Resting state arousal and functional connectivity in autism spectrum disorder

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AROUSAL REFERS TO PHYSIOLOGICAL states and behaviors associated with an alert state. Atypical arousal has been hypothesized to explain some of the symptoms of autism spectrum disorder (ASD). Recently, Eilam-Stock et al. (2014) showed that electrodermal activity (EDA), a sensitive measure of sympathetic arousal, is differentially related to the blood oxygen level-dependent (BOLD) signal during rest in people with ASD compared with typical controls. In this article, I discuss these findings and put them in a broader context with special emphasis on the implications for research on attention and emotional processes in ASD.

Scientific interest in arousal in ASD stems from various sources. Early theories hypothesized that either elevated or attenuated tonic arousal was a causal factor behind some of the core ASD symptoms, such as repetitive behaviors and avoidance of social interaction (Rogers and Ozonoff 2005). Other theories have linked arousal to atypical development of face perception and other forms of social cognition. According to other influential theories, atypical regulation of arousal could cause impairments in attentional functions, an associated feature of ASD (Keen et al. 2013; Orekhova and Stroganova 2014). In addition, brain functions involved in the generation and representation of arousal have been linked to social cognition in typical development (Crichtley 2005), which suggests that they may be important to disorders of social interaction such as ASD. However, although many theories link ASD to atypical arousal, the empirical findings are not conclusive. Previous studies have mainly assessed peripheral autonomic nervous system (ANS) arousal. However, arousal is a homeostatic process that critically involves brain mechanisms for representation and generation of peripheral responses (Crichtley 2005). Impairments in any of these processes could potentially lead to disruptions in behavior and cognition. The study by Eilam-Stock et al. thus represents an important methodological improvement.

Eilam-Stock et al. (2014) hypothesized that resting state EDA would have different neural correlates in subjects with ASD compared with typically developed (TD) participants. They further hypothesized that group differences in EDA would be related to functional hypoconnectivity in the ASD group. Although a number of previous studies have found evidence of hypoconnectivity between distal brain regions in ASD (e.g., Uddin and Menon 2009), the literature is so far inconclusive. Functional connectivity is typically operationalized as correlations in fMRI BOLD signal time series between distal parts of the brain. Thus group differences in functional connectivity can reflect differences in structural connectivity, mental processes, and artifacts such as head movement. Spontaneous fluctuations in EDA could be another variable influencing the correlations between the BOLD signals of various brain regions.

Eilam-Stock et al. (2014) assessed resting state EDA and MRI BOLD signal in 17 participants with ASD and an equal number of typically developed (TD) participants. EDA was measured at palmar sites of the hand. No group difference in average skin conductance level (SCL) was found, but the group with ASD had fewer skin conductance responses (SCRs) during the scanning session. A SCR can be distinguished as a brief increase in skin conductance. Both SCL and the average number of SCRs during a time period are indexes of tonic sympathetic nervous system (SNS) activity. In sum, the authors found evidence of group differences in EDA.

Linear correlations between the EDA and BOLD signal for each voxel were computed to test the hypothesis that resting-state EDA would have different neural correlates in ASD compared with TD participants. In support of the hypothesis, group differences emerged in a number of brain regions. In TD participants, higher correlations were found for voxels located in medial frontal areas including the medial prefrontal cortex (mPFC), anterior insula (AI), and supplementary motor area (SMA). In contrast, EDA in the ASD group was more strongly correlated with BOLD activity in posterior sensory areas.

A second aim of the study was to understand the contribution of EDA to resting-state functional connectivity. Functional connectivity can be operationalized as correlations in BOLD signal time series between distal parts of the brain. In this case, functional connectivity strength was compared before and after the EDA signal had been regressed out.

In support of their hypotheses, the authors found evidence of reduced connectivity within the default mode network (DMN)
in the ASD compared with the TD group. This difference was further qualified by an interaction with EDA. SCR had a larger effect on connectivity in the mPFC, anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), and right anterior insula in the TD compared with the ASD group. EDA was more important for connectivity in sensory cortical regions not implicated in the DMN in ASD than in TD participants as well as in the amygdala bilaterally. Similar results emerged when functional connectivity was operationalized as the average connectivity between the BOLD signal of each voxel with that of all other voxels in the brain. In sum, EDA was differentially related to functional connectivity in a number of regions.

Next, I will discuss the results of Eilam-Stock et al. (2014) in greater detail with emphasis on their potential relevance for research on cognitive and emotional processes in ASD. The most clear group difference that emerged in the study was a reduced number of SCRs in the ASD. This is a somewhat unexpected finding, since most studies have found either increased or equal baseline SNS arousal in ASD. An interesting possibility is that differences in social context between studies can explain this inconsistency. The participants in the present study were lying inside an MRI scanner. This is not a socially demanding task. The previous studies that found an increased number of SCRs have generally measured EDA in the presence of an experimenter (e.g., Hirstein et al. 2001) or during some kind of stressful task (e.g., Kushki et al. 2013). Further studies could shed light on the relationship between ANS arousal and behavior by manipulating the social context of the study. It is possible that subjects with ASD may respond with increased tonic EDA to contexts with automatically processed social cues such as emotional faces, but with decreased tonic EDA in situations that require more explicit social or cognitive processes. This would be consistent with previous studies that found hyperarousal during periods of direct gaze toward emotional faces in subjects with ASD (Kylliäinen and Hietanen 2006) and a blunted arousal response during an anxiety-evoking task (Kushki et al. 2013).

It is also possible that the decreased number of SCRs stems from an inability to uphold vigilant attention in the ASD group. In either case, the study does not lend support to theories of general hyperarousal in ASD.

Eilam-Stock and colleagues (2014) do not relate their findings to specific cognitive and emotional processes in ASD. However, some of their findings may have implications for research on long-standing questions in the field. In the following section, I discuss some potential implications for research in cognitive and emotional processes in ASD. The spontaneously occurring SCRs during rest were less integrated with functional activity in a number of regions linked to self-awareness and social cognition in the ASD group. This suggests a disconnection between ANS arousal and brain functions involved in higher cognitive and emotional functions.

The observed differences in the AI are interesting, since this region has been hypothesized to underlie some of the social and emotional impairments in ASD (Uddin and Menon 2009). For example, a previous study found that hypoactivity in the AI was related to impairments in emotion understanding and labeling in subjects with ASD (Silani et al. 2008). This region is also important for autonomic arousal. Influential theories state that mapping of somatic states by the AI is important for conscious feelings (Critchley 2005).

Another intriguing aspect of the study by Eilam-Stock et al. (2014) is the finding that the EDA signal was more strongly connected to amygdala BOLD activity in the ASD group and that EDA may modulate the connectivity between amygdala and other brain regions, including the AI. Influential theories link atypical amygdala activity to the development of ASD symptoms. The amygdala modulates EDA responses to emotionally salient stimuli. In addition, this region is important for detection of socially salient events and stimuli. Patients with damage to the amygdala often fail to orient to the eyes of other humans. As a consequence, they often fail to recognize the emotional expression of others (Adolphs 2010). This resembles the gaze avoidance and emotion understanding difficulties commonly seen in persons with ASD. Developmental theories state that an early atypical amygdala function biases persons with emerging ASD to attend to other kinds of information than their typically developed peers, which in turn affects brain development (Schultz 2005).

One potential explanation for the differential amygdala involvement is higher anxiety levels in the ASD group during the scanning session. Unfortunately, this could not be tested directly since no self-report measure of anxiety was included.

Eilam-Stock et al. (2014) reason that differences in focus of attention can explain the observed group differences in EDA and functional connectivity. ASD participants may have been focusing on sensory processes during the scanning session, whereas the TD participants attended to their own mental and bodily states. In this case, the difference would lie in the central generation of SCRs. It is difficult to disentangle the relative contribution of generation and representation in a correlational study such as this. The authors used mathematical modeling to identify regions that were specifically important in generation and representation. No group differences in brain activation and connectivity in these regions were found. This suggests that the source of the observed effects were due to both generation and representation of EDA.

Eilam-Stock and et al. (2014) do not discuss whether the observed group differences in EDA and functional connectivity may stem from a more fundamental difference in attentional functions. However, it is possible that a weaker coupling between arousal and cortical regions involved in attentional orienting could explain earlier behavioral findings in the ASD literature. Previous studies have found evidence of atypical attention in ASD. Subjects with ASD seem to be especially impaired in tasks of orienting and disengagement of attention (Keen et al. 2013). This is important, because impaired attentional disengagement could lead to overfocused attention and inflexible behavior.

The ability to regulate arousal levels is crucial for attentional orienting and disengagement. A recent review suggested that atypical coupling between arousal and cortical regions involved in orienting of attention may underlie the attentional impairments in ASD (Orekhova and Stroganova 2014). Interestingly, a number of brain regions implicated in the orienting of attention were more strongly coupled to EDA in the TD compared with the ASD group. These include the inferior parietal lobule (IPL), temporoparietal junction (TPJ), and insula. These results may reflect an atypical integration of arousal and orienting mechanisms in the ASD group. Further studies could explore this by including attentional tasks.
In summary, the study by Eilam-Stock et al. (2014) suggests that resting-state EDA may be differently linked to BOLD functional connectivity in people with and without ASD. The authors also found some evidence of reduced tonic EDA in the ASD group. A number of regions implicated in social cognition, emotion, and attention showed atypical links to EDA in the ASD group. This suggests that arousal may be important for understanding impairments in these domains in ASD.

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DISCLOSURES

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