Symposium Title: Utilizing Cognitive Neuroscience to Predict and Enhance Treatment Outcomes for Children and Adolescents with Autism

Chairs: Jennifer Frey¹ and Kevin Pelphrey¹ ²

Discussant: Kevin Pelphrey¹ ²

Overview: Children with autism spectrum disorder (ASD) exhibit pathognomonic deficits in social communication, and 40% of children with ASD also experience clinical levels of anxiety. While evidence-based behavioral treatments can lead to improved social communication skills and reduced anxiety, no singular treatment is universally effective. Advances in the identification of biological markers and neurobiological predictors of treatment response offer the promise of improved, personalized treatment for people living with ASD. Facilitated by Dr. Jennifer Frey, an experienced BCBA-D clinician with expertise in behavioral interventions to improve social communication, and Dr. Kevin Pelphrey, a neuroscientist and expert in brain development and neuroimaging in ASD, this symposium presents developmental neuroimaging findings – both fMRI and EEG - of the neural mechanisms and biological markers of treatment response in children and adolescents with ASD. The presenters (all leading experts in their areas of research and clinical work) and discussant will speak about the implications of this work for designing and evaluating treatments, including the use of new technology to enhance treatment effects. The first presentation describes the results of an intervention study using pivotal response treatment (PRT) to improve the social communication skills of young children with ASD. Dr. Pamela Ventola and her team identified changes in neural systems that correlated strongly with improvements in social communication skills following PRT, thereby improving our understanding of the neural mechanisms by which PRT is effective for some children. Even more importantly, this team has discovered neuroimaging-based, biologically informed stratification biomarkers that predict the magnitude of response to PRT. The second presentation, by developmental scientist, Dr. Michael Crowley, describes findings from parallel EEG studies to identify practicable pre-existing biomarkers in the timing of brain activity to predict which children will benefit most from PRT. In the third presentation, a clinical psychologist, Dr. Denis Sukhodolsky, will present fMRI data collected before and after implementation of cognitive behavioral therapy (CBT) in a randomized, controlled trial. This talk will illustrate the neural mechanisms of successful response to CBT for anxiety in adolescents with ASD and identify ways in which CBT can be adapted to more precisely address individual neural profiles. Armed with a mechanistic understanding of the neural circuits that predict and reflect treatment success for core symptoms in ASD (PRT) and associated anxiety (CBT), our final presentation, by biomedical engineer, Dr. Chung-Hyuk Park, will illustrate the use of social robots to “prime” neuropredictive circuits in children with ASD, thereby enhancing the effectiveness of existing evidence-based treatments.

Paper Title: Neural Predictors and Neural Pathway of Response to Pivotal Response Treatment in Young Children with Autism

Authors: Pamela Ventola³, Daniel Yang², Kevin Pelphrey¹ ²

Introduction: Advances in genetics, molecular biology, and cognitive neuroscience offer promise towards personalized treatment to improve outcomes in individuals with ASD. Recent clinical trials have shown favorable results; however, the promise of precision medicine is hindered by a lack of sensitive, objective measures of treatment response as well as biological markers that identify subgroups of children likely to respond to specific treatments. Instead, our field relies on availability of service, trial-and-error, and clinical judgment to make treatment decisions. Here we built upon our prior research characterizing

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the neural-systems-level basis of core social communication symptoms in ASD to identify 1) biological markers of treatment response and 2) stratification biological markers to predict outcome.

**Method:** We investigated neural systems-level changes using fMRI collected just prior to and just after the end of a 16-week trial of pivotal response treatment (PRT) treatment in 25 children with ASD (8 girls, 17 boys, age 4-7 years). Children were randomly assigned to PRT, a behavioral treatment focused on social communication skill development (N = 14; Mean IQ 106.2, SD 17.4) or a waitlist condition (WLC, N = 11; Mean IQ 93.1, SD 19.2). In addition, 12 matched typically developing (TD) children were recruited as a comparison group. Additionally, we examined the degree to which fMRI neurobiomarkers predict treatment response in 22 children with ASD (4-7 years; 8 girls, 14 boys, Mean IQ=103.45, SD=17.03) who also participated in a 16-week trial of PRT.

Treatment included 7 hours per week of individual work with the child and parent training. Primary clinical outcome was the SRS-2 Total Raw Score. To measures PRT-evoked changes in neural systems, children with ASD completed two fMRI scans at pre- and post- WLC/PRT. The participants viewed a two-minute task consisting of 5 blocks of face and 5 blocks of house images presented in alternating order. We evaluated the change in activation in response to Faces and Houses. To predict of treatment response, participants viewed well-validated neuroimaging stimuli depicting point light displays of coherent biological (BIO) or scrambled biological (SCRAM) motion. We evaluated the extent to which activation in response to viewing BIO vs. SCRAM at baseline predicted the change in the social responsiveness scale (SRS) score from baseline to the treatment endpoint, while controlling for the baseline SRS score.

**Results:** Social communication symptoms, as measured by the SRS Total Score, were significantly reduced following treatment ($p = 0.027$, $\eta^2_p = 0.212$, for the interaction between the groups (WLC vs. PRT) and time (T1 vs. T2). In examining neural markers of treatment response, at baseline, children with ASD showed reduced functional activity of core face processing regions, including the amygdala, posterior superior temporal sulcus (pSTS) and medial prefrontal cortex (MPFC), when looking at faces vs. houses compared to the TD group. Children, who received PRT displayed greater activity in the MPFC after treatment compared to the WLC group. Greater increases in MPFC activity at the second measurement point were related to a reduction in ASD symptoms.

In evaluating prediction of treatment response, strikingly, none of the demographic (age, IQ, sex) or baseline behavioral (ADOS, ADI-R, SRS, Vineland-II, CELF) variables predicted response to treatment. Using a whole-brain group analysis (mixed-effects modeling using FSL’s FLAME1+2, voxel-level thresholding $Z > 2.33$, cluster-level thresholding $p < .05$, controlling for sex), we estimated the correlation between change in SRS total raw score from baseline to treatment endpoint and magnitude of pre-PRT brain response to BIO vs. SCRAM. This revealed three clusters of neuropredictive activity. Cluster 1 was centered in the right ventrolateral prefrontal cortex, orbitofrontal cortex, anterior insula, and temporal pole. Cluster 2 was centered in the right fusiform gyrus, inferior and middle temporal gyri, and superior temporal sulcus. Cluster 3 was centered in the left putamen, pallidum, hippocampus, amygdala, and ventral striatum/nucleus accumbens. The predictive value of our findings for individual children with ASD was supported by a multivariate pattern analysis with cross validation. The neuropredictive network consisting of the three clusters survived cross validation—the multivariate pattern information from this brain network significantly predicted treatment outcome ($r = .85, p < .0001; R^2 = .72, p = .0001; nMSE = 1.33, p < .0001$).

**Discussion:** We demonstrate the neural response to improvements in social communication skills following a trial of PRT. PRT changes the functional neuroarchitecture underlying social perception in young children with ASD; PRT induced functional plasticity in the MPFC, a region, which crucially contributes to intact social cognition in TD children. Consequently, increases in MPFC activity were significantly related to reductions in ASD symptomatology. Additionally, we discovered a neuroimaging-based biologically informed stratification biomarker that predicts magnitude of response to an evidence-based behavioral treatment in young children with ASD. Neurosynth results suggest that baseline levels of activity in well-known emotional regulation (cluster 1), social perception and face recognition (cluster 2), and social reward/motivation and emotion (cluster 3) networks predicted the magnitude of clinical response to PRT. Importantly, these biomarkers outperformed pre-treatment behavioral measures of
social functioning, language level, and cognitive abilities. Our results provide the first-ever clear evidence of a neuroimaging-derived stratification biomarker in ASD and help the field progress to the goal of targeted, personalized treatment for individuals with ASD.

**Paper 2 of 4**

**Paper Title:** Mu Suppression During Biological Motion Perception as a Stratification Biomarker for ASD Clinical Trials  
**Authors:** Michael Crowley³, Jia Wu³, Courtney Paisley⁴, Sebiha Abdullahi³, Linda Mayes³, Kevin Pelphrey¹ ², Pamela Ventola³  

**Introduction:** Detecting pre-existing functioning in brain circuitry that predicts which children with ASD will benefit from specific interventions is a key goal of personalized medicine. As a treatment with established clinical efficacy, Pivotal Response Treatment (PRT) is a naturalistic behavioral intervention that uses Applied Behavior Analysis (ABA) principles to target social communication deficits in ASD. Utilizing PRT, we have found significant benefit in pragmatic language, social engagement, and adaptive functioning skills for some children with ASD and corresponding brain-based normalization. Here, we present electroencephalography (EEG) findings showing that pre-treatment functioning in the brain circuitry supporting biological motion predicts which children benefit most from a 16-week course of PRT. Such predictive power could lead to the establishment of a stratification biomarker to help precisely match patients to active ingredients of specific treatments.

**Method:** We present preliminary findings from an ongoing clinical trial in which we examine the degree to which an EEG neurobiomarker predicts treatment response in a sample (N = 12) of children (4-7 years; 5 female, 7 male) with ASD (Mean IQ=88.44, SD=19.61) who participated in a 16-week trial of PRT.

**Results:** We evaluated the extent of suppression in the EEG alpha frequency band range (8-12 Hz, mu suppression) in response to viewing biological or scrambled biological motion at baseline predicted the change in the social responsiveness (SRS score) from baseline to the treatment endpoint. Effects were similar for both lateralized cortical regions, though stronger on the left.

**Discussion:** Our findings suggest functioning in the neural circuitry that supports social perception predicts who will show the most clinical benefit from a 16-week course of PRT. Our results lead the way to help develop stratification and target engagement biomarkers for ASD clinical trials. The ease of assessment (10 minutes), and relatively low cost, suggests this EEG biomarker could be a very useful, practicable indicator of treatment response for children with ASD.

**Paper 3 of 4**

**Paper Title:** Neural Mechanisms of CBT for Anxiety in Children with Autism Spectrum Disorder  
**Authors:** Denis G. Sukhodolsky³, Kevin Pelphrey¹ ², Emilie Bertschinger³, Theresa Gladstone³, Shivani Kaushal³, Brent Vander Wyk³  

**Introduction:** Approximately 40% of children with ASD exhibit clinically significant anxiety. While Cognitive Behavioral Therapy (CBT) is a promising treatment for anxiety in ASD, its neural-systems-level targets are unknown.

**Method:** We collected fMRI data during an emotion regulation and a face perception tasks before and after CBT for anxiety in 5 children with ASD complicated by clinically significant anxiety symptoms. Subjects included 3 boys and 2 girls, mean age=12.2±1.2 and mean IQ=109.2±14.7. Three subjects were not receiving medication; one was receiving sertraline and one lisdexamfetamine and guanfacine, which had been stable for six weeks prior to and remained stable during the study. CBT was provided using a structured manual that has been modified for children with ASD by increasing parental participation and addressing the role of core ASD symptoms in the experience and expression of anxiety (Wood et al., 2009). Subjects were

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comprehensively characterized with regard to ASD diagnosis, IQ, adaptive behavior, and comorbid psychopathology. Anxiety symptoms were evaluated before and after treatment using a Pediatric Anxiety Rating Scale (PARS).

**Results:** There was a significant reduction in the mean PARS total score from 19.2±1.5 at baseline to 8.2±3.5 at endpoint. The 57% reduction in the PARS score is a clinically meaningful change and it is similar to the mean improvement in previous studies of CBT for anxiety in ASD. A whole-brain fMRI analysis using decrease vs. look-negative contrast of the emotion regulation task revealed *increased activation* in the emotion regulation circuit including vmPFC, vPFC, and dIPFC after CBT. We also observed *reduction of left amygdala* and bilateral insula activation in the look-negative vs. look-neutral contrast (emotional reactivity) after treatment. The magnitude of the effects of CBT on the levels of BOLD activation in the contrasts of interest calculated as the Cohen’s *d* effect size for the difference in post- to pre-treatment activation divided by the pooled standard deviation ranged from 0.68 to 1.23, indicating moderate to large effect sizes. Although not all changes were statistically significant, all were consistent with increased activation of the prefrontal regions during emotion regulation and decreased amygdala and insula reactivity from pre- to post-treatment with CBT. Using PPI analysis with structurally defined left and right amygdala seeds, we observed increased bilateral amygdala-vmPFC connectivity after CBT with the decrease vs. look-negative contrast of the emotion regulation task, voxel-level threshold Z>1.64, cluster-level *p*<.05. Consistent with findings on the emotion regulation task (look-negative vs. look-neutral), we observed reduction of amygdala activation during emotional face perception task after CBT.

**Discussion:** Reduction of anxiety after CBT was paralleled by the enhanced activation in the emotion regulation circuitry consisting of the prefrontal cortex, amygdala, and insular cortex. The results represent one of the very first efforts to examine neural mechanisms of anxiety in ASD and a pioneering effort to utilize an intervention as an experimental probe to understand the neural systems that might be targeted to reduce debilitating anxiety in young people living with ASD.

Paper 4 of 4

**Paper Title:** Quantitative Behavioral Analysis with Automation for Music-Based Robotic Therapy for Children with Autism Spectrum Disorder

**Authors:** Chung-Hyuk Park¹, Rachael Bevill¹, Myounghoon Jeon⁵, Ayanna Howard⁶

**Introduction:** Robots can be effective and intelligent therapeutic assistants for children with ASD. Humans, even trained therapists, may exhibit multiple emotions at once, through conflicting facial cues and body movements, which may make it more difficult for some children with ASD to discriminate and identify their social partner’s feelings. In comparison, robots excel at separating and “articulating” emotions to individuals with autism. Children paired with robots in therapy have shown increased shared attention and facial expression imitation compared to those paired only with human therapists.

**Method:** We used an autonomous, multisensory robotic framework to stimulate the emotional and social interactivity of the child during interactive play. Using the relationship between emotional state and movement, we analyzed the child’s response to the robot in real time, and programmed the robot to react and adjust its behaviors according to the child’s emotional state. Our robotic platform employs a custom character and network-based software architecture with facial expression-based robots and gesture/movement-based robots. Our monitoring system, utilizing Microsoft Kinect, provided automated behavior analysis using Laban Motion Analysis and kinematic parameters to determine the child’s level of engagement with and reaction to the robots during behavioral therapy sessions.

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Children (N=5) participated in experimental sessions where a robot moved along a path with diverse sensory modality stimulus settings, and the child was encouraged to follow the robot. Each session ran with or without music with emotional features that matched the session scenarios.

**Results:** Average motion units (Mus) were significantly higher in sessions with musical accompaniment compared to sessions without music. In addition, increased frequency of child movements and increased average speed were observed in the sessions with music. The motion unit increase during sessions with music also displayed a more smooth and continuous increase in Mus, suggesting more regulated emotional responses and a continuous increase in physical behaviors during sessions with music.

**Discussion:** Preliminary findings suggest that children with autism are responsive to the social robots and are more active and engaged in music-enhanced robotic therapy sessions. The use of social robots may “prime” neuropredictive circuits in children with ASD, thereby enhancing the effectiveness of existing evidence-based treatments.