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# Contributions of Working Memory and Inhibition to Cognitive Flexibility in Nigerian Adolescents

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## ABSTRACT

This study used a novel approach that combined the latency and accuracy scores to examine the relative involvement of inhibition and working memory in two measures of cognitive flexibility – mixing cost and switch cost in 110 Nigerian adolescents. Results showed that inhibition was significantly associated with switch cost. On the other hand, working memory was negatively associated with mixing cost. These findings support the assumption that cognitive flexibility skills are dependent on inputs from inhibition and working memory processes. Inhibition is involved in the deactivation of irrelevant stimuli during switching trials while working memory is essential to maintain the current rule in sets that require no shifting.

## ARTICLE HISTORY

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## Introduction

Executive functions refer to higher-level cognitive processes that enable adaptive, goal-directed behavior by exerting control over lower-level functions (Diamond, 2013). Executive functions are multifaceted and have been understood in the framework of three major cognitive processes – inhibition, cognitive flexibility, and working memory. Efficient functioning of these cognitive processes has been thought to depend on the integrity of the frontal areas (Alvarez & Emory, 2006; Collette, Hogge, Salmon, & Van der Linden, 2006), which undergo rapid maturation in adolescence. In this study, we attempt to examine the relative contributions of working memory and inhibition to cognitive flexibility in a group of Nigerian adolescents.

Facets of inhibition include the ability to withhold unwanted prepotent responses (i.e., simple inhibition, as measured by, e.g., the Stop Signal Task) and the ability to suppress irrelevant or interfering information (i.e., complex inhibition, as measured by, e.g., variants of the Stroop Task). Working memory enables the maintenance of information in mind while acting with the information to guide actions and behaviors. Working memory tasks typically consist of forward recall (dependent on attentional process) and backward recall which places higher demands on executive and working memory processes (Donolato, Giofrè, & Mammarella, 2017). Cognitive flexibility refers to the ability to shift attention between mental sets or responses in the midst of changing task contingencies (Miyake et al., 2000). Typically measured with task-switching paradigms, cognitive flexibility requires that test takers switch between two tasks and in the process incur some associated performance costs – switch cost (difference between task switching and repetition trials in mixed blocks) and mixing cost (difference between two repetitive trials either in single or mixed blocks trials; Archambeau & Gevers, 2018; Vandierendonck, Liefoghe, & Verbruggen, 2010).

Task-switching paradigms have been widely studied in both adult and children samples (Crone, Bunge, Van der Molen, & Ridderinkhof, 2006; Davidson, Amso, Anderson, & Diamond, 2006; Kopp,

Steinke, Meiran, Seer, & Lange, 2018; Meiran, 2005; Meiran, Chorev, & Sapir, 2000; Nweze, Eze, & Lange, 2020; Reimers & Maylor, 2005; Schneider & Logan, 2010; Zelazo, Craik, & Booth, 2004; Logan, 2004) and have been conceptualized as a top-down cognitive control process primarily because of its perceived dependence on other executive processes (Davidson et al., 2006). Performance costs in task switching have been accounted for by the roles of active preparation time and interference (Cepeda, Kramer, & Gonzalez de Sather, 2001). According to active preparation model, allowing time to prepare for task changes by cueing the target stimuli reduces the time needed to detect and classify the stimuli (Meiran, 2000). The basic assumption of this model is that it is structurally improbable that two task sets are activated simultaneously, thereby making task-set reconfiguration necessary. This has been shown to reduce the switch cost in adult and children samples as they are able to prepare for task changes (Grange & Houghton, 2014; Hughes, Ratcliff, & Lehman, 1998; Kiesel et al., 2010; Meiran, 2000; Monsell, 2003; Vandierendonck et al., 2010). On the other hand, interference theory as proposed by Allport and Wylie (1999, 2000) sees performance costs associated with task switching from decreased interference from previously presented stimulus as a result of decay in the working memory. According to this perspective, increasing the time between subject response and the presentation of the next stimulus rather than allowing time to prepare for the next stimulus, results in lower switch cost and reaction times.

Over the past decades, researchers have attempted to examine the correlations among cognitive flexibility, inhibition, and working memory. Findings have been mixed and contradictory. For example, Espy and Bull (2005) found high communality between cognitive flexibility and working memory tasks in preschool children with those performing high in memory span also more successful in disengaging from shifting trials than those low on memory span. While previous findings have observed high inter-correlations among inhibition, working memory, and switch cost of cognitive flexibility (Carlson & Moses, 2001; Miyake & Friedman, 2012), other studies that have used both latent modeling and individual tasks found these associations to be very weak and inconsistent (Miyake et al., 2000; Oberauer, Schulze, Wilhelm, & Süß, 2005). Similarly, although evidence show that working memory and inhibition are related to cognitive flexibility, this correlation is only limited to mixing cost of flexibility but not to switch cost (Brocki & Tillman, 2014; Chevalier et al., 2012). It should be noted that most of these studies used varying statistical approaches in the data analyses (e.g., analysis of speed and/or accuracy of task-switching measures).

The purpose of the current study is to examine the relative contributions of working memory and inhibition to cognitive flexibility in Nigerian adolescents. While previous studies have examined these associations, they relied primarily on children and adult samples (Cepeda et al., 2001). In addition, previous studies have utilized error rates and/or reaction times measures of the executive function tasks when examining the associations among the executive processes. This approach may complicate the interpretation of findings if there are discrepancies between the associations of accuracy and speed on a given executive function task as some past studies have observed. Equally, relying on reaction times only, without accounting for the proportion of errors does not give a holistic assessment of an individual's ability in any given task. An alternative approach – the binning procedure that uses rank-order scoring to combine the reaction time and accuracy into a composite score has been suggested (see Vandierendonck, 2016; Draheim, Hicks, & Engle, 2016 for details). However, this procedure has its drawbacks including over-reliance on difference score and disproportionate scoring of inaccurate trials (Draheim et al., 2016). These concerns taken together may account for the conflicting findings of the correlations existing between these executive processes and cognitive flexibility. In the current study, we used a novel approach called linear integrated speed-accuracy scores (LISAS) that combined the reaction times and the proportion of errors into a single score while accounting for the concerns of binning procedure. Using this approach, we not only ensured that the problem of differences in the correlation of speed and accuracy is accounted for, but also that the correlations between performance on executive function tasks can be studied in a more reliable and parsimonious way.

## Methods

### *Participants*

A total of 110 secondary school students (age: range = 12–21 years;  $M = 16.15$  years;  $SD = 1.67$ ) were recruited from six schools in the Nsukka district of south-east Nigeria. Given this sample size, sensitivity analysis revealed we have 90% power to detect correlation as high as ( $r = .27$ ). Participants reported having completed an average of 9.75 years in school ( $SD = 1.47$ ) and ranged from grade 7 to 11. A total of 58 participants identified themselves as males, compared to 45 female participants (gender information was unavailable for seven students). The participants were not reimbursed for their involvement in the study.

### *Procedure and assessment*

Students from participating schools were scheduled for individual appointments, which lasted for approximately 45 minutes. Participants first signed a consent form before providing demographic information and completing the Parental Socioeconomic Status Scale (PSSS) as a measure of socio-economic status. Next, they completed four computerized tasks measuring cognitive flexibility, inhibition, and working memory. The tasks were designed and run using OpenSesame version 3.1.4 (Mathôt, Schreij, & Theeuwes, 2011) and they were administered in the same fixed order (Color-Shape Shifting Task, Stop Signal Task, Numerical Stroop Task, Digits Span Task) to all participants.

### *Color Shape Shifting Task*

Cognitive flexibility was assessed with the Color Shape Shifting Task (Friedman et al., 2006, 2008, 2016). The task requires participants to respond to target stimuli that are defined by their shape (circle or triangle) and color (red or green). A cue (“C” for color, “S” for shape) preceded the onset of target stimuli by 350 ms to indicate the sorting rule to apply on any given trial. Participants responded to the target stimulus by pressing one of two keys (“Z” for red and circle, “/” for green and triangle). They first completed two single-task blocks of 24 trials (plus 12 practice trials) each, during which the valid task rule did not change. They then practiced switching between the two tasks (24 trials) before completing two mixed-task blocks of 56 trials each (see Nweze, Agu, & Lange, 2020 for full description). Error rates and mean response times were calculated separately for trials in the single-task blocks, repeat trials in the mixed-task blocks (on which the valid task rule remained constant between trial  $n-1$  and trial  $n$ ), and switch trials in the mixed-task blocks (on which the valid task rule changed from trial  $n-1$  to trial  $n$ ). For the computation of response times, responses were included only if they were greater than 200 ms, followed accurate trials and within 3 standard deviation of the participant’s mean response times. Error rates and response times were combined into a linear-integrated speed-accuracy score (LISAS; Vandierendonck, 2016). We computed two outcome measures as indicators of different facets of cognitive flexibility. Switch cost was calculated as the difference between LISAS on switch trials and LISAS on repeat trials. High switch cost indicates difficulty in shifting between stimuli (e.g., color and shape), and thus, poorer switching skills. Mixing cost was calculated as the difference between LISAS on repeat trials and LISAS on single-task trials. High mixing cost indicates difficulty in task set.

### *Stop Signal Task*

A modified version of the Stop Signal Task (van den Wildenberg et al., 2006) was used to measure response inhibition. Green arrows were presented in the center of the screen. During an initial block of 30 go trials, participants were required to press a left button (“z”) in response to left-pointing arrows and to press a right button (“/”) in response to right-pointing arrows. This block was

followed by three test blocks of 32 trials each. In these blocks, arrows turned red on 25% of the trials. Participants were instructed to withhold responses on these trials, but to respond as fast as possible when the arrow remained green. The delay between arrow onset and the change of color (i.e., the stop signal delay) varied depending on participants' performance. Initial stop signal delays were set to 200 ms. When, on a given trial, participants failed to stop responding, the stop signal delay was decreased by 50 ms on the subsequent trial. When participants succeeded in withholding their response, subsequent stop signal delay was increased by 50 ms. If participants follow task instructions and respond as fast as possible, this algorithm should produce error rates on stop trials close to 50%. Stop Signal Reaction Times (SSRTs) were calculated by subtracting the median of the stop signal delay from the median response time on all go block trials. Longer SSRTs indicate that participants need more time to inhibit responses and, thus, poorer response inhibition.

### **Numerical Stroop Task**

In designing the Numerical Stroop Task, we followed the processes described by Henik and Tzelgov (1982). The task served to assess participants' ability to inhibit irrelevant, interfering information. It contained strings of digits that appeared in the center of the screen and participants were required to indicate (by pressing the corresponding key of the NumPad of the computer keyboard) how many digits they saw. The kind of digits that appeared (i.e., whether it was a string of threes or a string of fours) was declared to be irrelevant. On some trials, the number of digits that appeared was compatible with the kind of digit shown (e.g., the string "3 3 3," requiring the response "3"). On other trials, the total number and the kind of digits shown were incompatible (e.g., the string "5 5 5 5," requiring the response "4"). The task consisted of 120 trials made up of 60 compatible trials and 60 incompatible trials. Error rates and mean response times were computed for compatible and incompatible trials. Only the response times greater than 200 ms, followed accurate trials and within 3 standard deviations of the participant's mean response times were included. As with the Color Shape Shifting Task, error rates and response times were integrated into LISAS. The difference between LISAS on incompatible trials and LISAS on compatible trials (i.e., the LISAS Stroop effect) was used as a measure of interference inhibition.

### **Digit Span**

The Digit Span was used to assess two facets of working memory capacity. Participants first completed the forward version of the task. Participants were informed that they would see a string of digits, one at a time, and that they would be required to type the list of digits in the same order as they saw it (after the presentation of the last digit). For example, if they see "24," they should type "24." The digits were presented in progressing order of difficulty beginning with three-digit sequences (e.g., "793") up to ten-digit sequences (e.g., "4729613088"). At each level, participants received two opportunities to correctly repeat the presented sequence of digits. If they provided at least one correct response, they moved to the next level of difficulty. For the backward version, the instructions and procedures were the same, except that participants were asked to type the sequence of digits presented in reverse order. For example, if they saw "793," they were required to type "397." The outcome measures were the last level of difficulty that participants correctly attempted in both the forward version and the backward version of the task.

### **Design and statistics**

We conducted two separate multiple regression analyses to predict two different facets of cognitive flexibility. As indicators of cognitive flexibility, LISAS switch cost and LISAS mixing cost were entered as outcome variables. For both models, we entered two indicators of inhibitory control (SSRT, LISAS Stroop Effect) and two indicators of working memory capacity (forward span, backward span) as predictors. The level of significance was set to  $\alpha = .05$ .

We excluded participants when we did not have sufficient evidence that they understood the basic instructions of each task. For the Color Shape Shifting Task, we excluded six participants who did not perform significantly better than chance on the mixed-tasks block trials. For the Stop Signal Task, we excluded 28 participants with stop-trial error rates below 35% or above 65% to ensure accurate computation of SSRTs as well as participants who did not significantly perform better than chance during the initial go trials (all participants met this condition). For the Numerical Stroop Task, participants were required to perform significantly better than random on compatible and incompatible trials to be included (all participants met this criterion). For the Digit Span, they had to correctly attempt at least one three-digits trial in both the forward and the backward versions to be included in the analyses. On this account, two participants in the forward span and four participants in backward span were excluded. These exclusions led to a final sample of 74 included participants (See previous study for full description of inclusion criteria; Nweze, Nwoke, Nwifo, Aniekwu, & Lange, 2020).

## Results

The descriptive statistics of the task-trials of the cognitive flexibility task are displayed in Table 1. The confidence intervals of error rates and response times in single, mixed repeat and mixed switch trials did not overlap, an indication of overall between-trials differences. Specifically, the proportion of errors increased from repeat trials in single-task blocks (3%) to repeat trials in mixed-task blocks (13%) to switch trials in mixed-task blocks (17%). Similarly, response times increased from single repeat trials (655 ms) to repeat trials in mixed-task blocks (1128 ms) to switch trials in mixed-task blocks (1231 ms).

The results of the descriptive statistics and zero-order correlations of the executive function measures are shown in Table 2. SSRT was positively correlated with LISAS Switch Cost ( $r = .24$ ;  $p = .039$ ) with an increase in SSRT resulting in a corresponding increase in LISAS Switch Cost. The correlations between LISAS Switch Cost and other predictors did not reach statistical significance. Similarly, the correlations between Mixing Cost and all the predictors were not significant.

Table 3 displays the results of the first multiple regression analysis, examining which facets of inhibition and working memory account for unique variance in Switch Cost. After controlling for the effects of other predictors, SSRT emerged with a unique positive association with LISAS Switch

**Table 1.** Descriptive statistics of task-trials of cognitive flexibility task.

	Trials	Mean	SD	CI
1	ER single	3.18	3.57	2.52,3.86
2	ER mixed repeat	13.65	10.70	11.63,15.67
3	ER mixed switch	17.45	11.84	15.21,19.69
4	RT single	655.58	229.52	612.20,698.95
5	RT mixed repeat	1128.45	416.72	1049.70,1207.20
6	RT mixed switch	1231.94	545.27	1128.90,1334.98

ER = Error rates; RT = Response times; SD = Standard deviation; CI = confidence interval.

**Table 2.** Descriptive statistics and intercorrelations of the executive function measures.

	Measures	Mean	SD	Outcomes			Predictors		
				1	2	3	4	5	6
1	LISAS Switch Cost	168.42	635.62	-					
2	LISAS Mixing Cost	681.34	594.24	.19	-				
3	LISAS Stoop Effect	151.22	81.15	-.04	.02	-			
4	SSRT	270.93	67.48	.24*	.22	-.05	-		
5	Forward Span	7.19	1.65	-.12	-.18	-.16	-.02	-	
6	Backward Span	6.45	1.69	.04	.06	-.01	-.04	.62*	-

SD = Standard deviation; \* = correlation is significant at 0.05 level (2-tailed).

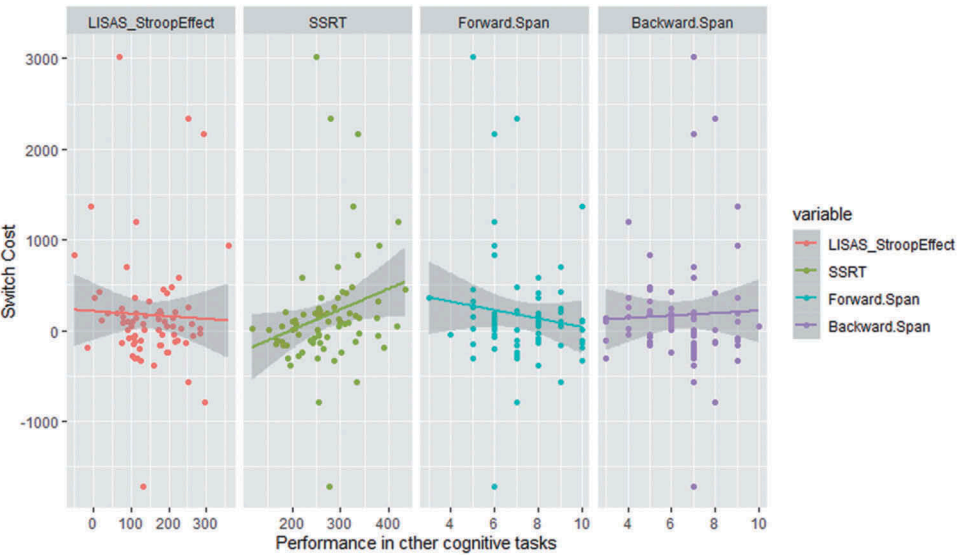
**Table 3.** Showing results of multiple regression analysis of the relationship between LISAS switch cost and the predictors ( $R^2 = .097$ ).

	Measures	b	CI	t	p-Value
1	LISAS Stroop Effect	-.50	.11,4.42	-.54	.589
2	SSRT	2.26	-2.32,1.33	2.10	.039
3	Forward Span	-95.84	-209.50,17.83	-1.68	.097
4	Backward Span	75.01	-34.84,184.87	1.36	.178

b = unstandardized beta; CI = CI = confidence interval, SSRT = Stop Signal Reaction Time.

Cost ( $\beta = .24$ ;  $p = .039$ ). As shown in Figure 1, participants who had more difficulty switching between trial sets in the Color Shape Shifting Task also performed more poorly on the Stop Signal Task. LISAS Stroop Effect ( $\beta = -.06$ ;  $p = .589$ ), Forward Span ( $\beta = -.25$ ;  $p = .097$ ), and Backward Span ( $\beta = .20$ ;  $p = .178$ ) did not account for significant portions of unique variance in LISAS Switch Cost.

In the second regression analysis shown in Table 4, we examined unique associations between the same set of predictors and LISAS Mixing Cost. After accounting for the effects of the other predictors, Forward Span showed a unique negative association with LISAS Mixing Cost ( $\beta = -.35$ ;  $p = .021$ ). This implies that Mixing Cost was smaller in those participants who were able to recall longer sequences of digits in the forward version of the Digit Span Task (Figure 2). The



**Figure 1.** Showing association between switch cost and the measures of inhibition and working memory. The shaded areas surrounding the lines represent the 95% confidence intervals of the estimated regression lines.

**Table 4.** Showing results of multiple regression on the association between LISAS mixing cost and the measures of inhibition and working memory ( $R^2 = .124$ ).

	Measures	b	CI	t	p-Value
1	LISAS Stroop Effect	-.13	-.04,3.93	-.15	.879
2	SSRT	1.95	-1.81,1.55	1.96	.054
3	Forward Span	-124.21	-228.89,-19.53	-2.37	.021
4	Backward Span	98.20	-2.97,199.38	1.94	.057

b = unstandardized beta; CI = confidence intervals, SSRT = Stop Signal Reaction Time.





**Figure 2.** Showing association between mixing cost and the measures of inhibition and working memory. The shaded areas surrounding the lines represent the 95% confidence intervals of the estimated regression lines.

unique associations between LISAS Mixing Cost and LISAS Stroop Effect ( $\beta = -0.01$ ;  $p = .879$ ), SSRT ( $\beta = 0.22$ ;  $p = .054$ ), and Backward Span ( $\beta = 0.28$ ;  $p = .057$ ) did not reach statistical significance.

Finally, we conducted exploratory Pearson and Bayesian correlational analyses involving demographic measures and measures of executive functioning displayed in Table 5. Pearson correlations between these variables were mostly small in size and we did not detect any consistent patterns of associations. Similarly, the corresponding Bayes Factors mostly indicated strong evidence in support of null hypothesis to inconclusive associations with  $BF_{10}$  ranging from .09 (minimum) to 1.83 (maximum).

## Discussion

The purpose of the current study was to examine the relative contribution of working memory and inhibition to cognitive flexibility measured with a task-switching paradigm involving both switch and mixing costs. We assessed working memory with Digits Span that provided information on children's ability to recall digits presented in forward and backward versions. Inhibition was measured with Stop Signal Task and Numerical Stroop Task. Consistent with previous studies (Brocki & Tillman, 2014; Chevalier et al., 2012), our results showed that working memory was

**Table 5.** Pearson and Bayesian correlations between executive function measures and demographic measures.

Demographic Measures	LISAS Switch Cost ( $BF_{10}$ )	LISAS Mixing Cost ( $BF_{10}$ )	LISAS Stroop Effect ( $BF_{10}$ )	SSRT ( $BF_{10}$ )	Forward Span ( $BF_{10}$ )	Backward Span ( $BF_{10}$ )
Age	.06 (.17)	.04 (.16)	.14 (.29)	-.02 (.15)	-.27* (1.83)	-.11 (.22)
Gender	.03 (.15)	-.11 (.23)	-.08 (.18)	-.06 (.17)	-.19 (.48)	-.17 (.38)
Education	.05 (.16)	.01 (.15)	.11 (.23)	.09 (.19)	-.09 (.20)	-.05 (.16)
Mother's Education	.06 (.17)	-.03 (.15)	-.24* (.09)	.11 (.22)	.22 (.82)	.11 (.22)
Father's Education	-.01 (.15)	-.02 (.15)	-.10 (.21)	.04 (.15)	.16 (.37)	.04 (.15)
PSSS	-.17 (.41)	-.11 (.22)	.08 (.19)	.19 (.58)	.14 (.28)	.09 (.19)

PSSS = parental socioeconomic status scale; LISAS = linear integrated speed-accuracy score; BF = Bayes Factor.

\* = correlation is significant at 0.05 level (2-tailed).



significantly associated with mixing cost. In addition, we also reported a significant association between inhibition and switch cost. The implications of these findings as well as the strengths and limitations are discussed below.

There was a significant association between inhibition and switch cost, underlying the involvement of inhibition in cognitive flexibility tasks during switching trials. To be able to switch (e.g., from shape to color) as was the case in our study, require inputs from inhibitory process to suppress the attention from shape to color trials. In fact, some studies that used pre-schoolers assessed that the difficulty experienced by these children during switching trials was a result of their inability to redirect attention to a new sorting dimension (Bialystok & Martin, 2004; Kirkham, Cruess, & Diamond, 2003), highlighting the importance of inhibitory process in task switching.

Our finding is inconsistent with previous studies that found no association between inhibition and switch cost (Brocki & Tillman, 2014; Chevalier et al., 2012). There are two plausible explanations for this discrepancy. First, these studies relied on latent switch cost (difference scoring of reaction times) and accuracy scores as well as multilevel modeling when comparing associations between these executive processes. While these approaches have been widely used in literature, their drawbacks are well documented (Draheim et al., 2016). LISAS approach enabled us to explore an alternative approach that attempts to account for the concerns of these statistical approaches used in past studies. Secondly, these studies relied on children and pre-schoolers, at a period when the flexibility skills may still be developing. In fact, at 3.9 years, Chevalier et al. (2012) observed no association between mixing cost and inhibition. However, at ages 4 and 5, these associations had emerged. This suggests that flexibility development may have a timecourse during which appropriate skills maybe formed. We utilized the unique features of adolescent samples, a period characterized by rapid brain maturation and development of key executive processes which could be essential to switching skills.

Additionally, consistent with previous studies (Brocki & Tillman, 2014; Chevalier et al., 2012), we found a significant association between working memory and mixing cost. High performing adolescent children in the working memory task also showed greater flexibility skills characterized by smaller mixing cost. This finding supports the assessment made by (Diamond, 2006) on the complementary roles of inhibition and working memory to task switching – while the former is involved in suppression of irrelevant stimuli during shifting in a task-switching paradigm, the latter is essential for the maintenance of relevant task rules in trials sets that require no switching. As the participants in our study were not expected to disengage or shift sets during these trials, it is very plausible that working memory which is responsible for maintaining these task relevant rules was mostly involved. It is worth noting that we did not find any significant association between Numerical Stroop and any of switch or mixing costs. Numerical Stroop is a complex inhibition that integrates inputs from both the inhibition and working memory processes. Given the conceptualization of simple inhibition and working memory as being essential to the successful development of cognitive flexibility skills, it is likely that complex inhibition that integrates these two executive processes is not heavily involved in flexibility skills that place independent demands on these two executive processes. However, future research is needed to understand the precise mechanism through which the variance in simple and complex inhibition processes occurs with respect to their association with flexibility skills.

## Strengths and Limitations of the study

First, this study is particularly relevant because it focused on the understudied population in Sub-Saharan Africa. Most neurocognitive studies have been sampled with western populations, and by sampling Nigerian adolescents, we are able to make generalization of the associations existing among these executive processes. Secondly, by using LISAS, we utilized a novel approach in the integration of reaction times and accuracy scores and subsequently accounted for the variance associated with using these approach measures separately. Third, we administered multifaceted cognitive batteries in

our assessments. For example, inhibition was measured with both simple and complex inhibition tasks. This enabled us to determine which sub-domain of executive function processes that are most essential to the development of flexibility skills. However, despite these obvious strengths, the study should be interpreted in the light in some limitations. We made efforts to explain the task instructions to the participants; however, a sizable number of them were eliminated from the final analysis due to random responding. We believe that this elimination and subsequent reduced sample size may have affected our statistical power.

## Conclusion

In conclusion, we found evidence of unique association between inhibition and switch cost as well as association between working memory and mixing cost. This is consistent with the assumption that both inhibition and working memory are essential to flexibility skills. Precisely, it supports Diamond's conceptualization that inhibition and working memory are important to switching in order to deactivate irrelevant stimuli as well as maintain sets using existing rules (Diamond, 2006).

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No funding information available.

## Conflicts of interest

We declare no conflicts of interest.

## Ethical approval

All procedures performed in this were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its amendments or comparable ethical standards.

## Informed consent

Informed consent was obtained from all individual participants included in the study.

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