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Brain responses to biological motion predict treatment outcome in young adults with autism receiving Virtual Reality Social Cognition Training: Preliminary findings

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ABSTRACT

Autism Spectrum Disorder (ASD) is characterized by remarkable heterogeneity in social, communication, and behavioral deficits, creating a major barrier in identifying effective treatments for a given individual with ASD. To facilitate precision medicine in ASD, we utilized a well-validated biological motion neuroimaging task to identify pretreatment biomarkers that can accurately forecast the response to an evidence-based behavioral treatment, Virtual Reality-Social Cognition Training (VR-SCT). In a preliminary sample of 17 young adults with high-functioning ASD, we identified neural predictors of change in emotion recognition after VR-SCT. The predictors were characterized by the pretreatment brain activations to biological vs. scrambled motion in the neural circuits that support (a) language comprehension and interpretation of incongruent auditory emotions and prosody, and (b) processing socio-emotional experience and interpersonal affective information, as well as emotional regulation. The predictive value of the findings for individual adults with ASD was supported by regression-based multivariate pattern analyses with cross validation. To our knowledge, this is the first pilot study that shows neuroimaging-based predictive biomarkers for treatment effectiveness in adults with ASD. The findings have potentially far-reaching implications for developing more precise and effective treatments for ASD.

1. Introduction

One of the major barriers in therapy for individuals with Autism Spectrum Disorder (ASD) (APA, 2013) is the difficulty to identify appropriate and effective treatments for a given individual with ASD. On the one hand, there is a remarkable variation and heterogeneity within the spectrum (Hahamy, Behrmann, & Malach, 2015; Lombardo et al., 2016), which makes it difficult for a single treatment to fit all individuals with ASD. On the other hand, people often need to spend considerable amount of resources (e.g., time, money) in trying out various treatment protocols before they are able to identify the most appropriate intervention. This problem is particularly severe in adults with ASD, where intervention research has been very limited. To facilitate the fitting process and reduce potential waste of resources, it is crucial to develop objective predictors for treatment outcome in ASD, especially for adults with ASD, which would directly accelerate the long-term goal of precision medicine (Insel, 2014) in ASD.

In this research, we used a well-validated biological motion functional magnetic resonance imaging (fMRI) paradigm (Kaiser et al., 2010), which robustly engages the neural circuits supporting both socio-emotional and socio-cognitive components of social information processing, to identify pretreatment predictive biomarkers that can accurately forecast the response to an evidence-based behavioral intervention in young adults with ASD. The biological motion videos feature an adult engaging in children's games and social actions (e.g., waving, pat-a-cake, and peek-a-boo). Prior research has shown that social orienting to biological motion is evolutionarily well-conserved and fundamental to adaptive social

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Abbreviations

ACS-SP	Advanced Clinical Solutions-Social Perception
ADOS	Autism Diagnostic Observation Schedule
ASD	Autism Spectrum Disorder
BIO	Biological Motion
BOLD	Blood Oxygen Level Dependent
CDT	Cluster-Defining Threshold
GLM	General Linear Model
LOSO	Leave-One-Subject-Out
MRI	Magnetic Resonance Imaging
MVPA	Multivariate Pattern Analyses
SCR	Scrambled Motion
SRS	Social Responsiveness Scale
VR-SCT	Virtual Reality-Social Cognition Training

engagement (Heberlein & Adolphs, 2004; Johnson, 2006; Simion, Regolin, & Bulf, 2008; Vallortigara, Regolin, & Marconato, 2005; Yang, Rosenblau, Keifer, & Pelphrey, 2015). The biological motion fMRI task has revealed key brain regions implicated in core ASD deficits (Allison, Puce, & McCarthy, 2000; Kaiser et al., 2010; McKay et al., 2012; Yang et al., 2015), including the ventrolateral prefrontal cortex (vlPFC), ventromedial prefrontal cortex (vmPFC), posterior superior temporal sulcus (pSTS), amygdala, and fusiform gyrus (FFG). These regions are implicated in various functions. Generally speaking, vlPFC, vmPFC, and amygdala are more closely related to socio-emotional processing and emotion regulation (Etkin, Buchel, & Gross, 2015; Kanske, Heissler, Schonfelder, Bongers, & Wessa, 2011; Phelps & LeDoux, 2005), while pSTS and FFG are more closely related to socio-cognitive processing and social information integration (Deen, Koldewyn, Kanwisher, & Saxe, 2015; Saggar, Shelly, Lepage, Hoeft, & Reiss, 2014; Yang et al., 2015). Recently, research has successfully applied the biological motion fMRI task in identifying predictive biomarkers for treatment outcome in young children with ASD receiving Pivotal Response Treatment (Yang et al., 2016), which marks the first evidence that neuroimaging-based task can effectively predict treatment effectiveness in ASD. This adds to the likelihood that the biological motion fMRI task may be used to identify neuropredictive biomarkers in young adults with ASD.

The treatment approach investigated in this research is Virtual Reality-Social Cognition Training (VR-SCT) (Kandalaft, Didehbani, Krawczyk, Allen, & Chapman, 2013), which is a short-term trial and consisted of 5-week treatment: two 1-h sessions per week with a total of 10 sessions. Recent research highlights the potential benefits of using Virtual Reality (VR) as an effective tool in training social skills for individuals with ASD (Bellani, Fornasari, Chittaro, & Brambilla, 2011; Kandalaft et al., 2013; Maskey, Lowry, Rodgers, McConachie, & Parr, 2014; Parsons & Mitchell, 2002; Wainer & Ingersoll, 2011). Reviews on VR studies suggest that there are several advantages of using VR environments to train social skills (Bellani et al., 2011; Parsons & Mitchell, 2002). Specifically, VR can simulate real-world contexts in a safe, non-threatening setting in which participants can practice commonly encountered social interactions (Bellani et al., 2011; Kandalaft et al., 2013; Parsons, Mitchell, & Leonard, 2005). VR also affords the user the opportunity to be immersed into the training by promoting engagement and a sense of presence within the simulated experience (Wallace et al., 2010). As presented in the previous studies (Didehbani, Allen, Kandalaft, Krawczyk, & Chapman, 2016; Kandalaft et al., 2013), the format of immersive role-play in VR-SCT can afford the participant a variety of opportunities to become engaged in training, while reducing social anxiety and allowing for a dynamic practice experience without negative real-world social consequences. It is safe to try and fail, because scenarios are controlled by a clinician and allow for repeated practice using targeted social strategies. As well, the technology itself supports the *realism* of immersive role-play conversation by allowing a clinician to change his/her appearance, voice or even the physical setting of the conversation, which are key elements that in-person treatment can hardly provide.

Furthermore, VR and computer technologies as a training method are highly motivating platforms for many individuals with ASD (Chen & Bernard-Opitz, 1993; Moore & Calvert, 2000; Parsons & Mitchell, 2002). The ability to customize and practice dynamic social scenarios across multiple training sessions is also a strength of VR, which facilitates opportunities for generalization of social skills learned in VR to everyday life interactions (Bellani et al., 2011; Didehbani et al., 2016; Parsons & Cobb, 2011; Tzanavari, Charalambous-Darden, Herakleous, & Poullis, 2015). Generalization of trained skills to the real-world was also reported in a previous study (Maskey et al., 2014), whereby gradual exposure to a specific anxiety was presented in a visual context through VR, which combined with cognitive behavioral therapy resulted in participants reporting reduced anxiety in their everyday life. Similarly, in the previous VR-SCT study (Kandalaft et al., 2013), participants reported that their social functioning has continued to improve several months after the end of training. For adolescents and young adults with ASD, previous research has also shown that VR offers the flexibility to target social skills in isolation, such as social appropriateness with spatial proximity and knowing what to say in a job interview (Cheng, Moore, McGrath, & Fan, 2005; Parsons, Mitchell, & Leonard, 2004; Smith et al., 2014; Trepagnier, Olsen, Boteler, & Bell, 2011), or to target multiple skills in one platform (Kandalaft et al., 2013), including emotion recognition, theory of mind, and social functioning collectively.

The main principles of the VR-SCT intervention utilized in this study were based on prior VR-SCT studies (Didehbani et al., 2016; Kandalaft et al., 2013). In these studies, VR-SCT involved a semi-manualized structured prompt used by the clinicians for all participants. Clinicians used a scripted personality and response style for each character they played that further promoted standardization across participants. Even though the prompts were structured and repeated across scenarios, participants' individual responses allowed for flexible real-time responses by both the clinician and the participant. Similarly, in the current study, a manualized approach was used to engage participants in a conversation and the participants partially customized their experience through their own responses. As shown in these prior studies (Didehbani et al., 2016; Kandalaft et al., 2013), the role-play method has been utilized in both young adult and pediatric populations with similar improvements, regardless of the age group, in emotion recognition and theory of mind. Overall, VR-SCT offers an engaging, interactive, and individualized platform for training and improving socio-emotional and socio-cognitive abilities for individuals with ASD.

In this study, we investigated whether a pre-treatment biological motion fMRI task could predict therapeutic response to VR-SCT in young adults with ASD. The biological motion fMRI task was chosen also because it measures key socio-emotional and socio-cognitive processing, which correspond to the treatment targets of VR-SCT. Linking to the biological motion fMRI task and VR-SCT, we utilized two separate behavioral tasks to measure behavioral changes in emotional and cognitive aspects of social information processing, respectively: for the emotional component, we measured behavioral changes in emotion-recognition ability, while for the cognitive component, we measured behavioral changes in theory-of-mind ability. As VR-SCT has been demonstrated to