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ORIGINAL RESEARCH REPORT

Association of salivary alpha-amylase and salivary flow rate with working memory functioning in healthy children

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ABSTRACT

The aim of this study was to examine the association between auditory and visual working memory (WM) performance and salivary alpha-amylase (sAA) and salivary flow rate (SFR) in a sample of 63 children (38 boys). WM was assessed by means of WISC-V subtests: four auditory subtests (*Digit Span* and *Letter-Number Sequencing*) and one visual subtest (*Picture Span*). SAA activity, output, and SFR were measured at baseline (10 min prior to testing), one minute prior to testing, one minute after the end of the auditory WM subtests and one minute after the end of the visual WM subtest. Our statistical analyses showed an association among SAA activity, output and SFR levels and the number of recalled digits in the last attempt score in *Letter-Number Sequencing subtest*. Specifically, our results showed that working performance in this task was associated with a concurrent decrease in SFR ($r(63) = -0.423$, $p < .05$). This salivary measure was the best predictor of this specific index of working memory performance ($\beta = -0.423$, $p < .05$). These results show that the changes in SFR, which represents changes in parasympathetic tone, could be employed in future studies as a noninvasive marker of working memory performance in child studies.

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KEYWORDS
Auditory working memory; visual working memory; WISC-V; salivary alpha-amylase; children; cognition

Introduction

Executive functions are a complex set of high-level cognitive abilities that allow us to adapt in the face of challenging conditions that occur in life (Ardila, 2013). This set of cognitive abilities includes *working memory*, *cognitive inhibition*, *problem-solving*, *planning, reasoning*, *verbal fluency*, and *motor regulation abilities* along with other more complex functions like *social cognition* or *decision-making* (Ardila, 2013; Zelazo & Muller, 2002). Working memory is considered a key cognitive function for the successful development of executive functioning (Christophel, Klink, Spitzer, Roelfsema, & Haynes, 2017). Working memory allows us to maintain and manipulate auditory (i.e. verbal) and visual information, which is a basic process for the development of more complex cognitive and emotional regulation functions (Baddeley, 2012; Zelazo & Muller, 2002). Working memory depends on a relatively well-known, complex network in the brain. This way, the prefrontal, somatosensory, and parietal cortices are considered to be the main areas related to this cognitive function. Hence, there is abundant experimental evidence supporting the concept that stimulus-related information that is saved in our working memory is correlated with greater activity in the prefrontal (Goldman-Rakic, 1995; Mendoza-Halliday, Torres, & Martínez-Trujillo, 2014; Riley & Constantinidis, 2016), sensory (Awh & Jonides, 2001; Pasternak, Lui, & Spinelli, 2015; Sreenivasan, Curtis, & D'Esposito, 2014), and parietal (Jeong & Xu, 2016) cortices. The dorsolateral prefrontal cortex is considered to be the main region for working memory. This cortical region is able to recruit posterior regions of the cortex to manage distributed auditory, or verbal, visual and episodic information from a given stimulus or stimuli (Baddeley, 2012; Christophel et al., 2017). This cortical region of prefrontal cortex is richly innervated by noradrenergic, dopaminergic, cholinergic, and serotonergic terminals releasing these neurotransmitters (Kuebler et al., 2014; Mückschel, Gohil, Ziemssen, & Beste, 2017; Ramos & Arnsten, 2007). A notable number of studies have provided information on the ability of different psychostimulants to lead to increased working memory performance (Spencer, Devilbiss, & Berridge, 2015; Warren, van den Brink, Nieuwenhuis, & Bosch, 2017). And in some recent studies, an association between *salivary alpha-amylase* (sAA), a salivary biomarker, and working memory performance has been reported in young participants under conditions of mild stress (Cornelisse, van Stegeren, & Joëls, 2011). This finding should be explored in-depth because we do not dispose of enough number of noninvasive biomarkers to assess and monitor, under field or clinical conditions of assessment, this important cognitive function not only important for a good cognitive development but also for familiar and social

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adjustment of children (Castagnola et al., 2017; Nater & Rohleder, 2009; Schumacher, Kirschbaum, Fydrich, & Ströhle, 2013).

sAA activity is a noninvasive salivary biomarker of stress secreted from the salivary acinar cells of major salivary glands in response to an increased sympathetic tone with the collaboration of parasympathetic nervous system, and what has been shown to exhibit a statistically significant correlation with autonomic nervous system (ANS) peripheral activation in studies on child and adult populations (Nater & Rohleder, 2009). Specifically, an inverse association of sAA activity with left ventricular ejection time (LVET) and root mean square of successive differences of normal-to-normal intervals (RMSSD) (an index of parasympathetic tone) was reported during a memory task (Bosch, de Geus, Veerman, Hoogstraten, & Nieuw-Amerongen, 2003), a direct association with LF/HF ratio, a heart rate variability (HRV) parameter which informs us about the balance between sympathetic and parasympathetic brands of ANS, was observed during a psychosocial stress condition and during a public speaking task (Filaire, Portier, Massart, Ramat, & Teixeira, 2010; Nater et al., 2006), a direct association with respiratory sinus arrhythmia (RSA) (Granger et al., 2006), with skin conductance level (SCL) (El-Sheikh, Erath, Buckhalt, Granger, & Mize, 2008), and with increases in blood pressure (Strahler, Kirschbaum, & Rohleder, 2011) have also been reported. Nevertheless, negative results have also been informed on this issue (Kobayashi, Park, & Miyazaki, 2012; Mueller et al., 2012). Likewise, sAA activity has been shown to be associated with peripheral noradrenaline (NA) levels in healthy, young adult students confronted with psychosocial and cognitive stressors (Ditzen, Ehlert, & Nater, 2014), and increases in sAA activity following the administration of the NA transporter blocker atomoxetine (Warren et al., 2017) or after NA infusions have also been reported (Kuebler et al., 2014). These findings suggest a potential use of sAA activity as an indirect and surrogate marker of the ANS activation and peripheral NA activity governed by the locus coeruleus-noradrenergic (LC-NA) system (Aston-Jones & Cohen, 2005).

Nevertheless, it might even possible to speculate, according to the hypothesis originally suggested by Ehlert, Erni, Hebisch, and Nater (2006), about a hypothetical association between sAA activity and central levels of noradrenergic activity regulated by this system. Due to the technical difficulties of obtaining direct measurements of NA in cerebrospinal fluid (CSF) in healthy participants, future studies using *transcutaneous Vagus Nerve Stimulation* (tVNS) would serve to test the validity of this, nowadays, speculative hypothesis (Van Leusden, Sellaro, & Colzato, 2015). tVNS, a noninvasive technique of electrical stimulation, promotes increases in brain NA in rats and, probably, also in humans (Roosevelt, Smith, Clough, Jensen, & Browning, 2006; Van Leusden et al., 2015). These changes in neurotransmission are related to the vagus nerve connections with the locus coeruleus (LC) (Aston-Jones & Cohen, 2005), the most important source of NA in the brain. On this respect, in a recent pilot study, Weymar et al. (2017) have observed a statistically significant increase in sAA activity in association with larger P300 amplitudes to targets in an oddball task after the use of tVNS in 20 healthy participants. In the same vein, the percentage of change in sAA activity has been associated with the change in pupil dilatation responses (a physiological response under the exclusive control of the sympathetic branch of the ANS; Nielsen & Mather, 2016). These results suggest a potential role of sAA activity as an indirect biomarker of central activity of locus coeruleus-noradrenergic (LC-NA) system under controlled conditions of register although this issue must be carefully examined in future studies.

With the independence of its possible association with the peripheral or central activity of the ANS, a detailed review of the studies centered on the usefulness of sAA activity as an indirect correlate of working memory and other related processes (i.e. executive functions) shows that only a small number of works have found a statistically significant association between this salivary biomarker and working memory performance. At present, these results continue to be puzzling in adult studies. For example, a recent study reported that young subjects exposed to psychosocial stress had more difficulties in completing 1-back, 2-back, and 3-back loading tasks for working memory in comparison to a control group (Schoofs, Preuss, & Wolf, 2008). In this study, sAA was measured concurrently with the cognitive output and, while increases were noted over the course of the stressful session in the cognitive performance, sAA activity was not associated to a better working memory performance. On the contrary, Cornelisse, van Stegeren, and Joëls (2011), also using the Trier Social Stress Test (TSST) as a standardized psychosocial stressor, found improved performance on working memory (during the first block of the 2-back task) with a parallel increase in sAA activity levels in young participants. Unfortunately for our interest, this relationship between sAA activity and working memory performance has not been adequately assessed in child populations. Only two recent studies, by Veld, Riksen-Walraven, and de Weerth (2014) and Maldonado (2016), have examined the association between sAA and working memory performance in child participants. In the first study, a linear relationship among stress, cortisol (but not for sAA) and a working memory forward capacity was reported. In the second study, Maldonado (2016) showed that salivary flow rate (SFR) and sAA activity were, respectively, the best predictors of auditory short-term and working memory on different subtests taken from the *Wechsler Intelligence Scale for Children* (WISC-IV) (Wechsler, 2015). In that pilot study, likewise in this, the authors did not include a standard psychosocial stressor given that the neuropsychological assessment session was considered itself to be a social and cognitive stressor for children due to the cognitive effort required to be conducted at a high level of performance (i.e. achieving the best cognitive performance) and the social interaction with unfamiliar personnel for children (i.e. the neuropsychologists engaged in the data collection) (Allen et al., 2017; Cox, DeVore, Harrison, & Harrison, 2017; Kirschbaum, Pirke, & Hellhammer, 1993; Nagy et al., 2015).

Hence, the main aim of the present study is to expand upon those preliminary findings in the child literature on sAA (Cornelisse et al., 2011; Maldonado, 2016), assessing the association among sAA activity with auditory and visual working memory capacities assessed through different subtests taken

Table 1. Descriptive statistics (mean ± SD) of age, body mass index (BMI), family income per month, and education levels of the parents of our participants.

Test category	*n*	M	SD	Range
Age	63	9.95	1.45	7.3–12.3
BMI	63	14.56	3.62	8.89–28.71
Family income per month (Euros per month)	50	2456.07	922.05	600–5300
Parental education				
Fathers ($n = 61$)				
No studies	1			
Less than primary school studies	3			
Primary school studies	22			
Secondary school studies	15			
University studies	5			
Master's degree	15			
Mothers ($n = 60$)				
No studies	0			
Less than primary school studies	0			
Primary school studies	15			
Secondary school studies	18			
University studies	11			
Master's degree	16			

from WISC-V in a sample of healthy children under field conditions. In our study, we also included for first time the measurement of sAA output (an alternative measure of sAA activity that takes into account the changes in SFR produced by the coactivation of the parasympathetic brach of ANS during its secretion from the main salivary glands) and SFR (which secretion is regulated, exclusively, by the parasympathetic activity of the ANS on the tissue of the main salivary glands, and that we will employ in our study as an indirect and pure marker of parasympathetic tone according to the results of Nagy et al., 2015) to examine the differential contribution of the two main branches of ANS on working memory performance.

Materials and methods

Participants

A sample of 63 participants from two different schools in the city of Malaga participated in this study. All participants were aged 7–12 years old (38 boys) and all were in good health. The exclusion criteria included neurological, cardiovascular, immunological diseases or psychological developmental disorders that could interfere with the salivary analyses (this information was reported by the family and the psychologists at each school). Stages of sexual development (i.e. Tanner stages) could not be assessed in the participants enrolled in our study. As such, it was substituted by other alternative indexes of development (i.e. BMI and age). The study protocol was reviewed and approved by the *Comité de Ética de la Universidad de Málaga* (CEUMA; R.N.: 15-2015-H). The study was designed and conducted according to the principles set forth in the *Declaration of Helsinki*. In each session, each participant was asked to provide informed consent, and before the child's participation in the study, every family (mother or father) was informed in a meeting-session about the protocol of the study. They also have to sign the consent form. In Table 1, the descriptive statistics (mean ± SD and range) of age, body mass index (BMI), family income per month and parental education are shown (only when this information was disposable).

Procedure

Each family was informed about the complete procedure of our study's protocol in an initial meeting held at each school. In these meetings, detailed information regarding the complete neuropsychological testing procedure and the collection of saliva samples by researchers was given. The neuropsychological assessments were always conducted during school days between 9:00 a.m. and 12:30 p.m. to reduce the variability associated to the circadian fluctuations of this enzyme (Nater, 2004; Nater & Rohleder, 2009; Rohleder & Nater, 2009). In each session, small groups of 2–4 participants were guided to a quiet room in the school where the neuropsychological assessment was conducted by a group of trained psychology students. During this session, four saliva samples were obtained from each participant during the cognitive assessment of working memory by means of five different subtests (see more details in the neuropsychological battery and salivary analysis section). Finally, as a courtesy, each family was informed about the neuropsychological scores obtained by his/her son/daughter on each task included in our neuropsychological testing protocol. In our complete procedure for this research, we repeated the same strategy with three different sets of neuropsychological tests. However, only data from the WISC-V subtests are shown here. The order in which these three groups of tasks were administered was varied. Order of testing, time taken to complete the entire battery of tasks, gender, age, and BMI were included in our statistical analyses as covariates. None was found to be a statistically significant covariate and, therefore, all were excluded in the subsequent statistical analyses.

Neuropsychological battery

A selection of subtests from the index scales obtained from the Spanish version of the *Wechsler Intelligence Scale for Children - Fifth Edition* (WISC-V) (Wechsler, 2015) was administered to each participant. This battery is used for assessing intelligence and cognitive performance in children in Spain (Wechsler, 2015). The WISC-V battery comprises 15 index scales. These index scales are organized into three different

Table 2. Descriptive statistics (mean ± SD and range) of WISC-V scores for our participants.

Test category	*n*	M	SD	Range
Auditory Digit Span Direct (ADSD)	63	7.59	1.69	4–13
ADSD_NDLA	63	5.16	1.06	3–9
Auditory Digit Span Inverse (ADSI)	63	8.60	2.24	4–15
ADSI_NDLA	63	3.90	1.05	2–7
Ascending Order Repeating task (ADSA)	63	7.78	2.60	2–14
ADSA_NDLA	63	4.89	1.15	2–8
Auditory Digit Span Total (ADST)	63	23.97	5.42	13–41
Letters & Numbers (LNT)	63	15.25	4.21	3–23
LNT_NDLA	63	4.14	0.94	2–7
Picture Span (PST)	53	30.85	7.87	12–45
PST_NSSSP	53	4.68	0.85	3–6
PST_NSSRP	53	9.28	1.88	6–12

NDLA: number of digits in the last attempt; NSSSP: number of stimuli included in the stimulus page with the last correct attempt, NSSRP: number of stimuli included in the response page with the last correct attempt.

levels to obtain different scores: the full-scale IQ score, the primary indexes (*Verbal Comprehension, Visual Spatial, Fluid Reasoning, Processing Speed* and *Working Memory*) and secondary indexes (*Quantitative Reasoning, Auditory Working Memory, Nonverbal, General Ability,* and *Cognitive Proficiency*). In our study, we only used the *Working Memory* Primary Index subtests. *Auditory Digit Span* was measured using direct (ADSD; a task which assesses short-term memory), inverse (ADSI; a task which assesses auditory working memory) and ascending order repeating tasks (ADSA; a task which assesses auditory working memory). These three previous tasks let calculate a total score for *Auditory Digit Span* (ADST). The fourth task was the *Letter-Number Sequencing* test (LNST; a task which assesses auditory working memory). *Visual Span* was measured through *Picture Span* test (PST; a task which assesses visual working memory). In the ADSD, ADSI, and ADSA tasks, each participant must repeat an ascending series of numbers pronounced slowly (one number per second) by the neuropsychologist according to a direct, inverse or ascending rule for repetition. In the LNST task, each participant must repeat an ascending series of numbers and letters according to the instructions, which indicate that he or she must first say the numbers in ascending order and subsequently the letters in alphabetical order. According to the manual for this battery, various derived parameters could be calculated to describe the performance of each participant on these tasks: direct scores (indicated only by the abbreviations), number of recalled digits in the last attempt score (indicated by the suffix NDLA after the abbreviation), number of stimuli included in the stimulus page with the last correct attempt score (indicated by the suffix NSSSP after the abbreviation) and number of stimuli included in the response page with the last correct attempt score (indicated by the suffix NSSRP after the abbreviation; See Table 2). These working memory tasks were always conducted in the same order by all participants (see Figure 1). These scales showed good psychometric validity (i.e. construct, concurrent, predictive, face, and content validity) and reliability (test-retest, inter-rater, and inter-method reliability) properties, according to their developers (Wechsler, 2015). The internal consistency of each scale was calculated using the direct scores on the five main tasks measured. Cronbach's alpha for the whole selection of subtests and scores was 0.806. Cronbach's alpha for the whole selection of subtests after removing of each individual subtests were (n = 63): ADSD = 0.796; ADSI = 0.776; ADSA = 0.770; LNST = 0.762; and PST = 0.852.

Salivary analysis

Saliva samples were obtained using the passive drool method (Navazesh, 1993). In each session, subjects were instructed to accumulate saliva and provided a sample after a period of 2 min of passive accumulation in the mouth for the first sample and 1 min for the remainder of the samples. Saliva samples were taken at baseline (baseline sample; BL), at pretest (before the start of the neuropsychological assessment: sample 1), one minute after the end of the auditory working memory tasks (sample 2) and one minute after the end of the visual working memory task (sample 3), as shown in Figure 1. Mean delta (or difference) levels between sample 2 minus sample 1 (Δ_{S2-S1}) and mean delta levels between sample 3 minus sample 2 (Δ_{S3-S2}) were calculated for sAA activity, sAA output, and SFR. Saliva samples were protected from temperature changes by placing them in a small portable cooler containing ice, immediately after the end of the testing session. Later, the samples were frozen in the laboratory at −20 °C until analyses. Saliva samples were diluted at 1:500 in bi-distill water after one unique defrost of each saliva sample. Salivary alpha-amylase activity and output assays were realized through an enzymatic colorimetric assay using a Dimension Vista system (see also Sánchez-Navarro, Maldonado, Martínez-Selva, Enguix, & Ortiz (2012) for more details). Previously, we created two saliva pools with high and low concentrations of sAA activity that were employed as controls in each assay. Intra- and inter-assay coefficients of variability for sAA activity in our analysis were below 10% for the measurements. In the case of violation of normality, the salivary data (sAA activity, sAA output and SFR) were square-root transformed. sAA activity is considered to be a measurement of the enzymatic activity of this enzyme in saliva (arbitrary units; U/ml) whereas sAA output (U/min) is a measurement of the secretion of this enzyme over time (sAA output = sAA activity × SFR; see Chicharro, Lucía, Pérez, Vaquero, & Ureña (1998) for more details on the gravimetric method). SFR is a measurement of saliva production in a specific period of time (ml/min) (Table 3).

Statistical analyses

Our initial statistical analyses were aimed at describing the socioeconomic, demographic, and basic anthropologic characteristics of our participants (see Table 1). sAA measurements (activity and output) were square root transformed due to violation of the normality assumption and mean delta scores were calculated. The order of testing, the time employed to complete the battery tasks, gender, age, BMI, and economical income of each family were included as possible covariates of salivary measurements using repeated-measure ANOVA tests to assess the possible changes in sAA or SFR along with the experimental session. Afterwards, our plan for the statistical analyses was aimed at first, assessing

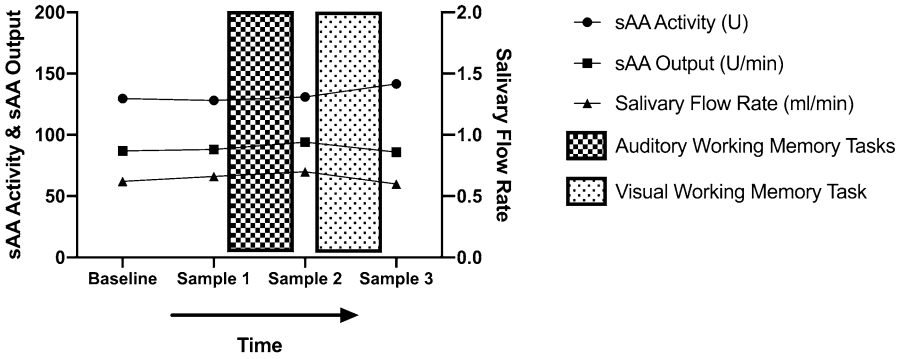

Figure 1. Time for saliva sampling collection and working memory tasks during the study and patterns of sAA activity, sAA output, and salivary flow rate on it.

Table 3. Descriptive statistics (mean ± SD and range) of sAA activity, output, and SFR levels in our all participants ($n = 63$).

	BL	S1	S2	S3	Δ_{2-1}	Δ_{3-2}
Salivary AA activity (SAAA)						
n	63	63	63	63	63	63
M	129.51	128.01	130.87	141.64	2.86	10.76
SD	88.78	74.29	79.68	113.40	45.40	75.92
Range	16–411.33	23–345	23–379.50	11.60–604.83	−192.50 to 159.50	−214.75 to 348.17
Salivary AA output (SAAO)						
n	63	63	63	63	63	63
M	86.87	88.05	94.05	85.86	0.34	−0.53
SD	101.57	101.28	96.48	106.55	2.05	3.05
Range	4.09–429.25	0.68–688.60	2–576.84	3.46–659.80	−8.50 to 11.08	−8.50 to 11.08
Salivary flow rate (SFR)						
n	63	63	63	63	63	63
M	0.62	0.66	0.70	0.60	0.04	−0.10
SD	0.46	0.48	0.43	0.39	0.29	0.27
Range	0.11–2.10	0.01–3.13	0.02–1.99	0.55–1.62	−1.61 to 0.95	−0.74 to 0.73

SAAA: Salivary Alpha-Amylase Activity; SAAO: Salivary Alpha-Amylase Output; SFR: Salivary Flow Rate; BL: Baseline Sample; S1: saliva sample 1; S2: saliva sample 2; S3: saliva sample 3.

the associations between the mean delta salivary and the WISC-V scores (using Bonferroni corrections for multiple comparisons), and second, determining, through linear regression analyses (using the stepwise regression method), which was the best salivary predictor of each score of WISC-V associated with these salivary markers. Statistical analyses were conducted using PASW Statistics, version 18. For all analyses, p values $< .05$ were considered significant. Nevertheless, correlational analyses were performed with a Bonferroni correction to control the overall level of significance (Keselman, 1998). Unless otherwise indicated, all results shown in tables are *n*, mean ± standard deviation (SD) and ranges (obtained from untransformed data) to facilitate comparison with other studies.

Results

First, the repeated-measures ANOVA analyses (using Greehouse-Geisser corrections) showed no time effects for sAA activity, output and SFR along the experimental session ($F(3, 189)$; $p = .452$; $F(3, 189) = 0, 279$; $p = .767$; $F(1, 189) = 2, 302$; $p = .090$, respectively).

Second, our correlation analyses showed a statistically significant association among SFR and the scores in LNST_NDLA (see Table 4). This association was inverse among LNST_NDLA and SFR levels measured for saliva samples 2 and 1 (see Table 4 and Figure 1). As only this statistical significant association among SFR and LNT_NDLA scores was found in our study, in our second step we only conduct linear regression analyses for this cognitive parameter.

In Table 5, information is shown regarding the linear regression analyses conducted according to the stepwise regression method in order to determine which salivary variable is the best (i.e. sAA activity, sAA ouptut or SFR) to predict LNST_NDLA. As can be observed in Table 5, the best predictor was mean Δ_{S2-S1} SFR level. This variable explained 16.5% of the variance in working memory.

Discussion

Our study, which aimed to examine and determine the best sAA measurement for predicting children's auditory and visual working memory performance, makes a significant contribution to the scarce research on this issue within the scientific literature. First, we described originally a concurrent statistically significant inverse association between SFR and auditory working memory performance. Second, we also observed that sAA activity, sAA output, and SFR measurements were not associated with visual working memory performance. These findings complete and extend a handful of the previous results obtained by a scarce number of studies conducted on this same issue (Cornelisse et al., 2011; Maldonado, 2016; Schoofs, Preuss, & Wolf, 2008; Veld, Riksen-Walraven, & de Weerth, 2014).

In 2011, Cornelisse et al. described that improved working memory performance was related to an increase in sAA

Table 4. Partial correlations (Pearson correlation coefficient) between WISC-V scores and delta salivary parameters ($n = 63$ for auditive-verbal tasks of WISC-V and $n = 53$ for visual tasks of WISC-V).

	ADSD	ADSD_NDLA	ADSI	ADSI_NDLA	ADSA	ADSA_NDLA	ADST	LNT	LNT_NDLA	PST	PST-NSSSP	PST-NSSRP
Δ_{S2-S1} (sAAA)	−0.167	−0.129	0.044	0.072	−0.059	−0.038	−0.062	−0.012	−0.008	0.117	0.095	0.212
Δ_{S3-S2} (sAAA)	0.125	0.017	0.227	0.146	0.295	0.175	0.275	0.298	0.326*	−0.034	−0.025	0.026
Δ_{S2-S1} (sAAO)	−0.201	−0.107	−0.107	−0.057	−0.261	−0.141	−0.232	−0.193	−0.346*	0.082	−0.047	0.115
Δ_{S3-S2} (sAAO)	−0.027	−0.125	0.071	0.029	0.126	0.077	0.082	0.064	0.052	−0.126	−0.167	0.019
Δ_{S2-S1} (SFR)	−0.080	−0.006	−0.133	−0.119	−0.276	−0.173	−0.213	−0.240	−0.423*	−0.036	−0.137	−0.083
Δ_{S3-S2} (SFR)	−0.018	−0.090	0.027	0.029	0.044	0.000	0.027	−0.047	−0.052	−0.113	−0.225	−0.047

*Using Bonferroni correction (significance level of α: 0.05/72) = $p \leq .00069$).

Δ_{S2-S1}: Levels of SAA in sample 2 less level of SAA in sample 1; Δ_{S3-S2}: Levels of SAA in sample 3 less level of SAA in sample 2.

NDLA: number of digits in the last attempt; NSSSP: number of stimuli included in the stimulus page with the last correct attempt; NSSRP: number of stimuli included in the response page with the last correct attempt.

Table 5. Regression model for salivary delta (Δ) parameters predicting scores on the WISC-V battery ($n = 63$ for auditive-verbal tasks of WISC-V and $n = 53$ for visual tasks of WISC-V).

Variable	B	SE	β	Adjusted R^2
LNT-NDLT				
Δ_{S2-S1}SFR	−1.345	0.369	−0.423	0.165*

*$p < .01$.

Δ_{S2-S1}: Levels of SAA in sample 2 less level of SAA in sample 1; Δ_{S3-S2}: Levels of SAA in sample 3 less level of SAA in sample 2; NDLA: number of digits in the last attempt; NSSSP: number of stimuli included in the stimulus page with the last correct attempt; NSSRP: number of stimuli included in the response page with the last correct attempt.

activity levels in a young and healthy sample. In a second pilot study, Maldonado (2016) observed that sAA activity was associated to a better short-term memory (using a working memory forward task) and working memory (using a working memory backward task) capacities using the ADSD and ADSI subscales of WISC-IV, respectively, in a small, healthy and child sample ($n = 12$; boys = 8). Nevertheless, while SFR was finally the best predictor for ADSD, the ADSI scores in WISC-IV were best predicted by mean sAA activity levels during the complete tasks of this study. Finally, in a third recent work (Veld et al., 2014), the researchers reported that better working memory forward performance was related to a higher cortisol but not to sAA activity in response to a psychological stressor in a child sample. Nevertheless, in that work, when a small sAA activity response to the stressful task was followed by a larger release of cortisol, this double physiological response predicted a worse delayed recall (DR) performance. On the contrary, when both sAA activity and cortisol responses were stronger, this physiological reaction was related to better DR performance. Interestingly, these last results accurately show us the importance of the predictions of the multisystem approach outlined by Bauer, Quas, and Boyce (2002) and other similar multisystem models on the usefulness in this issue of the combined measurement of the activity of sympathetic and parasympathetic nervous systems and the hypothalamic pituitary adrenal (HPA) axis activities of the stress system (Chrousos, 2009; Laurent, Ablow, & Measelle, 2011; Laurent, Powers, & Granger, 2013).

Contrarily to the previous studies, in the present work, the associations observed among SFR and *Letter-Number Sequencing* scores of the WISC-V show that a decrease in SFR correlated with a better auditory working memory performance in an experimental setting which resembles a child clinical neuropsychological one in which we did not include additional psychosocial stressors. This marked reduction in SFR observed in our study was probably the key to explain the no significant and inverse association observed between mean delta_{S2-S1} sAA output levels and auditory working memory performance according with the absence of concurrent association among delta_{S2-S1} sAA activity and auditory working memory, with the formula employed for its measurement (sAA output = sAA activity × SFR; see Chicharro et al., 1998 for more details), and with our results in linear regression analyses.

As SFR is a salivary parameter under exclusive control of parasympathetic branch of ANS (Ekström, Khosravani, Castagnola, & Messana, 2012), and it has been found to be associated with RMSSD in heart rate variability (HRV) studies (Nagy et al., 2015), we could establish that a decreased parasympathetic tone in our participants could let them realize a better performance in this working memory task (*Letter-Number Sequencing*), a contrary evidence with respect to some previous results (Cornelisse et al., 2011; Maldonado, 2016) and with respect to the *Neurovisceral Integration Theory* predictions (Thayer & Sternberg, 2006). That model (Thayer & Sternberg, 2006) proposes that increases in dorsolateral prefrontal activity (i.e. induced by a task or no invasive brain stimulation) would be associated to a reduction of parasympathetic suppression and to a reduction in sympathetic tone activation. Nevertheless, our results are in line with the conclusions of other recent psychophysiological studies focused in the changes in HRV under working memory performance in young and healthy participants (Nikolin, Boonstra, Loo, & Martin, 2017). This way, our results are in line with several studies on HRV what have shown how an increase in working memory performance and similar cognitive functions are associated with a concurrent, decreased activity in HF and LF bands of activity (Aasman, Mulder, & Mulder, 1987; Bernardi et al., 2000; De Rivecourt, Kuperus, Post, & Mulder, 2008; Duschek, Muckenthaler, Werner, & del Paso, 2009; Hansen, Johnsen, & Thayer, 2003; Mathewson et al., 2010; Mulder & Mulder, 1981; Svensson, Angelborg-Thanderez, Sjoberg, & Olsson, 1997). In conclusion, our results give support to the hypothesis that SFR would be considered as a surrogate marker of the ANS activity, and therefore, under the observation conditions of our study it would be reflecting a vagal withdrawal what facilitates the performance in working memory (Nagy et al., 2015). It is difficult to explain why we could not observe similar associations in the other three *Auditory Digit Span* subtests. The association between sAA and SFR and working memory under conditions of mild stress is mediated and modulated by variables such as gender, level of

difficulty of the task, the type of response (more or less active) that participant has to give (i.e. N-back tasks require more frequent updating whereas digit tasks are more passive), the modality of this type of memory (i.e. auditory, spatial and non-spatial or visual working memory tasks) and the motivational drive. Additional studies are needed to explain these findings.

Finally, another interesting, negative but original finding in our study was that visual working memory performance was not related to sAA or SFR. This fact could be explained according with the literature by the multivariate effect of factors like differences in gender, the type of task (i.e. auditory vs. visual), the difficulty of the task, the type of response that the participant has to give to the task and/or the unimpaired/impaired brain regions for working memory among the participant (Giles, Mahoney, Brunyé, Taylor, & Kanarek, 2014). For example, in a recent work by Oemisch, Johnston, and Paré (2016), it was reported that pharmacologically-increased DA and NA catecholaminergic neurotransmission was not related to enhanced visual working memory in non-human primates with unimpaired NA circuits in the LC-NA system. This result is consistent with some of the early works on spatial working memory function conducted in human and animals (Cai, Ma, Xu, & Hu, 1993; Marrs, Kuperman, Avedian, Roth, & Jentsch, 2005). For these reasons, and given the scarce number of works on this specific topic using human samples, it is difficult to speculate on the basis of this hypothetical dissociation of LC-NA system functional role in auditory and visual working memory in our study. Nevertheless, as we administered auditory and visual working memory tasks in a fixed order, we cannot exclude what these other factors (i.e. as fatigue or motor activity) could be affecting this finding.

Unfortunately, our study exhibits some weaknesses that reduce the generalization of its findings. First, it was conducted on a small sample of 63 healthy participants (that for visual stimuli was even smaller; $n = 53$) and although we included participants of both genders, we were not able to recruit a sample of a sufficient size to assess differences between genders, what has been underlined as an important moderating factor in literature on this issue. In this sense, differential effects of stress on working memory have been observed in female participants (Schoofs, Pabst, Brand, & Wolf, 2013). Second, auditory and visual working memory tasks were no counterbalanced along with the assessment session, a circumstance that affects, specifically, to the reliability of the negative results obtained for visual working memory. Third, the participants enrolled in our study came from just two different schools in our city and, therefore, we could not obtain a representative sample from each socioeconomic group in our environment (Hackman, Gallop, Evans, & Farah, 2015; Lawson & Farah, 2017; Ursache & Noble, 2016; Ursache, Noble, & Blair, 2015). Fourth, we did not measure cortisol levels in our study and, therefore, we could not examine the contribution of both branches of the human stress system (Bauer et al., 2002; Veld et al., 2014). Fifth, we did not obtain any psychological measure of stress, arousal or anxiety of participants about the neuropsychological assessment process (Sánchez-Navarro, Maldonado, Martínez-Selva, Enguix, & Ortiz, 2012). And sixth, we did not obtain a measurement of the motivational drive for the cognitive tasks included in our study.

In conclusion, the main findings of this study show for the first time an inverse association among SFR and auditory working memory performance in a sample of 63 healthy boys and girls aged 7–12 years old. These results suggest a differential contribution of the changes in sympathetic and parasympathetic branches of ANS to this cognitive function under clinical-like conditions of observation in healthy children. On the contrary, no associations were observed between these salivary biomarkers and visual working memory performance in our study.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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