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# Salivary alpha amylase levels in youths with anxiety disorders

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ABSTRACT

It is suggested that salivary alpha-amylase (sAA) may be a marker of sympathoadrenal medullary system activity. Thus, it can be a possible relationship sAA and anxiety disorders. The aim of this study is to investigate sAA in children and adolescents with anxiety disorders and healthy controls. Thirty drug-free youths, aged 8–16 years, who were diagnosed as any anxiety disorders and 36 healthy controls with similar socio-demographic characteristics were included in this study. The sAA was found to be significantly increased in anxiety group compared to control group. However, there was no correlation between sAA and any anxiety scores of the scales. Present study suggested that anxiety disorders in youths may be associated with increased autonomic activity.



## 1. Introduction

Mainly, two major systems have a role in the generating of a biological stress response: the sympathetic nervous system (SNS), one of the two branches of the autonomic nervous system (ANS), being activated immediately after the onset of the stressor and hypothalamic–pituitary–adrenocortical (HPA) axis with a time delay (Davis and Granger, 2009; Ali and Pruessner, 2012). It is suggested that HPA axis and ANS work in coordination to make a proper response (Allwood et al., 2011). Stress-system dysregulation is thought to increase the risk for anxiety disorders (van Veen et al., 2008). It is suggested that ANS plays an important role in stress-related mental disorders and pathological dysregulation of this system may be present in patients with psychopathology (Schumacher et al., 2013).

Activity of ANS can be assessed by several psychophysiological measures including heart rate (HR), blood pressure, pre-ejection period (PEP), urinary catecholamine concentrations, respiratory sinus arrhythmia (RSA), basal skin conductance level (SCL), salivary alpha-amylase (sAA) and salivary cortisol (Ali and Pruessner, 2012; Kossowsky et al., 2012; Schumacher et al., 2013, Tanaka et al., 2013; Payne et al., 2014; Kirsch et al., 2015). From these measures, only PEP is a, relatively, pure measure of sympathetic activity, while other measures are also markers of parasympathetic tone (Schumacher et al., 2013). It is stated that these measures can be clinically useful in anxiety disorders for understanding their etiology and predicting of treatment outcomes (Kossowsky et al., 2012).

Psychophysiological measures were investigated in some studies of children with anxiety disorders. Schmitz et al. (2011) showed that children with social phobia (SP) had higher levels of HR and lower levels of RSA activation at baseline, and similar HR responses but a limited RSA reactivity during the Trier Social Stress Test for Children (TSST-C), compared to controls. The authors suggested restricted autonomic flexibility in children with SP (Haile et al. (2013). This pattern of restrictive autonomic flexibility was also shown in high socially anxious children in comparison to low socially anxious children drawn from a community population (Schmitz et al., 2013). Similarly, restricted vagal flexibility was found in anxious children (Greaves-Lord et al., 2010; Monk et al., 2001). Also, elevated HR levels were reported by studies on children with anxiety disorders (Henje Blom et al., 2010; Sharma et al., 2011; Bakker et al., 2009; Yeragani et al., 2001). In another study, children with SP showed chronically elevated HR levels throughout the whole laboratory session, suggesting that these patients might have a more generalized autonomic hyperreactivity (Krämer et al., 2012, Kossowsky et al. (2012) reported that children with

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separation anxiety disorder (SepAD) displayed greater vagal withdrawal and higher reactivity in multiple cardiovascular, respiratory, and electrodermal measures compared to controls. Youth with posttraumatic stress disorder (PTSD) showed reduced habituation in skin conductance response compared to controls, during exposure to threat-related pictures (Grasso and Simons, 2012). On the other hand, in contrast to results from adults, no autonomic psychophysiological difference during the trauma script experiment were found in HR, RSA, SCL between youth with and without PTSD (Kirsch et al., 2015).

Association between anxiety disorders and sAA was investigated generally in adult studies, to a limited extent, in youth studies. High correlation between state anxiety and sAA was found (Takai et al., 2004; Noto et al., 2005; Takai et al. 2004) also found that sAA level was more significantly increased and reacted more rapidly than cortisol by psychological stressor and also detected that soothing video viewing significantly decreased the sAA level while did not affect the cortisol level. They suggested that sAA was a better index of stress and a soothing or relaxation index (Takai et al., 2004). Findings from two studies of patients with generalized social anxiety disorder (gSAD) suggested hyperactivity of the ANS in line with the observed hyperarousal and a vulnerability of the ANS more than the HPA-axis (van Veen et al., 2008; Tamura et al., 2013; Fisher et al. 2010) reported important physiological heterogeneity in generalized anxiety disorder (GAD). Also, it was suggested that sAA might be useful predictive biological markers of treatment responsiveness in patients with panic disorder (Tanaka et al., 2012; Kawano et al., 2013) suggested that an increase in sAA might be a characteristic change of obsessive–compulsive disorder. In a study of youths, children with SP showed heightened reactivity to the TSST-C on subjective anxiety compared to the healthy control children but not a heightened reactivity in HR, sAA or cortisol (Krämer et al., 2012). On the contrary, children reporting higher levels of social anxiety demonstrated significantly higher sAA, compared to children reporting lower levels of social anxiety (Payne et al., 2014).

In terms of relationships between sAA and other psychophysiological measures, it was reported that sAA might serve as an indicator for plasma catecholamines (specifically, norepinephrine) (Nater et al., 2006; Rohleder et al., 2004; Tanaka et al., 2013), and positive associations between sAA and RSA, and between sAA and SCL were shown (El-Sheikh et al., 2008). Also, some studies investigated associations between sAA and HR (Allwood et al., 2011; Fisher and Newman, 2013), HRV (Nater et al., 2006), left ventricular ejection time (Bosch et al., 2003), blood pressure (Strahler et al., 2011), and stress-induced cortisol (Nater et al., 2006; Payne et al., 2014).

Compared to other psychophysiological measures, sAA has some advantages, being non-invasive and easily measured parameter, and relatively independent of several possible confounders (gender, body mass index [BMI), activity level, smoking, eating and drinking) (van Veen et al., 2008; Schumacher et al., 2013). sAA is thought to be practical for assessing activity of ANS (Rohleder and Nater, 2009; Kawano et al., 2013). Some authors proposed that sAA might serve as a suitable index for ANS dysregulation (Granger et al., 2007; Nater and Rohleder, 2009; Schumacher et al., 2013). sAA has been mostly considered as an index of SNS activity or more detailed of the sympathoadrenal medullary (SAM) system (Schumacher et al., 2013). Also, sAA may be used in assessing noradrenergic arousal (Carr et al., 2015) and as a marker for anxiety reports (Kawano et al. 2013). While cortisol captures acute stress responses, sAA is suggested to reflect stable individual differences in levels of ANS arousal (Out et al., 2011; Payne et al. 2014).

Although dysregulation of ANS was investigated with sAA generally in adults with SAD (van Veen et al.,2008; Tamura et al.,2013), GAD (Fisher et al., 2010; Fisher and Newman, 2013), panic disorder (Tanaka et al., 2012) and obsessive-compulsive disorder (OCD) (Kawano et al., 2013), its investigation through sAA in youths was limited to some studies of those with SAD (Krämer et al., 2012; Payne et al., 2014). Also, patients with anxiety disorders generally displayed no difference in levels of basal cortisol (Tanaka et al., 2012; Tamura et al., 2013; Kawano et al., 2013), pointing to stable and trait differences in ANS. In light of studies above, it is important to learn more and increase knowledge about the association between less studied anxiety disorders (particularly GAD and SepAD) and ANS dysregulation in youths via sAA. We hypothesized that youths with less studied anxiety disorders including GAD, SepAD and SP might have similar dysregulation in ANS as generally found in adults. To this end, we aimed to investigate basal sAA levels in children and adolescents with anxiety disorders including GAD, SepAD, social phobia (SP).

## 2. Methods

### 2.1. Subjects

Thirty drug-free youths, aged 8–16 years, who were diagnosed clinically as any anxiety disorders including GAD ($n=26$), SepAD ($n=9$), and SP ($n=5$) according to the DSM-IV criteria (APA, 1994) were included in this study. Patients were assessed clinically and using children and parent completed the Screen for Child Anxiety Related Disorders [SCARED] (Birmaher et al., 1997) and parent completed the Child Behavior Check List/6–18 [CBCL/6–18] (Achenbach and Rescorla, 2001). Comorbidities of anxiety disorders were detected according to clinical evaluation and these rating scales.

SCARED is a 41-item self-report questionnaire that has been developed by Birmaher and his colleagues to identify and assess anxiety symptoms in children and adolescents, aged eight and above, according to the DSM IV-TR classification (Birmaher et al., 1997). It has the parent and child version. It includes five subscales: somatic symptoms/panic disorder (13 items), GAD (9 items), SepAD (8 items), SAD (7 items), and school avoidance (4 items). The participants are asked to determine the frequency of each symptom during the last three months on a 3-point scale: 0 (Almost never), 1 (Some-times), and 2 (Often). Score of 25 and above are considered to have the quality of an alert for an anxiety disorder. The Turkish version of the scale is valid and reliable for use in the Turkish population (Çakmakçı, 2004).

CBCL/6–18 is a 118-item rating scale for the identification of behavioral and emotional problems in children aged 6–18. The CBCL/6–18 contains eight syndrome scales (Internalizing Domain: Anxious/Depressed, Withdrawn/Depressed, and Somatic Complaints scales; Externalizing Domain: Rule Breaking Behavior and Aggressive Behavior scales; Social Problems, Thought Problems, and Attention Problems) and three competence scales. The raw score sum of all eight syndrome scales forms the 'Total Problems' scale which quantifies overall impairment. Items that do not belong to any specific syndrome scale form 'Other Problems' scale. The competence scales encompass the activities (e.g., sports, number of jobs), the social (e.g., participation in organizations, number of friends) and the school (e.g., academic performance, repeated grades) scales. CBCL is completed by parents or primary caregivers who describe how much a particular behavior was characteristic of their child during the previous six months, using a 3-point rating scale (0=not true; 1=somewhat or sometimes true; and 2=very true or often true). The scores on the scales are calculated according to the Achenbach system of empirically based assessment (Achenbach & Rescorla 2001). Higher scores reflect greater degrees of symptoms. The Turkish version of the scale was valid and reliable for use in the Turkish population (Erol, Simsek