1 **The Relation of Saturated Fats and Dietary Cholesterol to Childhood Cognitive Flexibility**

2 Naiman A. Khan, PhD, RD¹, Lauren B. Raine, BS¹, Eric S. Drollette, BS¹, Mark R. Scudder,
3 BS¹, Charles H. Hillman, PhD¹

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5 ¹Department of Kinesiology and Community Health, University of Illinois, Urbana, IL

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7 **Author last names:** Khan, Raine, Drollette, Scudder, Hillman

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11 **Corresponding author:** Naiman A. Khan, PhD, RD, Neurocognitive Kinesiology Laboratory,
12 Department of Kinesiology & Community Health, University of Illinois, 313 Louise Freer Hall,
13 MC-052, 906 S. Goodwin Avenue, Urbana, IL 61801. Telephone: 217-333-3893. Fax: 217-244-
14 7322. Email: nakhan2@illinois.edu

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INTRODUCTION

Childhood represents a period marked by extensive changes in both brain structure and function (1, 2). Therefore, identification of health factors – lifestyle behaviors and markers of physiological health – associated with childhood cognitive function has important implications for not simply children’s cognitive health, but cognitive function throughout the lifespan. This is particularly important given the current obesogenic environment, characterized by reduced opportunities for physical activity and concomitant consumption of calorically dense but nutritionally poor diets. Emerging literature suggests that specific aspects of childhood cognitive function are selectively related to health factors such as aerobic fitness and obese weight status. However, the extent to which diet influences childhood cognitive function remains unclear.

Cognitive control (also referred to as executive control) is of particular interest to this area of study because it encompasses cognitive processes that underlie goal-directed behavior and are orchestrated by activity within the prefrontal cortex (3, 4). The three interrelated, but dissociable, cognitive processes thought to comprise cognitive control include inhibition (the ability to resist distractions to maintain focus), working memory (the ability to store, maintain, manipulate information to be retrieved within a brief period), and cognitive flexibility (the ability to dynamically shift attention, select information, and alter response strategy in response to changing task demands) (5, 6). Thus, cognitive control processes enable us to adjust our behavior to changing environmental demands. Further, the prefrontal cortex exhibits a protracted developmental trajectory throughout childhood, marked by progressive and regressive changes (myelination and synaptic pruning, respectively) occurring in parallel and shaped in part by the child’s idiosyncratic experience (3). Therefore, understanding the impact of health behaviors (e.g., physical activity and diet) and their interrelated physiological markers of health (e.g.,

aerobic fitness and adiposity) on cognitive control process during childhood may identify modifiable targets for future interventions aiming to improve cognitive functioning in children (7).

Previous studies in children have associated key aspects of childhood physiological health, particularly aerobic fitness, to tasks assessing inhibitory control, working memory, and cognitive flexibility (8-10). These effects have been further supported by neuroimaging data demonstrating that greater aerobic fitness is positively and selectively associated with neural substrates subserving cognitive control (11). In addition, a relatively consistent finding is that obesity is associated with cognitive deficits, especially in cognitive control, in children, adolescents, and adults (12). Among prepubertal children, even following adjustment of aerobic fitness, increasing adiposity or obese weight status have been shown to be negatively related to children's performance on cognitive control tasks (13-16). Evidence implicating excess adiposity and obese weight status in compromised cognitive control in childhood is especially concerning given that approximately one-third of the children in the United States are estimated to be overweight or obese. While a converging body of literature points to the beneficial effects of higher aerobic fitness and maintenance of a healthy weight status for cognitive control in childhood, the evidence relating specific aspects of diet intake to children's cognitive control, particularly cognitive flexibility, remains limited.

Diet and cognitive function are thought to interact via multiple pathways. Diet may directly influence cognitive function by a variety of mechanisms including provision of essential nutrients for brain development (17), amelioration of neuroinflammation (18, 19), and provision of energy (20). Alternatively, impairment in cognitive control functions may contribute to poor dietary choices. Indeed, cognitive control functions are thought to be necessary to regulate eating

behaviors (21). Pertinent to the study reported herein, diets high in saturated fats (SFAs) and cholesterol have been previously linked to cognitive impairment in animal studies as well as human trials. Rodents consuming diets higher in saturated fats exhibit decrements on memory tasks as well as neurotrophic factors important for neuronal plasticity and learning (22, 23). Among humans, consuming a diet high in SFA during midlife is associated with an increased risk for cognitive impairment in later adulthood (24). Similarly, higher dietary cholesterol intake among older adults is significantly associated with an increased risk of impaired memory and cognitive flexibility (25). Among children, dietary lipids have been shown to be differentially associated with memory function (26) while overall diet quality was found to be positively correlated with academic performance among 5th grade students (27) and children's attentional inhibitory control (28). Therefore, specific dietary components may play an important role in children's cognitive control. However, links between nutrients and specific cognitive domains are not well characterized.

Specifically, the association of saturated fats and cholesterol intake to children's cognitive flexibility has received little to no attention in the literature. Although the influence of diet on inhibitory control has received considerable interest (28, 29), the relationship between habitual diet intake and cognitive flexibility has received comparatively less attention. Tasks tapping into cognitive flexibility are distinct from inhibitory control because the former requires switching between two or more mental sets rather than the inhibition of a single response or the suppression of interfering information (3, 30). Indeed, successful task switching may index a higher order of information processing and action control requiring both working memory and inhibitory control (3, 31). Previous studies have shown that aerobic fitness and obesity exert contrasting effects on cognitive flexibility among prepubertal children (10, 16, 32). Therefore,

examining whether or not diet also plays a role in cognitive flexibility stands to expand our understanding of modifiable lifestyle factors that may be targeted for improvement of all cognitive control processes, and not only inhibitory control.

Accordingly, the study reported herein examined associations between saturated fats and cholesterol intake and cognitive flexibility, assessed using a task switching paradigm, among a sample of prepubertal children between 7-10-years. Our central hypothesis was that increasing intake of saturated fats and dietary cholesterol would be related to poorer performance – indicated by lower accuracy, longer reaction times, and higher global and local switch costs – on a cognitive flexibility task, following adjustment of confounding variables including demographics, IQ, aerobic fitness and BMI.

MATERIALS AND METHODS

Participants

The results of this study are based on cross-sectional analysis of baseline data collected from a subsample of prepubertal children between 7 and 10 years ($N = 150$) who participated in a larger randomized controlled trial [Fitness Improves Thinking in Kids (FITKids; NCT01334359)]. Only FITKids participants who provided diet and the switch task were included in the sample studied herein. Participants' provided written assent and their legal guardians' provided written informed consent in accordance with the regulations of the University of Illinois Institutional Review Board. Children were screened for neurological disorders, physical disabilities, psychoactive medication status, and normal or corrected-to-normal vision. Data were also collected on 1) IQ, using the Kaufman Brief Intelligence Test (33),

2) socioeconomic status (SES) as estimated based on participation in a school meal-assistance program, maternal and paternal education levels, and how many parents work full-time, and 3) pubertal status using the modified Tanner Staging System (34). The sample comprised of both healthy weight (66%) and overweight/obese children (34%). Participants with low SES constituted 34% of the sample and 65% were categorized as Tanner stage 1.

Diet Assessment

Dietary intake was collected using one 24-hour food recall conducted by a Registered Dietitian. The recall was completed by the child with assistance from the parent. The Nutrition Data Systems-Research (NDSR; Nutrition Coordinating Center, Minneapolis, MN, USA) software was used to analyze dietary intake. Nutrient-level analyses were conducted using the intake properties file to determine macronutrient (carbohydrate, protein, and fat) intake.

Anthropometric Assessment

Height and weight were measured using a stadiometer (Seca; model 240) and a Tanita WB-300 Plus digital scale, respectively. The mean of three measurements of height and weight were used for the analyses. The Centers for Disease Control (CDC, 2000) growth charts were used to determine each child's BMI-for-age percentile (35).

Aerobic Fitness Assessment

Cardiorespiratory fitness was assessed using a test of maximal oxygen consumption ($\text{VO}_{2\text{max}}$) (36). Oxygen consumption was measured using a computerized indirect calorimetry system (ParvoMedics True Max 2400) while participants ran/walked on a motor-driven treadmill at a constant speed with incremental grade increases of 2.5% grade every two minutes until the participant was no longer able to maintain the exercise intensity (36). A Polar heart rate monitor

(Polar WearLink+ 31; Polar Electro, Finland) was used to measure heart rate throughout the test and ratings of perceived exertion were assessed every 2 min using the children's OMNI scale (37). $\text{VO}_{2\text{max}}$ was based upon maximal effort as evidenced by (1) a peak heart rate > 185 bpm (36) and a heart rate plateau (38); (2) $\text{RER} > 1.0$ (39); (3) a score on the children's OMNI ratings of perceived exertion scale > 7 (37); and/or (4) a plateau in oxygen consumption corresponding to an increase of less than 2 ml/kg/min despite an increase in workload.

Switch Task

Cognitive flexibility was assessed using a color-shape task switching paradigm (40). This task requires participants to learn a set of response mappings arbitrarily assigned to a set of colors (blue and green) and shapes (circle and square), then utilize a rule-set cue (the direction of the characters arms) to flexibly shift visuospatial attention towards the correct feature set and execute the correct response mapping [see (10)]. In this task, participants completed two blocks of 60 homogeneous trials (1 block of color only; 1 block of shape only) in which they attended to a centrally presented character. Participants were instructed to make a left hand thumb press on a Neuroscan STIM system response pad (Compumedics, Charlotte, NC) when the character was blue (in the color condition) or a circle (in the shape condition) and a right hand thumb press when the character was green (in the color condition) or a square (in the shape condition). During the heterogeneous condition, participants performed both the color and shape tasks together with the specific task on each trial indicated by the direction of the character's arms (arms up: respond based on the shape of the character; arms down: respond based on the color of the character). After a block of 40 practice trials, participants completed three blocks of 50 heterogeneous trials with equiprobable task occurrence and response directionality. The stimuli

were 5.5 cm tall and 9 cm wide characters presented focally for 3000 ms on a black background – or until a response was given – with a fixed inter-trial interval of 3500 ms.

Switch task measures of interest included accuracy and reaction time with greater accuracy and faster reaction times indicating superior cognitive flexibility. In addition to accuracy and reaction time, global and local switch costs were calculated to index the flexible modulation of cognitive control when faced with greater task demands. Global switch cost analyses examined differences between homogenous and heterogeneous conditions while local switch cost analyses examined differences between switch and non-switch trials during the heterogeneous block condition. Global switch cost related to accuracy was defined as the difference in performance between homogeneous and heterogeneous blocks (accuracy cost: homogenous – heterogeneous; reaction time cost: heterogeneous – homogenous). Thus, lower global switch costs reflect the greater efficiency of maintaining multiple task sets in working memory as well as the selection of the task to be performed next (41). Local switch costs were defined as the difference between performance on switch trials and non-switch trials within heterogeneous blocks (accuracy cost: non-switch – switch; reaction time cost: switch – non-switch). Lower local switch costs are thought to reflect greater effectiveness of cognitive control processes responsible for the activation of the presently relevant task set and the deactivation of the task set that was relevant on the previous trial (42). We hypothesized that intake of dietary cholesterol and saturated fatty acids will be associated with greater global and local switch costs, signifying increasing decrements in cognitive flexibility.

Statistical Analyses

Differences in cognitive flexibility across categorical variables (e.g., healthy vs. obese weight status, SES, and sex) were conducted using an independent *t* test. Initial Pearson's

correlations assessed bivariate relationships between demographic variables and cognitive flexibility measures among all participants. Subsequently, partial correlations were conducted between diet variables and cognitive flexibility following adjustment of control variables (age, sex, SES, K-BIT, VO_{2max} , and BMI). Control variables were chosen based on prior research relating these factors to measures of cognitive control (16, 43). One-tailed t tests were used because this study aimed to test directional hypotheses regarding the associations between cholesterol and saturated fatty acids and cognitive flexibility measures. To adjust for overall energy intake, nutrient intake was normalized to intake per 1000 kcal within participants before subsequent analyses. Statistics were performed using SPSS 22 (IBM, Somers, NY).

RESULTS

Participant characteristics (demographics, weight status, and aerobic fitness) and switch task performance are presented in **Table 1**. Mean reaction times were determined after averaging correct trials. **Table 2** summarizes the diet intake variables among participants. Participants reported meeting approximately 52% ($SD=9.54$) of their energy needs from carbohydrates, 15.3% ($SD=4.6$) from proteins, 32.6% ($SD=7.5$) from fats, and 12.4% ($SD=4.4$) from saturated fats.

There were no significant differences in diet intake, K-BIT, and switch task response accuracy and reaction time for homogeneous and heterogeneous trials between healthy weight and obese children. However, obese children exhibited greater global switch cost for accuracy ($P=0.02$) compared to healthy weight children. Aerobic fitness, assessed as VO_{2max} relative to body weight, was higher ($P<0.01$) among males while females had higher BMI ($P<0.01$). On the other hand, no differences in diet intake were observed between males and females. Further, there were no significant differences in K-BIT, switch task response accuracy and reaction time

for homogeneous and heterogeneous trials across sex groups. However, females exhibited greater global switch costs for accuracy ($P=0.03$). Differences between high ($n=61$) and low ($n=51$) SES groups revealed that high SES children had higher K-BIT ($P<0.01$), VO_{2max} ($P<0.01$), and consumed higher protein ($P=0.03$) while children categorized as low SES children exhibited greater local switch cost for reaction time ($P=0.04$).

Bivariate correlations were conducted to identify non-diet variables that may be associated with cognitive flexibility measures. Age was positively related to accuracy on the homogeneous ($r=0.20$, $P<0.01$) and heterogeneous trials ($r=0.28$, $P<0.01$) and negatively related to global accuracy switch cost ($r=-0.19$, $P=0.01$). Sex was related to global switch cost for accuracy ($r=0.18$, $P=0.01$) such that males had a lower global switch cost. K-BIT was positively related to heterogeneous accuracy ($r=0.23$, $P<0.01$) and negatively related to global switch cost for accuracy ($r=-0.19$, $P=0.01$), signifying that greater IQ was associated with the ability to maintain accuracy when task demands increased. BMI was related to greater global switch cost for accuracy ($r=0.20$, $P=0.01$) whereas VO_{2max} was related to greater accuracy on heterogeneous trials ($r=0.25$, $P<0.01$) and negatively related to global switch cost for accuracy ($r=-0.26$, $P<0.01$).

Results of the partial correlations between the diet variables and switch task performance – following adjustment of age, sex, K-BIT, SES, VO_{2max} , and BMI – are presented in **Table 3**. Following adjustment of covariates, total fats ($r=0.20$, $P<0.01$), saturated fats ($r=0.23$, $P<0.01$), and cholesterol ($r=0.17$, $P=0.02$) were related to greater local switch cost for accuracy. Saturated fats were related to increased heterogeneous reaction time ($r=0.17$, $P=0.02$) and global switch cost for reaction time ($r=0.14$, $P=0.04$). Cholesterol intake was related to increased local switch for both accuracy ($r=0.17$, $P=0.02$) and reaction time ($r=0.14$, $P=0.04$).

228

229 **DISCUSSION**

230 Previous studies have shown that cognitive flexibility is positively associated with
231 aerobic fitness and negatively related to adiposity among prepubertal children (10, 16). However,
232 data relating dietary components to childhood cognitive flexibility is limited. The current study
233 provides novel evidence linking diet intake to cognitive flexibility among prepubertal children.
234 The major findings were that fats, specifically saturated fats, were related to longer reaction time
235 during the heterogeneous trials – the trial type requiring greater cognitive flexibility – and greater
236 global switch cost for reaction time. Thus, increasing intake of saturated fats was associated with
237 impaired ability to maintain multiple task sets in working memory as well as the selection of the
238 subsequent task (44). Further, increasing intake of dietary cholesterol was related to greater local
239 switch costs for both accuracy and reaction time, reflecting lower efficiency of executive control
240 processes responsible for the activation of the presently relevant task set and the deactivation of
241 the task set that was relevant on the previous trial (45). Collectively, these data are among the
242 first to indicate that children consuming diets higher in saturated fats and cholesterol exhibit
243 compromised ability to flexibly modulate their cognitive flexibility, particularly when faced with
244 greater task demands.

245 A broader implication of this study was that it provided evidence identifying cognitive
246 flexibility as another core cognitive control process that may be susceptible to the detrimental
247 effects of saturated fats and cholesterol intake. Cognitive flexibility is important because it
248 comprises the ability to switch perspectives in daily life (e.g. viewing a problem from the point
249 of view of others or from a different direction) and involves being flexible enough to adjust to
250 changing demands or priorities. This capacity to switch perspectives depends on the child's

ability to inhibit (or deactivate) a previous perspective and load into working memory (or activate) a different perspective (31), integrating both inhibitory and working memory abilities. However, relative to other cognitive control processes, cognitive flexibility develops later, with the ability to flexibly switch, on a trial-by-trial basis, not emerging until 7 to 9 years of age (46, 47). This later emergence may partially explain the limited number of studies investigating the behavioral correlates of cognitive flexibility in childhood.

Nevertheless, emerging evidence demonstrates that the provision of physical activity can improve cognitive flexibility in both children and adults (10, 48). Further, increasing BMI and excess fat mass has been related to poorer performance on cognitive flexibility tasks among prepubertal children (16, 32). In the current study, BMI was also related to cognitive flexibility, such that children with higher BMI exhibited poorer ability to upregulate their cognitive control when faced with greater task demands.

Although data relating diet to cognitive flexibility is limited, previous studies have correlated specific nutrients to inhibitory control and memory function in children. Baym et al. (2014) observed that increasing intake of omega-3 fats was selectively and positively related to hippocampal-dependent relational memory among prepubertal children (26). In contrast, saturated fats were negatively related to both hippocampal-dependent and hippocampal-independent forms of memory, suggesting a generalized negative effect of saturated fats on memory function (26). Among a similar sample of children, Khan et al. (2015) observed that overall diet quality and dietary fiber were positively related to inhibitory control while total fat intake was negatively related to the ability to suppress interference when cognitive demands were increased (28). Further, increasing intake of dietary cholesterol has been shown to be negatively related to children's performance on a digit span task (49). Similar to Baym et al.

(2014), the current study's findings support a generalized negative association between saturated fats and cognitive function since increasing saturated fats were related to both global and local switch costs. On the other hand, increasing dietary cholesterol was only related to greater local switch costs, reflecting selective association with lower efficiency of cognitive control processes. Therefore, the findings from the current study complement previous work by detecting that cognitive flexibility is another core cognitive control process that may be susceptible to the deleterious effects of saturated fats while identifying dietary cholesterol as a negative correlate of cognitive flexibility in children as well.

Given the association between saturated fat and cholesterol intake and metabolic risk, it is curious that the influence of these nutrients on childhood cognitive flexibility has not been directly investigated. Intake of saturated fats has been linked – primarily through increased concentration of low-density lipoprotein (LDL) – to an increased risk for cardiovascular disease (50). However, the deleterious effects of saturated fats on cognitive function have been observed in rodent studies as well as human trials. Rats fed 20% of their calories from saturated fats exhibit decrements in learning and cognitive function, relative to rats consuming monounsaturated, or polyunsaturated fats (51). Subsequent studies indicated that the mechanism underling this effect may involve saturated fat-induced oxidative stress and reduced BDNF resulting in compromised synaptic plasticity (52). Further, saturated fats increase insulin resistance in the brain (53) and diminish the integrity of the blood brain barrier (54). When fed in combination with cholesterol, saturated fat diets of up to 10% have been shown to reduce dendritic integrity in rats (55). Among adult humans, higher dietary cholesterol intake was significantly associated with an increased risk of impaired memory and cognitive flexibility. However, the effects of saturated fat intake on impaired memory, speed, and cognitive flexibility

was not statistically significant (56). Further, use of drugs that lower blood cholesterol concentrations (e.g. statins) may be associated with a lower risk of dementia among older adults (57). However, among children, the evidence remains mixed, with some studies finding associations between saturated fats and cholesterol and cognitive functioning and others not observing a relationship (26, 28, 49). Nevertheless, consistent with data from animal studies and adult trials, findings from this study indicate that increasing saturated fat intake and dietary cholesterol may exert independent effects on cognitive functioning in children as well.

Although the current study provides support for the negative association between saturated fats and dietary cholesterol and cognitive flexibility, there are several limitations worth considering. Given that these results are based on cross-sectional analyses, we cannot make statements of causality. While it is assumed that variability in cognitive flexibility was driven by the diet measures, it is possible that the opposite may be true, such that lower cognitive flexibility may be implicated in poorer dietary choices. Future longitudinal and/or intervention studies examining the effects of saturated fat and cholesterol intake on cognitive flexibility could provide definitive support for the directionality of the associations observed in the current study. Further, although there is validity in using one 24-hour recall to assess diet intake among groups of people, additional studies that utilize other multiple diet assessment techniques such as food records or food frequency questionnaires would provide further support for this work. In addition, our analyses did not account for all nutrients consumed. Therefore, we cannot exclude the possibility that micronutrients (i.e., vitamins and minerals) may have contributed to our results. Finally, future studies should assess serum or plasma markers of metabolism and inflammation to uncover the mechanisms that may underlie these observations. Nevertheless, the strengths of the current study included the adjustment of several key covariates known to

influence childhood cognitive function e.g., age, sex, SES, IQ, aerobic fitness, and BMI. Therefore, the finding that specific dietary components significantly correlated with cognitive flexibility – following adjustment of key covariates – highlights the importance of assessing saturated fat and cholesterol intake along with cognitive flexibility outcomes in future studies among child populations.

CONCLUSIONS

Given that rapid rise and persistence of the childhood obesity epidemic, the detrimental effects of physical inactivity and excess fat mass on childhood cognitive function are becoming increasingly recognized. However, the extent to which specific dietary components influence cognitive functioning among children, without clinical nutrient deficiencies, remains unclear. The current study provides novel evidence relating saturated fats and dietary cholesterol to cognitive flexibility among prepubertal children. Critically, we demonstrate that increasing intake of saturated fats and cholesterol is associated with the compromised ability to flexibly modulate cognitive control, particularly when task demands are increased. Diet recommendations for lowering saturated fat intake and dietary cholesterol have been shown to result in improved cardiovascular health among children and adults. The cross-sectional findings from this study provide preliminary support for future intervention studies that may aim to optimize cognitive health by reducing saturated fat and cholesterol intake among pediatric populations.

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Table 1. Participant characteristics and switch task performance

	Mean	SD
Age, <i>years</i>	8.8 (0.6)	0.6
Socioeconomic Status, %		
Low	34.0	
Medium	25.0	
High	41.0	
Pubertal Timing, %		
Tanner Stage 1	65.0	
Tanner Stage 2	35.0	
BMI, <i>kg/m²</i>	18.5	3.9
BMI-for-age, % <i>tile</i>	65.4	28.3
<85 th	66.0	
≥85 th	34.0	
VO _{2max} , <i>kg/ml/min</i>	39.0	6.8
Intelligence Quotient	112.0	14.2
Switch Task		
Response Accuracy, %		
Homogenous Trials	86.7	8.1
Heterogeneous Trials	66.3	15.0
Global Switch Costs	20.4	13.6
Local Switch Costs	2.0	7.4
Reaction Time, <i>ms</i>		
Homogenous Trials	807.1	160.8
Heterogeneous Trials	1439.2	252.8
Global Switch Costs	632.1	250.2
Local Switch Costs	174.3	164.4

Table 2. Dietary intake among study participants

	Mean (SD)	RDA/AI ¹
Energy, <i>kcal</i>	1982.6 (920.0)	1593-2043 ²
Carbohydrate, <i>g</i>	262.3 (126.6)	130
Total Fats, <i>g</i>	73.9 (39.6)	31
Protein, <i>g</i>	73.0 (35.7)	34
Saturated Fats, <i>g</i>	28.1 (17.1)	ND
Cholesterol, <i>mg</i>	218.3 (148.2)	ND

¹Recommended values based on the Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (2002/2005)

²Based on energy intake recommendations for sedentary – active children (58, 59)
RDA, recommended dietary allowance; AI, adequate intake; ND, not determinable

Table 3. Partial correlations between diet variables and cognitive flexibility measures

		Total Fats	Saturated Fats	Cholesterol
Response Accuracy				
Homogenous Trials	<i>r</i>	0.01	0.03	0.12
	<i>P</i>	0.47	0.36	0.07
Heterogeneous Trials	<i>r</i>	0.03	-0.04	0.06
	<i>P</i>	0.37	0.32	0.22
Global Switch Costs	<i>r</i>	-0.03	0.06	0.01
	<i>P</i>	0.38	0.24	0.47
Local Switch Costs	<i>r</i>	0.20**	0.23**	0.17*
	<i>P</i>	<0.01	<0.01	0.02
Reaction Time				
Homogenous Trials	<i>r</i>	0.04	0.06	0.03
	<i>P</i>	0.31	0.23	0.35
Heterogeneous Trials	<i>r</i>	0.12	0.17*	0.07
	<i>P</i>	0.09	0.02	0.17
Global Switch Costs	<i>r</i>	0.09	0.14*	0.06
	<i>P</i>	0.14	0.04	0.24
Local Switch Costs	<i>r</i>	-0.01	0.05	0.14*
	<i>P</i>	0.43	0.20	0.03

Control variables included age, sex, SES, K-BIT, VO_{2max}, and BMI

**Significance $P < 0.01$ (one tailed)

*Significance $P < 0.05$ (one tailed)