ORIGINAL ARTICLE

Alterations in autonomic nervous system in autism spectrum disorders: Means of detection and intervention

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Abstract

Autism spectrum disorders are a group of developmental disorders, which display significant heterogeneity of symptoms. Besides the core symptoms, various comorbidities are common for individuals with autism. A growing body of evidence suggests dysfunction of autonomic nervous system within the ASD population. The detection of autonomic abnormalities could help in more personalized approach, which takes into account individual etiologic differences. It has also been suggested that interventions focused on autonomic function could possibly be beneficial for treatment of aggression, anxiety, as well as the core symptoms of autism.

Introduction

Autism spectrum disorders (ASD) represent a group of neurodevelopmental disorders, manifested in early childhood, and defined by impaired social interaction, deficits in communication, and restricted or repetitive behaviors (American Psychiatric Association 2013). Recently, diagnosis of autism is based exclusively on expert observation, no etiology or biological marker is available. Although diagnosis of ASD is based on behavioral assessment, various physiological measures have also been used to determine the neurological or autonomic dysfunctions underlying ASD (Eilam-Stock *et al* 2014, Lydon *et al* 2015). A large body of literature suggests that ASD symptoms can be associated with complex abnormalities in the central nervous system (Parellada *et al* 2014), including alterations in structures and networks involved in the regulation of the autonomic nervous system (ANS). ASD has been associated with abnormalities in the amygdala (Baron-Cohen *et al* 2000), brainstem (Jou *et al* 2009) the anterior cingulate cortex (Posner *et al* 2007), or the insula (Uddin & Menon 2009), which all are involved in ANS regulation. The hypothesis of dysregulation of locus coeruleus-noradrenergic (LC-NE) system in autism has also been proposed (Mehler & Purpura 2009). The assessment of such abnormalities remains to be an important question in autism research, which can provide basis for potential interventions, and may represent non-invasive and inexpensive markers for this disorder.

Detection of autonomic alterations in autism spectrum disorders

Invasive methods

The measurement of circulating catecholamines belongs to most common methods of assessment of sympathetic nervous system function (SNS) (Zygmunt & Stanczyk 2010). Activity of the SNS can be assessed using the measurement of the plasma or urine concentration of norepinephrine, or its metabolites. Measure-

ment of catecholamines provides useful information about the activity of SNS, however, they are determined by location of vessel used for blood collection and therefore do not reflect the whole amount of neurotransmitter secreted from axon terminal (Sinski *et al* 2006).

Acetylcholine, neurotransmitter released by postganglionic fibers of the parasympathetic system, is very quickly inactivated by acetylcholinesterase, so its plasma levels cannot be used as a marker of parasympathetic nervous system activity (McCorry 2007).

Interestingly, plasma norepinephrine concentrations have been reported to be elevated in autism (Launay *et al* 1987). However, blood and urine samples acquisition represent extremely stressful stimuli for children with autism spectrum disorders and thus pose a challenge for researchers in obtaining such samples from both ethical and methodological reasons. Therefore, various non-invasive methods of ANS activity detection have been developed.

Non-invasive methods

To assess autonomic nervous system activity, various non-invasive methods are used. For example, measurement of sympathetic skin response is used frequently (Claus & Schondorf 1999, Kucera *et al* 2004). This method is based on determination of the alterations in skin electrical resistance in response to activation of sweat glands which are stimulated by impulses conducted by cholinergic postganglionic sympathetic fibers. However, it is important to note, that in general, skin conductance level are not stable and therefore it is difficult to define baseline values and there are large intra- and inter-individual differences (Boucsein *et al* 2012). Another widely used method has become pupillometry, biomarker of LC-NE system. Several studies found both dysregulated tonic pupil responses to various stimuli (e.g. Anderson *et al* 2006, Martineau *et al* 2011) and greater skin conductance level (Prince *et al* 2016) in children with ASD.

One of the most reliable methods for measurement of ANS activity, namely cardiac autonomic responses, has become heart rate variability (HRV). HRV refers to beat-to-beat variations of the heart rate that is determined by autonomic nervous system. In resting conditions, the variability of beat-to-beat intervals remains large and becomes more regular when influenced by stressful environmental factors (Task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996). Because of the fast degradation of acetylcholine by acetylcholinesterase, the influence of parasympathetic activation is quick and thus accounts for fast changes in heart rate. Sympathetic influence changes more slowly, its effect is observable as a change in heart rate after longer period, and thus is responsible for slower oscillations. HRV has been found to be decreased in autism spectrum disorders in number of studies (Daluwatte *et al* 2013, Ming *et al* 2005). These data indicate that in autistic children SNS is more active than in neurotypical controls. Even if it is not known whether exaggerated SNS activity represents cause or consequence of behavioral alterations in autistic children, reduction of SNS activity may provide beneficial effects.

Interventions affecting vagal activity for adjuvant treatment of children with ASD

In the light of above mentioned findings, several new treatment options are now being explored. Vagus nerve stimulation, which involves surgical implantation of electrodes around cervical portion of the vagus nerve, was found to increase HRV. Study of Hull *et al* (2015) showed decreased severity and duration of seizures in children with refractory epilepsy and autism after stimulation of vagus nerve. Moreover, they found the improvement in ASD symptoms not related to epilepsy, such as communication skills, or stereotyped behavior. Furthermore, considerable improvement in regulation of aggressive behavior and receptive communication skills were noted and maintained over 1 year. The biggest drawback of vagus nerve stimulation method is cost and requirement of invasive neurosurgery. However, recent studies confirmed the possibility of non-invasive transcutaneous stimulation of the vagus nerve with electrodes located in the auricular concha area that is densely innervated by branches of the vagus nerve (Fang *et al* 2016). Electrical stimulation of the cervical vagus nerve with handheld device represent another non-invasive method (Schoenen *et al* 2016). In preterm infants or high-risk infants, kangaroo care or massage therapy may increase vagal tone and promote optimal neurodevelopment (Feldman & Eidelman 2003). Similar preliminary data were obtained on children with ASD, as well (Escalona *et al* 2001).

Few studies investigated the treatment with propranolol, a nonselective beta-adrenergic antagonist, with promising results in increasing conversational reciprocity and nonverbal communication skills in twenty individuals with ASD after single dosage (Zamzow *et al* 2016).

Conclusion

Although above mentioned findings seem promising, further research with larger sample sizes is needed to examine underlying autonomic nervous system alterations and related treatment options for individuals with autism spectrum disorders, as convincing evidence is still lacking.

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