a battery of tests to quantify this measure, will aid in controlling for these additional extrinsic factors. Additional follow-up work should confirm the 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, using neuroimaging methods. Neuroimaging tools, such as fMRI, can provide valuable information to the particular regions involved in this motor learning task, and through this, we can confirm the striatal link to obesity through motor sequence skill learning.

Regardless of these mechanistic limitations, our results confirm that the level of obesity is an inherent concern of basal ganglia function. This extends our understanding of obesity and cognition links beyond reward processing to long-term motor sequence learning. The basal ganglia are highly plastic and have been shown to structurally vary over time (Raz et al., 2003; Raz et al., 2005. This may explain why these nuclei are particularly sensitive to health-related factors. We confirmed through well-established behavioral methods that obesity is associated with types of motor learning that depend on the basal ganglia. This has wide-ranging implications on the role of physical obesity

in skill learning and opens new avenues of research into the effects of physical fitness

on the brain, beyond just reward processing.

Figures

a)

Ж Є Њ Л   *Cue Response*

1   2 3   4   *Digit Response*

b)

600ms Max

Ж

Ж

(Correct trial)

1

50ms Inter-trial
interval (ITI)

Є

Є

(Incorrect trial)

1

Figure 1: Experimental Setup *a)* Digit-Key mapping. Participants performed the experiment using the four digits, excluding the thumb that corresponded to one uniquely mapped key. *b)* Schematic of the stimulus presentation. Each trial consisted of a one-stimulus presentation in which participants were asked to respond to the cues using the given key mappings. Correctly pressing the corresponding key to the cue resulted in the cue flashing green. Incorrectly pressing a key to the cue, or failure to respond within the response window resulted in the cue flashing red.
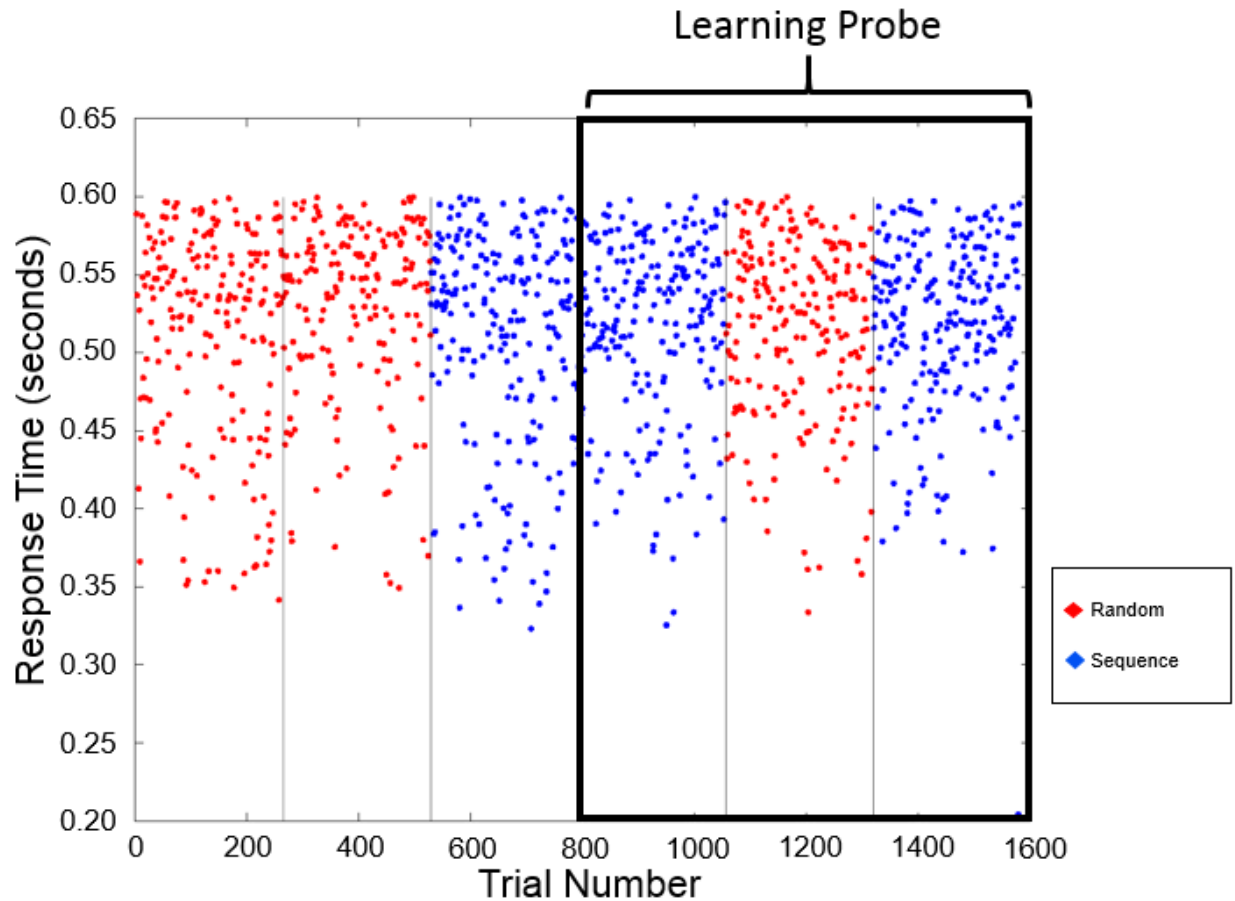
Figure 2: Sample Day 1 training session in which a participant is exposed to a total of

six experimental blocks, red: Random, blue: Sequence. Demarcation of each block is

represented by the vertical lines. Individual dots represent performance on a single trial

within the given block. The learning probe consists of the last three blocks used to

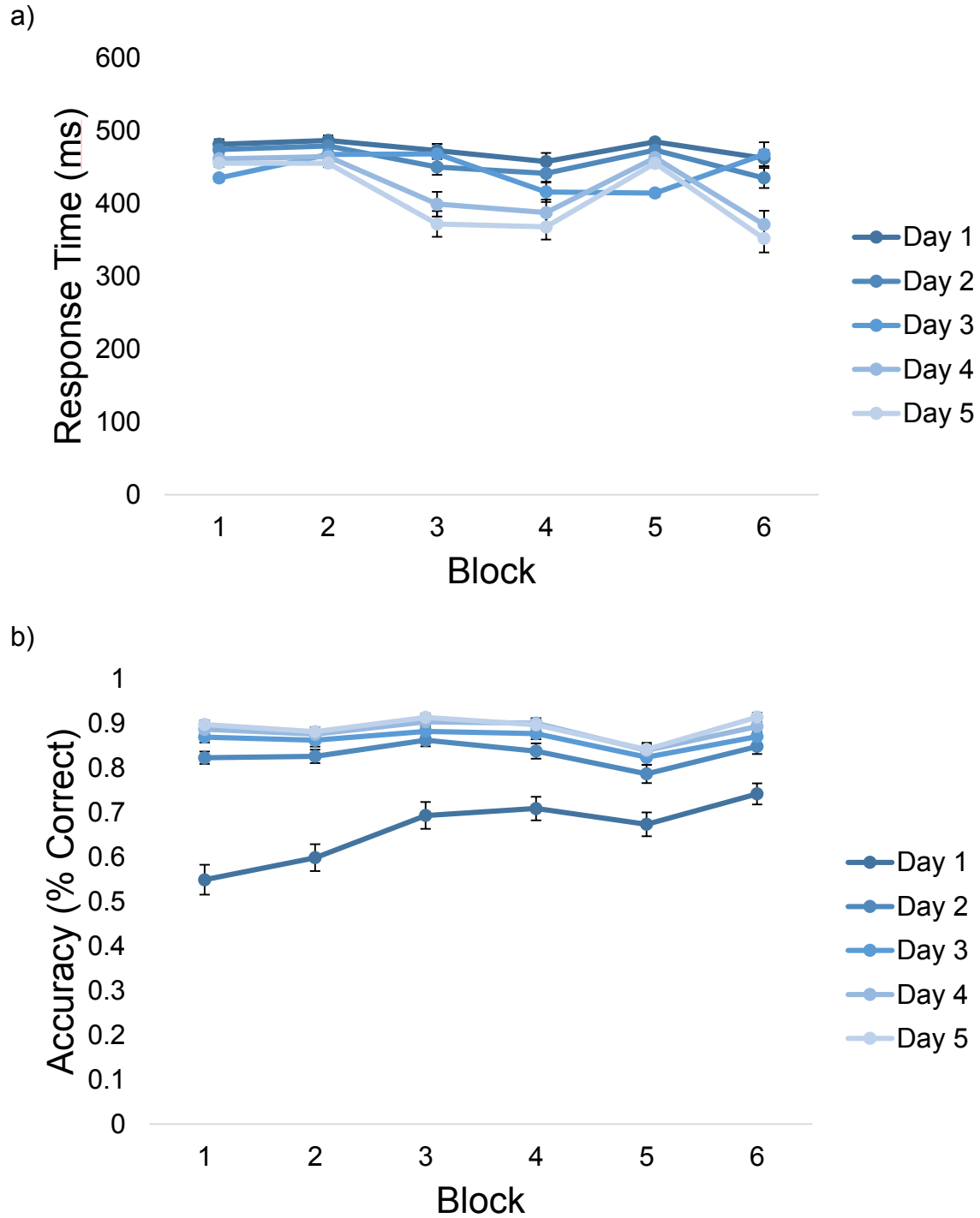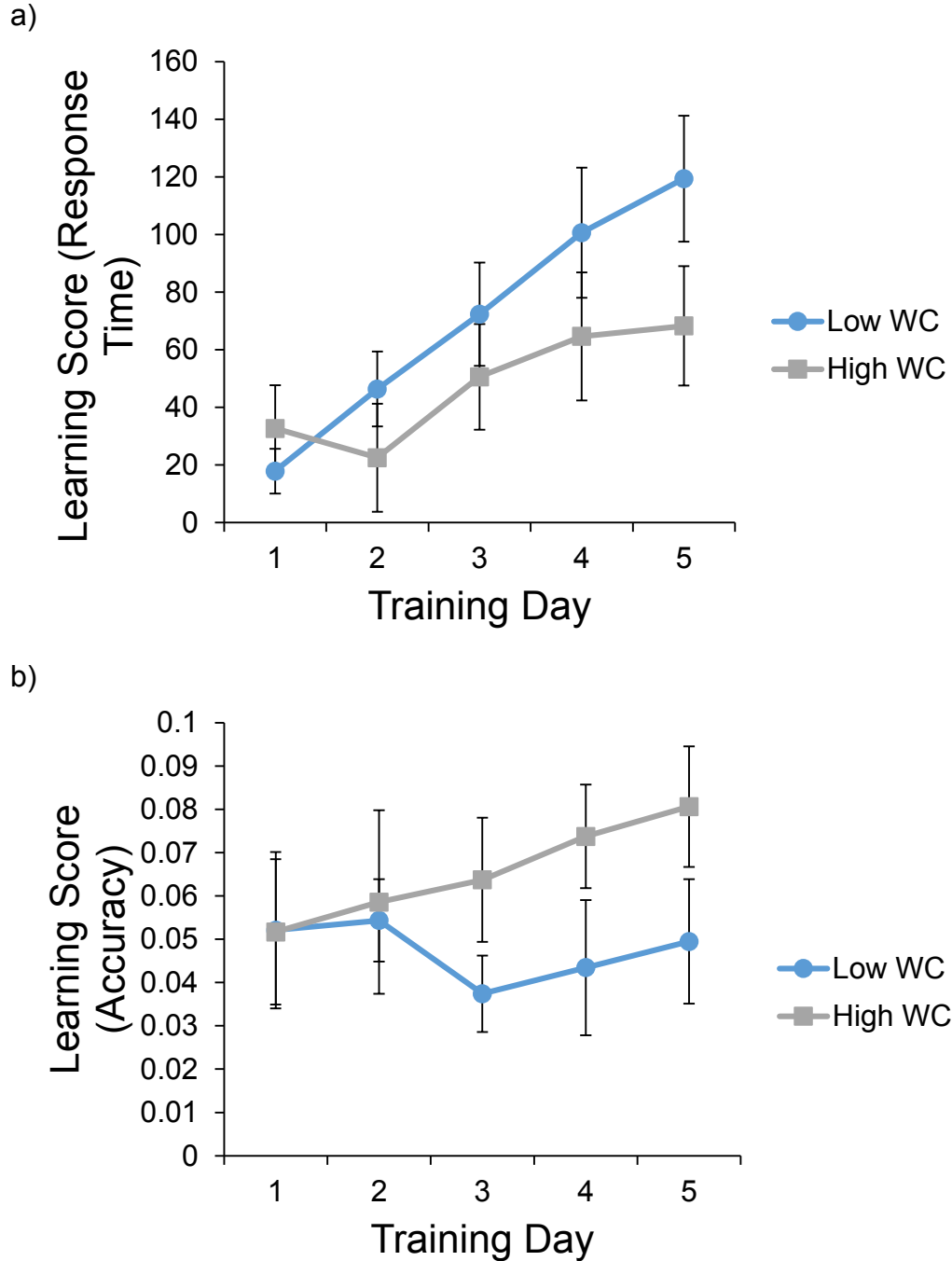assess implicit motor sequence learning.

a)

b)

Figure 3: Example of block-wise responses within the sample, *a*) Mean response time across blocks for the experimental cohort. *b*) Mean accuracy across blocks for the experimental cohort. All error bars are SEM.

a)

b)

Figure 4: Learning Scores across training days by binary waist circumference

categories, *a*) Response time learning scores across training days. *b*) Learning scores

of the accuracy across training days for the binary waist circumference category. All

error bars are SEM.

Table 1:	Lean (n = 10)	Overweight (n = 10)	Obese (n = 10)
Sex			
Male	4	8	5
Female	6	2	5
Age (in years)			
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
BMI (kg/m^2)			
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
Waist Circumference (in inches)			
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. A total of thirty participants, categorized by their body-mass index measurements, were included in the final analysis. There were a total of ten participants in each body-type category; lean, overweight, and obese.

	Sex	Age	BMI	Waist Circumference (WC)	Learning Slope Response Time
Age	-.035	-	-	-	-
BMI	-.054	.257	-	-	-
WC	-.327	.357	.740**	-	-
LS-Response Time	.307	-.236	-.230	-.401*	-
LS- Acc	-.023	-.178	.103	.191	-.115

* Significance at alpha < 0.01
** Significance at alpha < 0.05

Table 2: Correlation Table of factors. Spearman's non-parametric correlation coefficient

between each variable and covariate.

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