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TITLE: Family Studies of Sensorimotor and Neurocognitive Heterogeneity in Autism Spectrum Disorders (ASD)

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Autism spectrum disorders (ASD) are complex heritable neurodevelopmental disorders. It is likely that these disorders include individuals with different familial etiopathological mechanisms, and thus identifying biologically homogeneous subgroups of affected individuals and families is an important step to speed identification of risk genes and the development of more individualized and effective treatments. Using eye movement testing, we previously identified a profile of neurophysiological alterations in unaffected parents and siblings of individuals with ASD that was strikingly similar to that we and others have reported in ASD patients. During the past year, we have enrolled 11 family trios with a child with ASD. Each family member has completed oculomotor and manual motor testing. Initial analyses performed during the past year have documented manual motor dysmetria and reduced inhibitory control of manual motor and oculomotor responses in individuals with ASD. These findings, combined with our prior study of oculomotor deficits in individuals with ASD and their unaffected first-degree relatives, suggest that data from our ongoing family study may greatly enhance our understanding of familial phenotypes in ASD and the sensorimotor deficits that characterize this disorder.
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April 19, 2012

To Dr. Niu:

The requested information for our Year 1 Annual Report is attached. Please feel free to contact me directly if clarification or any additional information is needed.

Sincerely,

John A. Sweeney, Ph.D.
Director, The Autism Center at UT Southwestern
Professor, Psychiatry and Pediatrics

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I: INTRODUCTION
Autism spectrum disorders (ASD) are complex heritable neurodevelopmental disorders. It is likely that these disorders include individuals with different familial etiopathological mechanisms, and thus identifying biologically homogeneous subgroups of affected individuals and families is an important step to speed identification of risk genes and the development of more individualized and effective treatments. Using eye movement testing, we previously identified a profile of neurophysiological alterations in unaffected parents and siblings of individuals with ASD that was strikingly similar to that we and others have reported in ASD patients. These data implicated ponto-cerebellar circuitry, left hemisphere frontotemporal circuitry, and prefrontal systems that were relatively independently affected. The proposed study aims to examine these promising biological intermediate phenotypes by evaluating eye and hand movement neurophysiology in family trios consisting of an individual with ASD and their unaffected biological parents. This combined use of oculomotor and manual motor tasks will not only enhance our search for and understanding of familial phenotypes in ASD, but importantly it will provide a fuller characterization of sensorimotor deficits in these disorders.

II: BODY
a. Overall Progress. We have successfully completed each of the first year tasks laid out in our original Statement of Work. During the past year, we have both completed study start up efforts and transitioned to recruiting and enrolling family trios in our studies. Start up efforts were completed within the first 6 months of the award and included hiring and training research staff, obtaining human subjects approvals, setting up the proposed experiments, developing secure research databases, and establishing and implementing recruitment procedures for subject enrollment. During the latter half of the first year, we transitioned to subject enrollment and assessment, quality assurance testing to check the integrity of test administration, data processing, data analysis and data entry. A brief synopsis of our progress in each of these areas is provided below.

Staff recruitment, hiring, and training: Upon moving to UT Southwestern two months prior to the initiation of this award, we began recruiting and hiring new staff, including two computer programmers/bioengineers (who joined two other programmers who moved with us from Chicago), two administrative assistants, two research coordinators, and one psychologist to perform clinical evaluations for the study. Each new member of our team successfully completed training on all study procedures. This has included training research coordinators to administer and analyze all neuropsychological, psychological, and sensorimotor tests that are included in our family studies. Our coordinators also participated in training on human subjects research ethics, organizing and maintaining IRB protocols, recruitment procedures, testing young children and individuals with developmental disabilities, scoring neurocognitive and sensorimotor data, and data entry. Our four computer programmers/bioengineers have worked to develop new research databases, program neurocognitive and sensorimotor tests, develop automated systems for logic checks to ensure data quality, generate scoring programs for experimental tasks, set up our new sensorimotor equipment, integrate sensorimotor hardware with our presentation platforms, and test and ensure the quality of experimental data. Administrative staff were hired and trained to help with the considerable number of steps required to transfer grants, initiate new grant supported studies, hire new staff, purchase laboratory equipment, and track and document expenditures. Our psychologist has completed all training on diagnostic and clinical evaluation procedures and has obtained reliability on all diagnostic measures.

Obtaining IRB approvals: We obtained IRB approval for the family studies presented in our grant application and successfully completed credentialing procedures at both our home
institution (UT Southwestern) and the Children’s Medical Center (CMC). CMC conducted an independent review of our studies because we recruit subjects with ASD through the UT Southwestern/Children’s Medical Autism Center’s clinics (the PI is the Director of the Autism Center). In addition to receiving initial approval, we have made the following minor modifications during the past year:

Modification – Approved 1/18/2012 - The autism clinics at the Children’s Medical Center were added as recruitment sites within the procedures for recruitment. Also, recruitment materials were updated to reflect changes requested by the new UT Southwestern Director of Publications. These changes included removing “at Dallas” from the institution name, correcting the email address from autism@UTSoutwestern.edu to autism@utsouthwestern.edu, revising the telephone number to the correct format of xxx-xxxx, modifying the wording from “between ages 5-55 years” to “between ages 5 and 55 years”, and including the updated version of the UT Southwestern logo.

Modification – Approved 2/21/2012 - The protocol was modified to include five additional oculomotor tasks which together last approximately 20 minutes. These tests are administered as part of subjects’ current eye movement testing session using the same eye movement system. They have been used during our previous studies to assess sensorimotor and cognitive dysfunction in individuals with ASD. The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) was removed from the “Secondary Analyses” section because this clinical report measure is not in the protocol. Finally, all consent forms (ASD Participants, Parent Participants, Control Participants, and Blood Draw) were updated to clarify payment and travel reimbursement procedures.

Modification – Approved 7/10/2012 - Blood draw procedures were amended to only include Fragile X testing when clinically indicated for an individual. Fragile X testing will be completed if there is a reported family history of either a pre- or full mutation, or if the parents or caregivers report that the individual has had a prior positive Fragile X test. We also removed the following tests from the battery because they are not primary study objectives and we hoped to lighten the burden on participating families (approximately 0.75 fewer hours):

i. Differential Ability Scales- Second Edition (DAS-II) (replaced by the Wechsler Preschool and Primary Scale of Intelligence – III (WPPSI – III) to measure intelligence in child participants ages 5 - 6 years).
iii. The Aberrant Behavior Checklist-Community Version (ABC-CV); The Child Behavior Checklist (CBCL); The Autism Study Family History Interview; The Childhood Routines Inventory (CRI); Obsessive Compulsive Inventory (OCI)

The following tests were added:

i. Conners Adult ADHD Rating Scales (CAARS) are used as a self-report measure to assess attention deficit/hyperactivity disorder (ADHD) behaviors in individuals ages 18 and older.

ii. Conners 3rd Edition (Conners 3) is a screening questionnaire that uses observer and self-report ratings to assess attention deficit/hyperactivity disorder (ADHD) and evaluate problem behavior in children and adolescents.

iii. Conners Early Childhood (Conners EC) assesses behavior for preschool-aged
children 2 to 6 and aids in the early identification of behavioral, emotional and social problems.

iv. Wechsler Preschool and Primary Scale of Intelligence – III (WPPSI – III) is an intelligence test designed for children ages 2 years 6 months to 7 years 3 months. It provides subtest and composite scores that represent intellectual functioning in verbal and performance cognitive domains, as well a composite score that represents a child’s general intellectual ability.

v. Beck Depression Inventory – II (BDI – II) investigates symptoms of depression in individuals 13 years and older.

Laboratory setup: The majority of our testing equipment needed to be purchased after we moved to Dallas. This involved selecting appropriate equipment to conduct these studies given what was available on the market, and working with individual vendors to develop custom-made response and recording devices for our experiments. Our bioengineers and computer programmers helped construct the experimental environments and then integrate the new equipment with our software programs. Many of the sensorimotor tests performed in this study had been previously developed using different software packages. We have now integrated these tests by transferring all experiments to a common software package. Presentation software was selected for this purpose because it provides greater temporal control of stimulus presentation and recording. As consultants, Drs. Daniel Corcos and David Vaillancourt each met with the study investigators to help design the experiments and oversee their development. The experiment movies, as well as the scoring programs used to analyze the data, have all been written and validated and are now being used to test subjects and collect data. We have worked with our programming team to develop a novel analysis program which will allow us to reliably quantify a greater number of parameters for manual motor testing. Specifically, while we previously were calculating the accuracy and variability of sustained force production in our family members, this new scoring program also allows us to examine the rate at which subjects increase and decrease their force production. These aspects of motor control have been shown to be affected in other neurological disorders in which the basal ganglia and cerebellum are impacted (Vaillancourt et al., 2011), but they have not been studied in ASD with the precision that we are able to achieve. We further developed new study databases for blindly assigning de-identified individual and family research ID’s, tracking task completion for each subject, storing all data collected as part of this study, automating regular logic checks and developing data entry software that requires double-entry of all data to ensure data integrity. These databases have been linked to the high security UT Southwestern server system which provides online backup of all data and 24 hour security to prevent anyone outside of the study team from accessing subject data.

Subject recruitment: During the first six months of this award, we established procedures and relationships with community providers to support family recruitment for our study. This has involved making contact with many providers in the Dallas-Ft Worth region and speaking with them about our studies, including the best means to get our information to interested families. We also carefully developed protocols to recruit families seen in our Autism Center clinics without interfering with their clinical care. Our current enrollment (11 family trios and 7 healthy controls, or 40 subjects) is commensurate with our target rate for the year (10 family trios and 8 healthy controls, or 38 subjects). Each of these individuals has completed oculomotor, manual motor, psychological and neuropsychological testing. Our goal moving forward is to assess 5 family trios and 8-9 IQ- and age-matched healthy controls per quarter over the course of the award.
Quality assurance: The PI and Dr. Mosconi have completed quality assurance testing to ensure the integrity of sensorimotor and neurocognitive task administration and scoring. Dr. Mosconi has regularly observed neuropsychological test administrations performed by trained staff, as well as oculomotor and manual motor testing. Drs. Sweeney and Mosconi also have led weekly meetings with trained staff to ensure the quality of test administration and data analysis. Dr. Sweeney has overseen the scoring and analysis of eye movement data, and Dr. Mosconi has done the same with the manual motor testing. Dr. Vaillancourt visited UT Southwestern in May and July to examine the manual motor task administration and scoring. All clinical data collected up to this point has been double-entered into research databases.

b. New data. As we have only completed year 1 of this 3 year study, there is an insufficient number of families and controls to begin analyzing our new data. However, we previously collected data from individuals with ASD while they performed the motor tasks used in this study. This data was collected as preliminary data for our original grant proposal, and we continued to administer these tests to a large number of patients with ASD and healthy controls because initial results were so promising. Indeed, our findings from these case-control comparisons highlight significant impairments in individuals with ASD during manual motor and oculomotor control. Results from these tests have been presented at multiple scientific meetings (see “Reportable Outcomes” section below) and currently are being prepared for publication. They are as follows:

**Experiment 1: Manual motor control in individuals with ASD.**

**METHODS:** Twenty-six individuals with ASD and 26 age- and IQ-matched healthy controls performed two manual motor control tasks during which they sustained a constant grip force level in order to stabilize a visually presented white force bar at the level of a green target bar for 15 sec. To examine how motor accuracy and the complexity of force output are affected by changes in the amplitude of force output, the amplitude of the target force was varied between 5-85% of individual subjects’ maximum force contraction. To examine how changes in the precision of visual feedback affect motor control, the vertical distance the white force bar moved per Newton of force applied was varied. The precision of visual feedback was decreased by moving the force bar a smaller distance for every Newton of force applied.

**RESULTS AND CONCLUSIONS:** Subjects with ASD showed reduced force accuracy during both manual motor tasks (p’s<.001). This impairment was more robust at larger force amplitudes (Group X Amplitude interaction: p=.009), but it did not vary across different visual angles (Group X Angle interaction: p=.43). Individuals with ASD also showed reduced complexity of their force output during both the amplitude and visual feedback manipulations (p’s<.03). Again, this deficit was more severe at larger amplitudes (Group X Amplitude interaction: p=.03) but was not affected by changes in the precision of visual feedback (Group X Angle interaction: p=.12). Reduced force accuracy was associated with communication impairments in individuals with ASD.

These results provide evidence that visuomotor impairments in ASD are due to deficits in controlling motor output and are independent of the quality of visual feedback. This pattern of motor deficit implicates cerebellar lobules V-VI and Crus I/II whereas cortico-cerebellar visual feedback processing systems may be relatively spared. These results suggest that abnormalities in controlling motor output may underlie the dyspraxia that is present in the majority of individuals with this disorder.

**Experiment 2: Inhibitory control of oculomotor and manual motor responses in ASD.**

**METHODS:** We examined response inhibition in 45 individuals with ASD and 40 healthy controls matched on age (range 6-38 years) and Performance IQ. Subjects performed
manual motor and oculomotor stop-signal tasks (SST) and baseline measures of reaction time. During the SST, subjects were instructed to either press a button (manual version) or make a saccade (oculomotor version) when a peripheral target appeared ('GO' trials), or inhibit these responses when a central stop signal appeared following the appearance of the peripheral cue ('STOP' trials). We examined subjects' reaction times during both baseline and SST GO trials, as well as the rate at which they failed STOP trials (i.e., they pressed a button or looked towards the peripheral target).

RESULTS AND CONCLUSIONS: Subjects with ASD made more STOP trial errors than healthy controls on the manual motor and oculomotor SST (p’s<.05). Stop trial error rates were associated with the degree to which subjects slowed their reaction times from baseline to task GO trials, such that increased slowing was associated with fewer STOP trial errors (p<.01). Subjects with ASD did not slow their reaction times as much as controls (p<.05). Increased stop trial error rates were related to increased rates of repetitive behaviors independently ascertained via clinical observation for individuals with ASD (p<.05).

These results indicate that individuals with ASD show inhibitory control deficits that affect both manual motor and oculomotor systems. Both of these deficits appear to reflect a reduced ability to strategically slow reaction times to enhance the ability to suppress unwanted or context inappropriate responses. These findings suggest that the frontostriatal brain systems supporting inhibitory control are altered in ASD and may underlie the disabling repetitive behaviors that characterize this disorder.

III. KEY RESEARCH ACCOMPLISHMENTS

- Completed start up efforts including hiring and training research staff (i.e., research coordinators, computer programmers, administration staff, research psychologists), developing secure study databases, setting up laboratory experiments, establishing IRB protocols, and developing recruitment pipelines
- Initiated subject recruitment and exceeded enrollment targets for the first year of the study
- Completed data analysis on subjects with ASD performing oculomotor and manual motor tasks and presented results at multiple scientific meetings

IV: REPORTABLE OUTCOMES

Peer Reviewed Manuscripts:

Peer-reviewed Academic Presentations:


7. Sweeney JA. Clinical studies during adolescence: Autism and bipolar disorder. American College of Neuropsychopharmacology (ACNP), December 2011, Honolulu, HI.

V. CONCLUSIONS
Despite having moved to a new institution just prior to beginning this award, we have successfully maintained a pace of research progress that is consistent with that laid out in our original Statement of Work. Startup efforts are completed and we have developed strong staffing and data processing infrastructures as well as a program of referral services that has allowed us to recruit and examine 11 family trios during the first year. We also have maintained active collaborations with the consultants on this award, Drs. Daniel Corcos and David Vaillancourt, each of whom has worked directly with the study team over the past year to develop manual motor tests and help ensure the quality of this data.

Initial results from the tasks used in this study also are promising. We have found significant motor control deficits in subjects with ASD during manual motor tasks and oculomotor tasks. As the manual motor tasks used in this study had not previously been studied with subjects with ASD or their unaffected family members, this is encouraging novel data that will strongly propel the present study efforts forward as we examine how these motor abnormalities run in families with ASD.

VI. REFERENCES