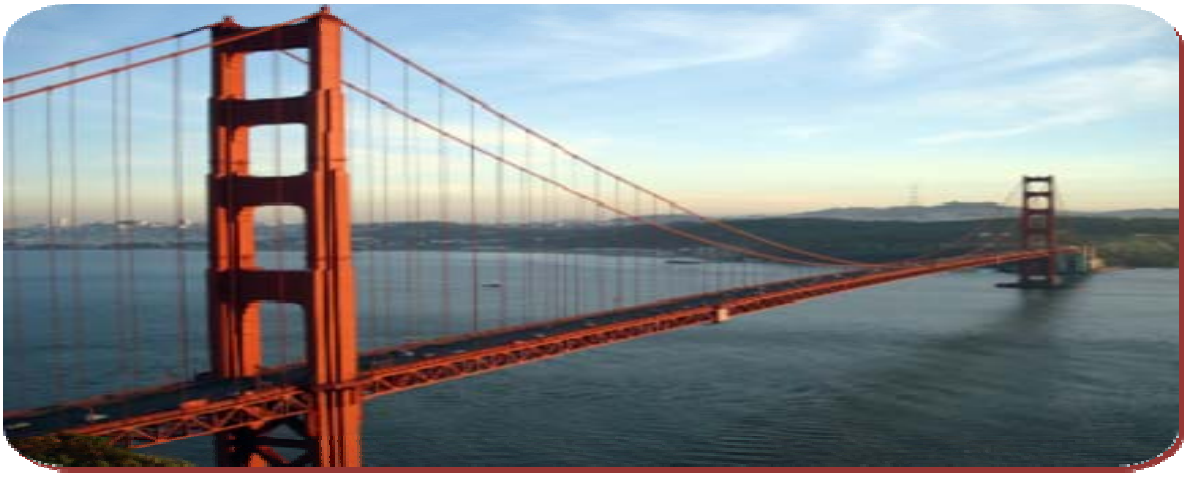
PROGRAM



Scientific Meeting of the International Society for Research on Impulsivity

Hyatt Regency, San Francisco, California USA

May 11, 2011

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THE INTERNATIONAL SOCIETY FOR RESEARCH ON IMPULSIVITY AND IMPULSE CONTROL DISORDERS

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About the International Society for Research on Impulsivity (ISRI)

The ISRI is a nonprofit scientific society founded to promote research collaboration on impulsivity and impulse control disorders by scientists around the world.

The purpose of this society is to foster international research collaboration on impulsivity and its psychiatric and social consequences.

What is Impulsivity?

Impulsivity has been variously defined as human behavior without adequate thought, the tendency to act with less forethought than do most individuals of equal ability and knowledge, or a predisposition toward rapid, unplanned reactions to internal or external stimuli with diminished regard to the negative consequences of these reactions.

Impulsivity is implicated in a number of psychiatric disorders including Mania, Personality Disorders, and Substance Use Disorders; yet, there is significant disagreement among researchers and clinicians regarding the exact definition of impulsivity and how it should be measured.

Impulsivity is also a key construct in many social decisions. For example, in jurisprudence, forensic psychiatrists often testify in mens rea decisions. If an alleged criminal act like murder is shown to be impulsive, the penalty is different than if it is premeditated.

The goals of this society include:

1) Establishment of guidelines for measurement of impulsivity which would make comparisons across research projects more meaningful

2) Examination of the current diagnostic criteria for disorders of impulse control based on results of biological, social, cognitive, and behavioral research

3) Dissemination of clinical and pre-clinical impulsivity research to other researchers and clinicians through symposia, publication, and newsletters.

ISRI Meeting Schedule

Wednesday, May 11, 2011

7:30 - 8:00 am	Registration and Continental Breakfast
8:00 - 8:15 am	Alan C. Swann, M.D. - Overview and Introduction
	Mechanisms and Consequences of Impulsivity: Chair, Alan C. Swann, M.D.
8:15 – 10:00 am	***Panel Session 1***: Mechanisms of Impulsivity
	1.) F. Gerard Moeller, M.D. - "Definitions and Models"
	2.) Catharine Winstanley, Ph.D. - " Animal Models and Mechanisms"
	3.) David Goldman, M.D. – "Genetic Mechanisms in Impulsivity"
	Panel: Drs. Moeller, Winstanley, and Goldman
10:00-11:15 am	***Panel Session 2***: Consequences of Impulsivity and Interaction with Other Mechanisms
	1.) James Blair, Ph.D. - "Aggression"
	2.) Donald M. Dougherty, Ph.D. - "Suicidal Behavior"
	Panel: Drs. Blair, Dougherty, and Moeller
11:15 -12:15pm	**Young Investigator Data Blitz:**

1. Jodie Finlayson-Burden

2. Lana Depatie, M.Sc.

3. Arielle Sheftall, Ph.D.

4. Melisa Carrasco, M.S.

12:15 - 1:45 pm Lunch Break

Impulsivity and Clinical Psychobiology
Chair, F. Gerard Moeller, M.D.

1:45 – 3:05 pm ***Panel Session 3:*** Bipolar Disorder

1.) Jair Soares, M.D. – "Impulsivity and Brain Function in Bipolar Disorder"

2.) Alan C. Swann, M.D. – "Impulsivity and Course of Illness in Bipolar Disorder: Adaptation and Sensitization"

Panel: Drs. Soares, Swann

3:05 – 3:25 pm Break/Afternoon Snack

3:25 – 5:10 pm ***Panel Session 4***: Impulsivity and Regulation of Behavior

1.) R. Andrew Chambers, M.D. – "Impulsivity in Dual Diagnosis: Insights from Animal Models"

2.) Victoria C. Wing, Ph.D. – "Schizophrenia, Addiction, and Impulsivity"

3.) Marc N. Potenza, M.D., Ph.D. – "Impulsivity and Compulsivity: Mechanisms of Impulse Control Disorders"

Panel: Drs. Chambers, Wing, and Potenza

5:10 – 5:15 pm **Synthesis:** Drs. Moeller, Swann, and Potenza

SPEAKER ABSTRACTS:

Definitions and Models of Impulsivity

F. G. Moeller, M.D., UT Health

F. G. Moeller, S.D. Lane, K.L. Kjome, A.C. Swann

Introduction: The purpose of this talk is to review definitions and models of impulsivity and the related construct of compulsivity in animal and human research. Methods: Several authors have proposed definitions of impulsivity based on human clinical populations and animal models of impulsivity. These definitions will be presented and compared and data will be provided to support the various definitions and models that arise from these definitions. In addition, definitions for the related and sometimes confused construct of compulsivity will be discussed and will be related to impulsivity.

Results: Although most clinical definitions of impulsivity focus on rapid, premature, or unplanned actions, behavioral definitions have also included choices of more immediate rewards over delayed rewards or at the expense of longer term losses. Behavioral laboratory measures based on the two constructs (rapid response impulsivity or delayed reward impulsivity) often have very low correlations with each other or with questionnaire measures of impulsivity.

Conclusions: As discussed by many authors, impulsivity is a multifaceted construct. The delayed reward measures of impulsivity appear to be poorly correlated with rapid response impulsivity. This raises the question of the role of the ability to choose a larger delayed reward in the overall construct of impulsivity

The potential utility of rodent models of impulsivity and gambling for understanding and treating impulse control disorders.

C.A. Winstanley, Ph.D., University of British Columbia

Impulsivity can be broadly defined as acting or making decisions without appropriate forethought, thereby enhancing the potential for negative consequences. High levels of such impulsive behaviours are associated with psychiatric disorders such as bipolar disorder and ADHD, and impulsivity is increasingly recognized as a risk factor for drug addiction. Rodent models of impulsivity, designed to resemble neuropsychology tests used clinically, have the

potential to contribute to the assessment and development of treatments for these disorders, particularly with regards to establishing their mechanism of action. We have observed, for example, that repeated treatment with atomoxetine during adolescence results in a long-lasting decrease in impulsive decision-making in adulthood that may arise due to changes in synaptic plasticity within the orbitofrontal cortex. Furthermore, chronic treatment with the mood stabilizer lithium can improve attentional function and reduce stressor-induced increases in motor impulsivity. Preliminary data likewise suggests that these changes are accompanied by changes in gene expression within the frontal cortices. Pathological gambling has recently been described as a behavioural addiction, and high impulsivity has also been observed in this clinical population. Building on the success of behavioural models of drug addiction and impulse control, researchers have begun to develop rodent analogues of gambling-related decision-making in order to investigate the extent to which behavioural and chemical addictions might overlap in terms of their brain circuitry and neurochemical control. Our own data so far suggests that rats' performance in gambling-like tasks resembles that of humans, even with respect to potential cognitive biases or "irrationality". Furthermore, different aspects of gambling-like behaviour can be modulated by serotonergic and dopaminergic drugs, paralleling some clinical findings. These rodent models of gambling processes may therefore provide useful data regarding the neurobiological basis of gambling and putative pharmacotherapies for problem gambling behaviour.

A Common, Population-Specific, HTR2B Stop Codon That Can Lead to Severe Impusivity

David Goldman, M.D., National Institute on Alcohol Abuse and Alcoholism

Deep sequencing can detect rare and uncommon alleles that play a role in rare Mendelian diseases (Eichler and colleagues, 2009, 2010). Recently, we used a sequencing-based approach to detect a Stop Codon that plays a role in impulsivity, a trait of complex origins. We sequenced 14 candidate genes in 96 severely impulsive criminals with ASPD and IED, all Finnish. 96 matched controls were also sequenced. Four putatively functional variants were detected that were associated with impulsivity in a larger case/control dataset, using a global test of significance. The association was due to Q20*, a stop codon truncating the HT2B receptor, which was individually significant and cosegregated with impulsivity in eight families. *20 was shown to halve receptor expression in lymphoblastoid cells of heterozygous carriers, and it led to variable nonsense-mediated decay of HTR2B mRNA. *20 is restricted to Finns and occurs on a single haplotype background, representing a founder mutation with a frequency of >1% in Finns. Most carriers are apparently normal in behavior and cognition. Criminals carrying the stop codon, including 3/3 double murderers in our study, were distinctive in that they were male, violent only when inebriated, and had committed crimes of impulse. Mice knocked out for htr2b were novelty seeking on multiple measures, and impulsive as assessed by Delay Discounting. Detection of *20 represents one of the first instances in which deep sequencing has been used to detect a novel gene contributing to a complex trait. In Finns, *20 can be a necessary factor in severe impulsive behavior, but it is not in itself sufficient.

Impulsivity and Aggression

James Blair, Ph.D., National Institute of Mental Health

The paper will begin with a brief differentiation of frustration/ threat based reactive aggression and goal directed instrumental aggression. The clearest relationship between impulsivity and

aggression is with reactive aggression (sometimes referred to as impulsive aggression). The neural systems mediating and regulating reactive aggression will be discussed. In addition, psychiatric and neurological conditions that either enhance the responsiveness of the systems mediating reactive aggression or diminish the responsiveness of systems regulating this aggression (or both) will be briefly considered. However, the relationship between impulsivity and instrumental aggression will also be considered. Instrumental aggression, while goal-directed, can occur as a result of inadequate representation of the potential costs and benefits of the actions and therefore appear impulsive. Psychopathy will be considered as the paradigm condition where this can occur

The Role of Impulsivity in Suicide Spectrum Behaviors

Donald M. Dougherty, M.D., University of Texas Health Science Center at San Antonio

The purpose of this presentation is to provide an overview of some leading models of suicidal behavior, the relevance of impulsivity to these models, and recent outcomes testing relationships between impulsivity and suicidal behaviors. Impulsivity has been variously theorized as either directly or indirectly related to suicidal behavior. Differences of opinion on the proximity of the influence of impulsivity on the expression of suicidal behavior stem from different approaches to impulsivity measurement. Theories suggesting a more direct connection have been developed from self- or observer report of a variety of impulsive behaviors expressed in everyday life. More distal theories have focused on whether the suicidal act itself was impulsive in nature, rather than impulsive personality traits of behavioral states. Expanding on these measurement debates has been the more recent application of behavioral measures of impulsivity among a variety of suicide spectrum behaviors. Finally, as has been recognized in the measurement of impulsivity, suicidal behaviors involve a spectrum of distinct clinical phenomenon rather than a unitary clinical symptom, adding to the multi-faceted approach to measurement. Data will be presented directly testing some of the individual relationships between different aspects of impulsivity and suicidality. Also a strategy for ongoing research will be presented that will more comprehensively assess the development of impulsivity, suicidality, and clinical symptoms across adolescence.

Impulsivity and Brain Abnormalities in Bipolar Disorder

Jair C. Soares, M.D., UT Health

We completed a series of studies in bipolar disorder (BD) patients (with and without comorbid alcoholism) and healthy controls to investigate, with structural brain imaging and magnetic resonance spectroscopy, the neurobiological underpinnings of these comorbid conditions and the brain mechanisms possibly involved in impulsivity in these disorders. Our preliminary results will be discussed and suggest increased levels of impulsivity in BD patients with alcoholism compared to BD patients without alcoholism and a differential pattern of fronto-limbic brain abnormalities in these patient groups.

Acknowledgments: This research was partly supported by grants MH 068766, RR 020571, and the Veterans Administration (VA Merit Review).

Impulsivity and course of bipolar disorder: adaptation and sensitization

Alan C. Swann, M.D., UT Health

Alan C. Swann, M.D., Marijn Lijffijt, Ph.D., Michelle Acas, Scott D. Lane, Ph.D., Joel L. Steinberg, M.D., F. Gerard Moeller, M.D.

Background: Bipolar disorder is characterized by impulsive behavior and a variably recurrent course. Susceptibility to substance-use disorders (SUD) and overlap with cluster B personality disorders complicate bipolar disorder, with a more severely recurrent course of illness and increased risk for suicidal behavior in combined illnesses. Recurrent episodes, through behavioral sensitization, could increase impulsive and addictive behaviors; alternatively, SUD could predispose to recurrent illness and impulsivity.

Methods: Subjects were 78 healthy controls (HC), 35 with only SUD, 50 with antisocial personality disorder (ASPD), and 110 with bipolar disorder; of these, 32 had bipolar disorder only and the rest also had SUD (78) and/or ASPD (24). Impulsivity was assessed as integrated trait impulsivity (Barratt Impulsiveness Scale, BIS-11) and performance on a continuous performance test designed to measure impulsivity (Immediate Memory task, IMT). Analyses used general linear model and logit analysis.

Results: Course of bipolar disorder was more recurrent if SUD or ASPD was present, and history of suicidal behavior was more severe. BIS-11 was strongly increased in bipolar disorder (Effect size (ES) = 1.4) and was increased less in subjects with SUD or ASPD without bipolar disorder. Uncomplicated bipolar disorder was associated with nonimpulsive IMT performance (increased omission errors, slow reaction time, and conservative response bias). Subjects with bipolar disorder plus SUD or ASPD had more impulsive performance on tests of impulsivity, with increased commission errors, faster reaction time, and more impulsive response bias. Highly recurrent course accounted for impulsive performance on the IMT with no significant contribution from concurrent SUD or ASPD, and for increased history of suicidal behavior.

Conclusions: Highly recurrent illness increases questionnaire- and task-measured impulsivity and suicidal behavior in bipolar disorder. Effects of SUD and ASPD appeared to be a result of recurrent course. These findings are consistent with early adaptation where conservative response bias and slowing of responses protects against impulsive responses. This is absent when the illness is severely recurrent, possibly predisposing to SUD, ASPD, and suicidal behavior. These characteristics may be acquired during recurrence, or already present in those susceptible to recurrent illness.

Acknowledgements: This work was supported in part by R01 MH069944.

Impulsivity in Dual Diagnosis: Insights from animal Models

R. Andrew Chambers, M.D., Indiana University School of Medicine

Impulsivity is a robust trait marker of addiction vulnerability and a key phenomenon that links mental illness and addiction in the causality of dual diagnosis. This talk will present animal modeling of dual diagnosis that emulates the central role of impulsivity as measured across different behavioral paradigms, and neurobiological findings that reveal how prefrontal cortical substrates of impulsivity may mechanistically alter the neurobehavioral effects of drugs within striatal/motivational circuits to enhance addiction vulnerability.

Schizophrenia and co-morbid drug addiction: the role of impulsivity

Victoria C. Wing, Ph.D., University of Toronto

Impulsivity is often thought of as a core feature of schizophrenia and supporting this notion laboratory studies have reported impairments in both self-report and behavioral assessments of impulsivity including response inhibition (e.g., Nolan et al., 2011) and delay discounting (Heerey et al., 2007). However, patients with schizophrenia often suffer from co-morbid substance use disorders, which independent of schizophrenia are associated with high rates of impulsivity. Despite the pivotal role that impulsivity plays in the initiation and maintenance of drug use there has been little investigation of the nature or direction of this relationship in schizophrenia. Interestingly, the high rates of cigarette smoking in schizophrenia (up to three times that of the general population) are thought to be an attempt to remediate the widespread cognitive deficits associated with the disorder. The pro-cognitive effects of nicotine and cigarette smoking in schizophrenia have been demonstrated in abstinence and challenge paradigms (George et al., 2002, 2005; Smith et al., 2002) and recently we have completed a cross-sectional assessment of cognitive function showing more severe deficits in domains such as sustained attention exist in non-smokers with schizophrenia compared to their smoking counterparts (Wing et al., In Press). However, it is unclear if the pro-cognitive effects of cigarette smoking in schizophrenia extend to impulsivity deficits. To this end we sought to conduct a cross-sectional examination of delay discounting (i.e., the preference for smaller immediate rewards over future delayed rewards), in patients with schizophrenia in comparison to non-psychiatric controls as a function of cigarette smoking status (Wing et al., Under Review). In contrast to our prediction, we found no differences between patients with schizophrenia and controls when collapsed across smoking status. Smokers with schizophrenia discounted delayed rewards more than non-smokers, as is seen in controls, thus the notion of beneficial effects of cigarette smoking on delay discounting in schizophrenia were not supported in this study. Interestingly, however, when parsing by smoking history (i.e., current, former and never smokers), current and former smokers with schizophrenia were much more impulsive than never smokers with schizophrenia, whereas similar to other studies, control current smokers were more impulsive than both former and never smokers. Our pattern of results in schizophrenia suggests that deficits in delay discounting in these patients appear to be a trait rather than a state-dependent phenomenon, which may constitute an additional vulnerability factor for cigarette smoking in schizophrenia. Longitudinal studies are needed to confirm the stability of delay discounting during abstinence from cigarette smoking and to determine if, like in adolescent smokers (Krishnan-Sarin et al., 2007), delay discounting can predict smoking cessation success in schizophrenia. It will also be important to establish if these findings extend to other drugs of abuse. In conclusion, our results may have implications for understanding the relationship between schizophrenia and the high vulnerability to drug addiction, and the potentially pivotal role of impulsivity may play in mediating this co-morbidity.

Impulsivity and compulsivity: Mechanisms of impulse control disorders

Marc N. Potenza, M.D., Ph.D., Yale University School of Medicine

Impulse control disorders such as pathological gambling have been viewed alternatively as "behavioral" addictions and obsessive-compulsive spectrum disorders. These different conceptualizations suggest that both impulsivity and compulsivity may hold relevance to impulse

control disorders. Data supporting this notion will be presented, as will data suggesting that aspects of impulsivity and compulsivity may relate to specific behavioral, clinical and biological features of impulse control disorders. Implications for prevention and treatment development will be discussed.

ORAL DATA BLITZ PRESENTERS:

Jodie Burden-Rawlings, University of Nottingham

Hypomania and the Occurrence and Experience of Impulsivity in a Non-Clinical Sample

Jodie Burden-Rawlings, Dr. Rhiannon Corcoran, and Prof. Richard Morriss

Background: Research has indicated strong links between bipolar disorder and impulsivity, with the suggestion that impulsivity may be a key causal factor for many behaviours commonly found in bipolar disorder. This research intended to (1) test whether relationships between impulsivity, bipolar disorder and behaviour could be replicated throughout the bipolar spectrum and (2) investigate qualitatively how impulsivity and impulsive behaviour is experienced in a non-clinical continuum sample.

Methods: A battery of questionnaires including the UPPS and BIS was completed by 650 students. Using purposive sampling, a selection of participants were invited to take part in a semi-structured interview.

Results: Questionnaire data indicated that students who had experienced hypomania (*Hyp+*) had higher levels of self reported impulsivity when compared to individuals who had no experience of hypomania (*Hyp-*) ($p<0.001$). Hyp+ individuals were also more likely than Hyp- individuals to endorse engaging in a wide range of impulsive and risky-type behaviours.
Data from the qualitative stage of the research indicates that impulsive behaviour in Hyp+ individuals is frequently triggered by intense emotional states, with behaviour functioning as a means of managing these emotions. Over time, many originally impulsive behaviours become habitual. At this stage the impulsive aspects of the behaviour in fact bear more relation to compulsivity.

Conclusions: Impulsivity is an important factor in predicting behaviour throughout the bipolar spectrum. The relationship between impulsivity and compulsivity needs further investigation.

Arielle Sheftall, Ph.D., UT Health Science Center San Antonio

Serotonin markers, psychiatric inpatient status, and self-reported impulsivity

Arielle Sheftall, Charles W. Mathias, Nathalie Hill-Kapturczak, Martin Javors, Matthew S. Stanford, and Donald M. Dougherty
A variety of lines of evidence have suggested a relationship between the serotonin system, its function and impulsivity. This study extends that line of evidence by testing serotonin markers

among impulsive psychiatric inpatients. One hundred fifty adolescents (ages 12-17) were recruited into three groups: healthy controls (n = 84), psychiatric inpatients with high self-ratings of impulsivity (n = 33), and psychiatric inpatients with average to low levels of impulsivity (n = 33). Impulsivity was assessed using the Barratt Impulsiveness Scale. Serotonin markers included serotonin transporter promoter functional genotypes and platelet serotonin transporter uptake potential (V_{max} / K_m). Patients with average to low levels of self-reported impulsivity were more likely to have the l/l homozygote than highly impulsive patients or controls, suggesting this homozygote may be protective for impulsive personality traits among adolescents experiencing significant psychopathology. Highly impulsive patients had lower uptake potential (V_{max} / K_m) than the less impulsive patients and controls, further supporting the link between lower serotonin function with high levels of impulsivity among clinical populations.

Lana Depatie, M.Sc., McGill University

Functional Neuroanatomy of Antisaccade Impairments in Subtypes of ADHD

Dépatie L, Caro J, Starmans C, Holahan A-LV, Douglas VI, O'Driscoll GA

Background: A characteristic of the ADHD-Combined subtype is disinhibition. We used fMRI to investigate the neural substrates of oculomotor inhibition in subtypes of ADHD. We hypothesized that the ADHD-Combined group would show reduced activation of frontal-subcortical circuitry during antisaccades, and that task-related activation would be related to antisaccade errors.

Methods: Control (n=10), ADHD-Inattentive (n=8) and ADHD-Combined (n=9) males performed the antisaccade task and a matched control task during fMRI. Eye movements were monitored in the scanner. Brain areas more active in antisaccades were identified in the three groups. Group differences in activation were compared using FMRISTAT. Correlations were used to investigate the relationship between activation and performance, and between activation and parent ratings of ADHD symptoms.

Results: Both ADHD subtypes showed increased antisaccade errors and reduced right frontal eye field (FEF) activity compared to Controls. The ADHD-Combined group also showed reduced activation of left precuneus, right medial superior parietal lobule, and cerebellar lobule VI. High antisaccade errors were associated with low activation of left FEF, left precuneus and right superior parietal lobe. Higher parent symptom ratings were associated with lower activation of left precuneus across all participants and within ADHD participants.

Conclusions: Our data suggest FEF dysfunction in ADHD. FEF is involved in attention, working memory and saccade inhibition, all areas of impairment in ADHD. Our data also implicate dorsal precuneus in ADHD. This region of precuneus showed a pattern of activation consistent with the dorsal attentional network (rather than the default mode network) and subserves voluntary attentional and motor control.

Melisa Carrasco, M.S., University of Michigan

ERP correlates of error processing and impulsiveness in children with an Autism Spectrum Disorder (Data Blitz)

Autism spectrum disorders (ASD) are characterized by disturbances in social function and communication, and the presence of repetitive behaviors. In addition, ASD is associated with externalizing behaviors, present in 50-80% of children diagnosed with an ASD (Gadow et al., 2004). Externalizing behaviors include impulsivity, attention problems, aggression, and rule-breaking behavior (Bauminger et al., 2010). Relatively little research has been done to describe the electrophysiological correlates of impulsiveness in high-functioning ASD youth using event-related potentials (ERPs). The purpose of this study was to assess two error-related ERPs (the error-related negativity and the error positivity) and their behavioral correlates in ASD youth performing an Eriksen flanker task. The dataset consisted of 18 ASD children and 24 healthy controls ages 10 - 17. ASD and control subjects were equivalent for IQ, age (range 11-17), sex, and manual preference. In addition, ASD adolescents were diagnosed using the ADOS and ADI-R and the diagnosis was confirmed by clinical consensus. Externalizing behavior symptom severity was measured using the externalizing behavior subscale of the Child Behavior Checklist (CBCL). Preliminary analyses of this dataset are forthcoming. It is predicted that results will provide further support for a relationship between ASD externalizing symptoms and exaggerated medial-frontal error processing.

Bauminger N, Solomon M, Rogers SJ (2010) Externalizing and internalizing behaviors in ASD. Autism Res 3:101-112.

Gadow KD, DeVincent CJ, Pomeroy J, Azizian A (2004) Psychiatric symptoms in preschool children with PDD and clinic and comparison samples. J Autism Dev Disord 34:379-393.