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14. ABSTRACT Aim A: To determine if the immunologic bias in autism spectrum disorder (ASD) confers greater risk for co-occurring depression than severity of ASD. If depression severity is associated with increased cytokine levels (reported in non-ASD adults), this would support the notion that depression is a valid clinical syndrome within the ASD clinical phenotype, but not necessarily the same disorder as in neurotypical populations. Aim B: To determine if depression symptoms are associated with clinical features similar to previous research about depression in neurotypical adults {e.g., brain activation in response to social stress and correlation with cytokine levels and depression severity). If findings are consistent, this would support the notion that depression may be a "true" co-morbidity. Method: Participants will be men {N=SO) 18-45 years old with IQ BO and ASD diagnosis, no previous head trauma, no seizure or autoimmune disorder, and no current immunologic medication. Participants will be complete diagnostic and psychosocial assessments and a blood draw. A significant other will also complete emotion symptom measures. Individuals with low and high depression symptoms will be selected for participation the imaging phase. Functional scans will be acquired during a social acceptance/rejection task (Cyberball), followed by an exploratory hedonic reward task, Monitory Incentive Delay. The research is in progress with no results to report to date.

1S. SUBJECT TERMS

AUTISM, BRAIN IMAGING, DEPRESSION, SOCIAL REJECTION

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1. INTRODUCTION:

Background: The main reason for conducting this study is to use brain imagining technology to better understand how the immune system and environmental stressors contribute to emotional symptoms in higher functioning adults with ASD. Hypotheses: (1) Severity of ASD and emotional symptoms in participants with ASD will each be associated with an elevated systemic inflammatory state indicated by increased peripheral levels of inflammatory cytokines (e.g., IL-6, TNF-a). (2) Participants undergoing fMRI will show (a) greater dorsal anterior cingulate cortex (dACC) activation following social rejection than social acceptance, and this will be (b) differentially greater in participants with elevated versus low emotion symptoms. (3) Higher levels of inflammatory cytokines will predict higher dACC activation following social rejection versus inclusion, and this will be moderated by emotional status (i.e., relation will be stronger among those in the high versus low emotion symptom group). Exploratory hypotheses will address parallel relations using an fMRI reward anticipation task. Method: Phase 1 participants will be men (N=50) between 18 and 45 years of age with a full scale IQ≥ 80 and diagnosis of ASD, and not be receiving psychotropic medication. ASD participants will be administered ASD and emotional assessment measures and complete a blood draw. A significant other will also complete emotion symptom measures. Individuals with low and high emotion symptoms will be selected for participation the Phase 2 imaging study. Functional scans will be acquired during a social acceptance/rejection task (Cyberball), which will be followed by an exploratory hedonic reward task, Monitory Incentive Delay.

2. KEYWORDS:

autism, brain imaging, depression, social rejection

3. ACCOMPLISHMENTS:

In this report, we detail the accomplishments met on the study to date, and propose a revised SOW for a second no-cost extension (Appendix A). All objectives enumerated in the revised SOW are consistent with those in the existing approved SOW.

YEAR 1: Revised SOW

What were the major goals of the project for Year 1?

Aim #1: Obtain Institution Review Board (IRB) approval for DOD application

1a. Task: Obtain IRB approval Responsible personnel: Dr. Gadow Milestone: IRB approval secured
SOW Timeline: Prior to award Week 0 (9/30/2014)
Actual Completion Date: 4/17/2014

1b. Task: Submit IRB DOD amendment to existing IRB approval
Responsible personnel: Dr. Gadow
Milestone: Complete and submit IRB amendment
SOW Timeline: Weeks 1-4 (10/7/2014 -10/28/2014)
Actual Completion Date: 7/28/2014

1c.Task: Obtain IRB amendment approval
Responsible personnel: Dr. Gadow
Milestone: Complete and submit revised IRB forms SOW Timeline: Weeks 4-6 (10/28/2014 - 11/11/2014) Actual Completion Date: 7/31/2014

Aim #2: Prepare for subject recruitment

2. Task: Prepare subject recruitment materials Responsible personnel: Dr. Gadow, Coordinator
Milestones: Solicitation lists, advertisements
SOW Timeline: Weeks 6-11 (11/11/2014- 12/16/2014) Actual Completion Date: 8/1/2014; 2/23/2015

Aim # 3: Recruitment, data collection, and data processing for Phase 1

3a. Task: Recruitment of first block of 28 Phase 1 participants Responsible personnel: Dr. Gadow, Coordinator Milestone: Initiate participant solicitation
SOW Timeline: Weeks 12-52 (12/23/2014- 9/30/2015)

% of Milestone Complete: 86% (Please see below for details and revised timeline)

3b. Task: Collect psychosocial data
Responsible personnel: Dr. Gadow, Dr. Lerner, Dr. Sprafkin, Coordinator Milestones: Administer diagnostic and psychosocial measures, collect blood samples SOW Timeline: Weeks 12-52 (12/23/2014- 9/30/2015)·
% of Milestone Complete: 0% (Please see below for details and revised timeline)

3c. Task: Record and enter diagnostic and psychosocial data Responsible personnel: Dr. Gadow, Dr. Lerner, Coordinator Milestones: Score assessment measures and enter data for analyses SOW Timeline: Weeks 12-52 (12/23/2014- 9/30/2015)
% of Milestone Complete: 0% (Please see below for details and revised timeline)

3d. Task: Collecting, storing, and processing Phase 1 immunologic data
Responsible personnel: Dr. Trujillo
Milestones: Collect and properly store blood samples
SOW Timeline: Weeks 12-52 (12/23/2014- 9/30/2015)
% of Milestone Complete: 0% (Please see below for details and revised timeline)

Aim # 4: Recruitment, data collection, and data processing for Phase 2

4a. Task: Recruitment of first block of 17 Phase 2 participants
Responsible personnel: Dr. Gadow, Dr. Lerner, Dr. DeLorenzo, Coordinator
Milestone: Initiate participant solicitation
SOW Timeline: Weeks 12-52 (12/23/2014- 9/30/2015)
% of Milestone Complete: 0% Please see below for details and revised timeline)

4b. Task: Conduct fMRI
Responsible personnel: Dr. Gadow, Dr. Lerner, Dr. DeLorenzo, Coordinator
Milestone: Conduct fMRis
SOW Timeline: Weeks 12-52 (12/23/2014- 9/30/2015)
% of Milestone Complete: 0% (Please see below for details and revised timeline)

4c. Task: Storing and processing Phase 2 fMRI data
Responsible personnel: Dr. DeLorenzo
Milestones: Storing and initial processing fMRI data Weeks 12-52
SOW Timeline: Weeks 12-52 (12/23/2014- 9/30/2015)
% of Milestone Complete: 0% (Please see below for details and revised timeline)

What was accomplished under these goals for Year 1?

Aim #1: Obtain Institution Review Board (IRB) approval for DOD application

IRB approval at each step was secured well ahead of SOW timelines. Additionally, IRB renewal was required within this reporting period. Continuing Review materials were submitted to IRB on 2/23/2015, and approved on 5/5/2015; approval of Continuing Review was then submitted to USAMRMC ORP HRPO on 5/8/2015, and was acknowledged on 5/11/2015.

Aim #2: Prepare for subject recruitment

IRB-approved web postings and recruitment materials were disseminated upon amendment approval (i.e., 8/1/2014). A revised advertisement was submitted to IRB in Continuing Review (2/23/2015), which contains more information about the purpose and procedures of the study than original advertisement and updated telephone contact for the Coordinator. Upon IRB approval of the revised advertisement (5/5/2015), this new material was disseminated.
While these dates note specifically the preparation of subject materials, distribution efforts have been ongoing since 8/1/2014. As indicated in the IRB application, the primary recruitment method for this study is the distribution of approved recruitment materials via local clinical facilities, organizations, and individual providers who support this project, to target the ASD population, as opposed to disseminating recruitment materials to the public more broadly. Thus, our efforts on this task have focused on building and maintaining relationships with and providing recruitment

materials to local clinical contacts that have a combined reach of 200+ adult HFASD males. See Aim 3 below for preliminary yield.

Aim# 3: Recruitment, data collection, and data processing for Phase 1

3a.Milestones: Initiate participant solicitation
3b. Milestones: Administer diagnostic and psychosocial measures, collect blood samples
3c. Milestones: Score assessment measures and enter data for analyses
3d. Milestone: Collect, store, and process Phase 1 blood samples

Progress to Date: Recruitment efforts to date have yielded a pool of 24 prospective participants who have met preliminary screening criteria (e.g., existing diagnosis of HFASD, male) and have provided contact information, requesting to be contacted to enroll in the study. Additionally, PI Dr. Gadow, Co-I Dr. Lerner, and Coordinator have approval to hold informational tables advertising this study and other research participation opportunities of the PI Dr. Gadow and Co-I Dr. Lerner at two relevant local conferences: 1. Asperger Syndrome & High Functioning Autism Association's Fall Conference;10/24/2015; attendees include educators, clinicians and administrators who work with ASD, as well as individuals with ASD and parents of individuals with ASD.2. Meeting of the Minds Symposium on Autism Spectrum Disorders hosted by Stony Brook University Neurosciences Institute; 10/30/2015; open to all physicians, nurses, researchers, students and other healthcare professionals or caregivers with an interest in autism spectrum disorders, open to the public.

No subject was consented or enrolled in the full. As described in greater detail in Section 5 of this report and the supporting Appendices, data collection for the imaging phase of the study was delayed due to difficulties with the scanner. In order to (a) ensure that diagnostic and psychosocial data and blood samples from Phase 1 are collected temporally close enough to imaging data in Phase 2 to be confidently incorporated in the planned statistical analyses, and (b) not unduly risk attrition between Phase 1 and 2, we chose to hold off on Phase 1 data collection until scanner issues were resolved and Phase 2 data collection is imminent.

Aim # 4: Recruitment, data collection, and data processing for Phase 2

As described in greater detail in Section 5 of this report and the supporting Appendices, data collection for the imaging phase of the study were delayed due to difficulties with the scanner. Please see Appendix A: Revised SOW for the timeline to complete this Aim.

YEAR 2: Revised SOW

What were the major goals of the project for Year 2?

Aim # 3: Recruitment, data collection, and data processing for Phase 1

3a.Task: Recruitment of first block of 10 Phase 1 participants
Responsible personnel: Dr. Gadow, Coordinator
Milestone: Continue participant solicitation
Timeline: Weeks 1-34 (10/1/2015 – 6/1/2016)

3b. Task: Collect psychosocial data
Responsible personnel: Dr. Gadow, Coordinator
Milestones: Administer diagnostic and psychosocial measures, collect blood samples
Timeline: Weeks 34-52 (6/1/2016 – 9/30/2016)

3c. Task: Record and enter diagnostic and psychosocial data
Responsible personnel: Dr. Gadow, Coordinator
Milestones: Score assessment measures and enter data for analyses
Timeline: Weeks 34-52 (6/1/2016 – 9/30/2016)

3d. Task: Collecting and storing Phase 1 immunologic data
Responsible personnel: Dr. Gadow, Coordinator
Milestones: Collect and properly store blood samples
Timeline: Weeks 34-52 (6/1/2016 – 9/30/2016)

Aim # 4: Recruitment, data collection, and data processing for Phase 2

4a. Task: Recruitment of first block of 3 Phase 2 participants
Responsible personnel: Dr. Gadow, Dr. DeLorenzo, Coordinator
Milestone: Initiate participant solicitation
Timeline: Weeks 39-52 (7/1/2015 – 9/30/2016)

4b. Task: Conduct fMRI
Responsible personnel: Dr. Gadow, Dr. DeLorenzo, Coordinator
Milestone: Conduct fMRIs
Timeline: Weeks 39-52 (7/1/2015 – 9/30/2016)

4c. Task: Storing and processing Phase 2 fMRI data
Responsible personnel: Dr. DeLorenzo
Milestones and timeline: Storing and initial processing fMRI data Weeks 39-52 (7/1/2015 – 9/30/2016)

What was accomplished under these goals for Year 2?

Aim# 3: Recruitment, data collection, and data processing for Phase 1

3a.Milestones: Initiate participant solicitation
3b. Milestones: Administer diagnostic and psychosocial measures, collect blood samples
3c. Milestones: Score assessment measures and enter data for analyses
3d. Milestone: Collect, store, and process Phase 1 blood samples

Progress to Date: Recruitment efforts to date have yielded a pool of 70 prospective participants to date who have met preliminary screening criteria (e.g., existing diagnosis of HFASD) and have provided contact information, requesting to be contacted to enroll in the study. Additionally, PI Dr. Gadow, Co-I Dr. Lerner, and Coordinator have approval to hold informational tables advertising this study and other research participation opportunities of the PI Dr. Gadow and Co-I Dr. Lerner at two relevant local conferences: 1. Asperger Syndrome & High Functioning Autism Association's Fall Conference; 10/15/2016; attendees include educators, clinicians and administrators who work with ASD, as well as individuals with ASD and parents of individuals with ASD.

Five subjects have consented to and enrolled in Phase 1 of the study to date. As described in greater detail in Section 5 of this report and the supporting Appendices, data collection for the imaging phase of the study was previously delayed due to difficulties with the scanner. In order to (a) ensure that diagnostic and psychosocial data and blood samples from Phase 1 are collected temporally close enough to imaging data in Phase 2 to be confidently incorporated in the planned statistical analyses, and (b) not unduly risk attrition between Phase 1 and 2, we chose to hold off on Phase 1 data collection until scanner issues were resolved and Phase 2 data collection was imminent.

Aim # 4: Recruitment, data collection, and data processing for Phase 2

Two date one participant successfully completed the Phase 2 scan, and a second participant completed the scan 10/12/16. Please see Appendix A: Revised SOW for the timeline to complete this Aim.

YEAR 3: Revised SOW

What were the major goals of the project for Year 3?

Aim # 3: Recruitment, data collection, and data processing for Phase 1

3a.Task: Recruitment of first block of Phase 1 participants
Responsible personnel: Dr. Gadow, Coordinator
Milestone: Continue participant solicitation
Timeline: Weeks 1-34 (10/1/2016 – 6/1/2017)

3b. Task: Collect psychosocial data
Responsible personnel: Dr. Gadow, Coordinator
Milestones: Administer diagnostic and psychosocial measures, collect blood samples

Timeline: Weeks 34-52 (6/1/2017 – 9/30/2017)

3c. Task: Record and enter diagnostic and psychosocial data
Responsible personnel: Dr. Gadow, Coordinator
Milestones: Score assessment measures and enter data for analyses
Timeline: Weeks 34-52 (6/1/2017 – 9/30/2017)

3d. Task: Collecting and storing Phase 1 immunologic data
Responsible personnel: Dr. Gadow, Coordinator
Milestones: Collect and properly store blood samples
Timeline: Weeks 34-52 (6/1/2017 – 9/30/2017)

Aim # 4: Recruitment, data collection, and data processing for Phase 2

4a. Task: Recruitment of first block of 3 Phase 2 participants
Responsible personnel: Dr. Gadow, Dr. DeLorenzo, Coordinator
Milestone: Initiate participant solicitation
Timeline: Weeks 39-52 (7/1/2016 – 9/30/2017)

4b. Task: Conduct fMRI
Responsible personnel: Dr. Gadow, Dr. DeLorenzo, Coordinator
Milestone: Conduct fMRIs
Timeline: Weeks 39-52 (7/1/2016 – 9/30/2017)

4c. Task: Storing and processing Phase 2 fMRI data
Responsible personnel: Dr. DeLorenzo
Milestones and timeline: Storing and initial processing fMRI data Weeks 39-52 (7/1/2016–9/30/2017)

What was accomplished under these goals for Year 3?

Aim# 3: Recruitment, data collection, and data processing for Phase 1

3a.Milestones: Initiate participant solicitation
3b. Milestones: Administer diagnostic and psychosocial measures, collect blood samples
3c. Milestones: Score assessment measures and enter data for analyses
3d. Milestone: Collect, store, and process Phase 1 blood samples

Data collection for the imaging phase of the study in Year 3 was delayed in January when our IRB met but could not review our renewal application as they did not have a quorum. The renewal application was submitted on schedule. The following review slot was delayed as a result of a snowstorm. Both issues have been resolved and will not be a problem going forward. However, it was of course necessary to delay recruitment until the IRB approved the renewal.

Another delay has been the reliance on part-time nurses to be in the scanner during the scan. This issue is being resolved by the Hospital's hiring a dedicated fulltime nurse for the scanner. This has been resolved as the post is now filled. We continued to conduct new Phase One evaluations while we were waiting for the new hire.

I have been able to recruit three students, one of whom is a PhD candidate in neuropsychology, and all have been well-trained over the past ten months. My PhD candidate will be with me for the next two and half years and is a highly capable Project Coordinator.

We have made good progress in conducting preliminary analyses of our Phase One data, and our preliminary efforts to set up the pipeline for our fMRI data analyses are well underway.

We are actively collaborating with colleagues in CUBIT who are also conducting studies on the same scanner, and moving forward we will be able to conduct analyses comparing scan data from their subjects with our sample. In sum, the project is doing well with a high probability of success as all the technical issues associated with a new scanner have clearly been resolved as the data generated are exactly what we have expected in terms of quality and validity. Furthermore, the resolution of the staff issue is already nearing completion.

Twenty three participants have consented to and enrolled in Phase 1 of the study to date. An additional three participants are scheduled for Phase 1 evaluations in October 2017 (10-17-17, 10-19-17, 10-20-17).

Aim # 4: Recruitment, data collection, and data processing for Phase 2

Two date nine participants successfully completed the Phase 2 scan, and a tenth participant completed the scan 10/5/17. An additional four participants are currently scheduled for scans in November 2017and they are scheduled for 11-3-17, 11-14-17, 11-20-17, 11-22-17. Please see Appendix A: Revised SOW for the timeline to complete this Aim.

What was accomplished under these goals for Year 4

We have made excellent progress in conducting preliminary analyses of our Phase One data (which are described below), and our preliminary efforts to set up the pipeline for our fMRI data analyses are well underway.

We are actively collaborating with colleagues in CUBIT who are also conducting studies on the same scanner and performing analyses comparing scan data from their subjects with our sample. **To date, Co-I Dr. Lorenzo has evaluated 18 male adults with major depressive disorder on the same scanner and also collected data on important measures relevant to this study. In addition to the obvious economies of scale, this will be a huge asset in our bid for follow-up, large-scale grant funding which is the desired outcome for this DoD Pilot Award.** In sum, Phase I of the project went well considering the initial issues with the scanner that were all successfully resolved generating data that are exactly what we expected in terms of quality and validity. Thirty-four participants with HFA consented to and enrolled in Phase 1 of the study.

Aim# 3: Recruitment, data collection, and data processing for Phase 1:

3a. Milestones: Completed all participant solicitation

3b. Milestones: Completed administration of all diagnostic and psychosocial measures; collected required blood samples

3c. Milestones: Completed all scoring of assessment measures and entered all data for analyses

3d. Milestone: Collected, stored, and processed all Phase 1 blood samples

Aim # 4: Recruitment, data collection, and data processing for Phase 2

Data collection for Phase 2 (the imaging phase of the study) in Year 4 was delayed in January when our IRB met but could not review our renewal application as they did not have a quorum. The renewal application was submitted on schedule. The following review slot was delayed as a result of a snowstorm. Both issues were resolved and were not be a problem going forward. However, it was of course necessary to delay recruitment until the IRB approved the renewal. Nineteen participants successfully completed the Phase 2 MRI scan.

FINDINGS TO DATE FROM ONGOING DATA ANALYSES

INTRODUCTION

The final scan was completed in August 2018, and data entry was completed at the end of September 2018. Presented here are our initial results for the full sample of HFA as well as preliminary analyses completed December 2017 for a subsample of participants with HFA. We were able to conduct preliminary analyses of a subsample our adults with HFA and with a subsample of adults with diagnosed major depressive disorder (MDD) who were participating in Dr. Christine DeLorenzo's NIMH-funded treatment study (*Advancing Personalized Antidepressant Treatment Using PET/MRI*) and who were undergoing brain scan on the same MRI scanner using some of the same sequences.

Owing to the limited amount of time between the completion of the last participant and the submission of the Final Report, our findings for the full sample are confined largely to descriptive statistics and measures of association. Nevertheless, these results clearly point the direction for future data analyses, posters at scientific meetings, and journal articles as well as future grant submissions consistent with the objectives of this USAMRMC pilot grant awards. **To this end, the investigators have already submitted one grant application (February 2018) and one letter of intent (July 2018) based in part on this research, one to NIMH (PI: K.D. Gadow; Title: *Neuro-Imaging Model of Depression in Autism Using Multimodal, Simultaneous PET/MR*; Application #: 1 R01 MH118493-**

01) and a second to the Department of Defense (PI: K.D. Gadow; Title: *Multi-modal Brain Imaging of Depression in Autism*; Log Number: AR180080). Future grant submissions based in part on these findings are currently underway.

In addition to the results reported here, there are two important data analysis objectives in progress. The first pertains to cytokine levels based on blood samples collected at baseline as well as on the day of the scan. For methodological reasons, all samples were analyzed at the same time and with the same ELISA Kit. The second are the analyses of the data from our Cyberball and MID tasks. Plans are currently underway for these data analyses to be conducted by our colleague Johanna Jarcho, a recognized authority on fMRI research.

During the coming months, the entire research team, which is currently collaborating on revisions of our earlier NIMH and DoD grant submissions, will be working on a number of additional conference presentations and journal articles.

DESCRIPTION OF HFA SAMPLE (PHASE 1)

Baseline behavioral data for HFA participants are presented in Table 1. The highest rates if impairing co-occurring psychiatric symptoms were for anxiety disorders and attention-deficit/hyperactivity disorder (ADHD) (Table 2).[10-12]

Laboratory Measures

Laboratory measures assessed six blood-based variables: thyroid stimulating hormone (TSH) and free thyroxine (T4), C-reactive protein (CRP), serotonin (whole blood), prolactin, and creatine (Table 1).

Thyroid stimulating hormone (TSH) and free thyroxine (T4). Free T4 correlated with Ham-Anxiety scores (n=22, r=-.43, p=.047).

C-Reactive Protein (CRP). CRP was negatively correlated with High Sensitivity Personality Scale scores (n=27, r=-.51, p=.007) suggesting a relation between peripheral measures of inflammation and sensory processing sensitivity.

Serotonin (whole blood). Serotonin was negatively associated with SRS-2 Motivation subscale (n=24, r=-.45, p=.027).

Prolactin. Prolactin was negatively correlated with ADOS-2 Classification (n=29, r=-.38, p=.043) and ADOS-2 Social Affect subscale (n=29, r=-.42, p=.025).

Creatine. No significant correlations.

Summary. Collectively these findings support an interrelation of various laboratory measures with ASD, anxiety, and social motivation constructs.

IQ

There were positive correlations between Kaufman Brief Intelligence Test, Second Edition (KBIT-2) and STAI severity (r= .415, p= .025) and BDI severity (r= .447, p= .015). Hamilton depressive inventory (HAM-D) severity was positively correlated with KBIT scores, for scanned participants only (r= .523, p= .031, n = 17). Nonverbal IQ positively correlated with severity of social communication questionnaire scores (SCQ; r= .455, p= .050) and social anhedonia severity (Revised Social Anhedonia Scale RSAS; r= .373, p= .042).

BRAIN SCAN PRELIMINARY FINDINGS FOF HFA SAMPLE (PHASE 2)

^{1}H-Magnetic Resonance Spectroscopy (Proton MRS)

MRS is an imaging technique used to determine the relative concentrations of a variety of brain *metabolites* based on their different resonance frequencies (chemical shift). H-MRS data were acquired with a 3T scanner for the several metabolites including gamma-aminobutyric acid (GABA), glutamate-glutamine (Glx), creatine (Cr), choline (Cho), and N-acetyl aspartate (NAA) for 16 HFA participants.

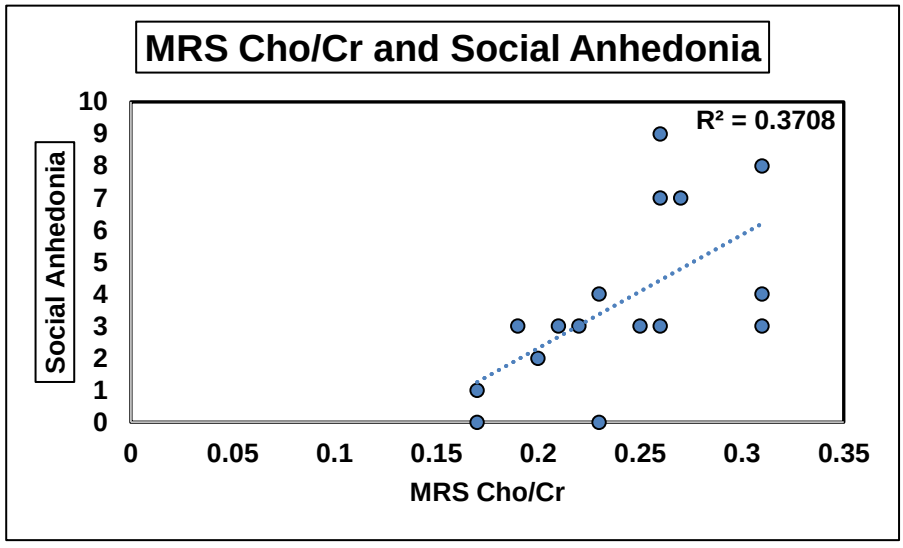
Glutamate-glutamine (Glx). Using J-editing MRS or other techniques at 3T clinical MR magnet, it is feasible to measure levels of glutamate/glutamine (Glx) and γ-aminobutyric acid (GABA), the chief excitatory and inhibitory neurotransmitters, respectively, in the mammalian CNS. Dysregulation of these neurotransmitter systems figure prominently in current models of ASD[17,22] and MDD.[59,122-124] Because glutamate and glutamine share structural and neurochemical similarities and therefore have similar and overlapping MR spectrum, it is difficult to isolate in 3T and commonly treated as one combined variable (Glx). It is noteworthy that inflammatory processes influence glial glutamate regulation.[19] Meta-analyses of MRS studies reveal decreased levels of Glx in several brain regions, including the ACC, in ASD[17,22] and in MDD,[59] compared with typically developing individuals. Similarly, both populations evidence decreased levels of GABA[17,59,60,123,124] in the ACC. It is noteworthy that inflammatory processes enhance the release of Glx/GABA from glial cells adversely affecting synaptic integrity and loss,[19] potentially impacting the relation between brain function and clinically important symptoms.

In the full HFA sample, Glx was positively correlated with rumination severity (Ruminative Response Scale; r= .552, p= .033) and lifetime antidepressant use (r= .710, p= .003).

Gamma-aminobutyric acid (GABA). In the full sample, GABA concentration was correlated with severity of Beck Depressive Inventory scores (BDI-2, r = .513, p =.042) and severity of State-Trait Anxiety Inventory scores (STAI; r= .557, p= .025).

Creatine (Cr). In the full sample, Cr was positively correlated with Glx (r = .555, p =.026). Cr was negatively correlated with severity score of the Social Affect domain of the Autism Diagnostic Schedule-2 (ADOS-2; r = -.615, p =.011), and the total raw scores on the ADOS-2 (r = -.558, p =.025).

Choline (Cho). In the full HFA sample, after controlling for ASD severity there was a positive correlation between choline levels and severity of social anhedonia (r= .548, p= .034), and rumination (r= .560, p= .037). Choline was associated with depression after controlling for ASD severity (r= .621, p= .018).Cho was also positively correlated with non-verbal IQ scores (r= .5467, p= .022), severity of communication scores from the Social Responsive Scale (SRS communication; r= .567, p= .022), severity of mannerism scores from the SRS (SRS mannerisms; r= .694, p= .003), severity of STAI scores (r= .553, p= .026), and severity of social communication questionnaire scores (SCQ; r= .609, p= .047).



Cho/Cr positively correlated with nonverbal IQ (r =.645, p = .007), social anhedonia (RSAS; r = .632, p =. 009) (FIGURE), SRS total, awareness, cognition, communication and manner (r <.504, p <.05).

N-acetylaspartate (NAA). NAA is synthesized exclusively in the mitochondria of neurons, is a marker of neuronal viability (neuronal loss, axon damage) and mitochondrial dysfunction,[54] and it has consistently demonstrated to be decreased in the ACC of ASD across the age span[22,55-57] as well as in MDD.[58] Analyses involving the full sample fount that NAA was positively correlated with rumination severity (Ruminative Response Scale; r= .594, p= .020).

Cerebral Blood Flow (Perfusion; Arterial Spin Labeling)

Arterial spin labeling (ASL) is an MRI technique that measures blood flow (tissue perfusion) by using magnetically-labelled arterial blood water protons as an endogenous tracer. Research indicates reduced perfusion in ASD in several brain regions including the ACC,[16] and the same is true for MDD.[62,63] It has been suggested that hypo-perfusion may contribute to depressive symptoms by adversely affecting brain circuits involved in emotion regulation.[61]

HFA with and without depression. Preliminary analyses involving a subset of the final sample indicated HFA/depression group differences for ASL. When we divided our HFA sample (*n*=8) according to median split on BDI-II scores into higher versus lower depression severity groups, the higher depression group evidenced lower perfusion in the ACC (*t* =3.394, *p*=.015), thus supporting the potential value of ASL for differential diagnosis and as a biomarker within the ASD clinical phenotype. These results are illustrated in FIGURE with a representative image for a non-depressed participant (second lowest CBF) and for a depressed participant (second highest CBF). In other words, these two individuals were closest to the mean value for each group.

The extant literature and our own preliminary analyses support diagnostic group differentiation with CBF. **If our CBF finding holds for the completed HFA sample (HFA+D<HFA/-D), this would be the first report linking CBF and depression *in vivo* in ASD.** Microglia-blood vessel interactions in other CNS disorders[137,138] suggest CNS inflammation *may* be a mediator of relations between brain function and symptoms.

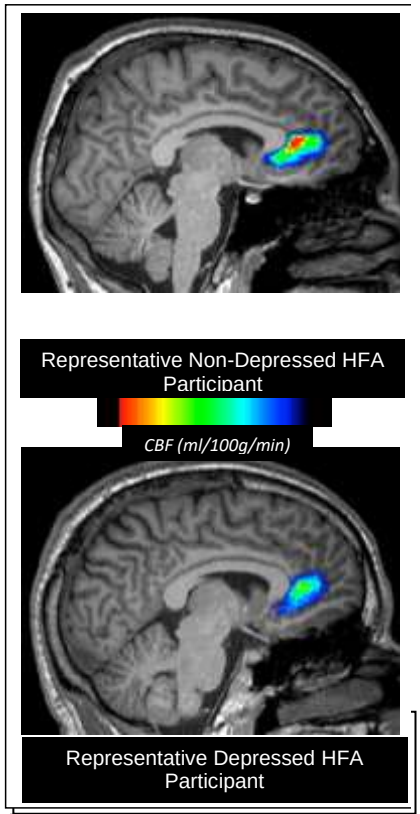


Fig. 7: Cerebral blood flow in the ACC for a representative high vs. low depression adult with HFA.

Analyses for full sample. There was one significant finding between ASL and MRS. Perfusion in the right caudal anterior cingulate cortex was negatively correlated with GABA levels (*r*=-.56, *p*=.038).

Associations with behavioral phenotypes indicated profusion in the right rostral anterior cingulate cortex was positively correlated with rumination severity (*r*=.57, *p*=.025), and the right caudal anterior cingulate cortex was positively correlated with severity of communication scores of the Social Responsive Scale (SRS communication; *r*=.495, *p*=.05). Other ASL findings include marginal correlations between ASL regions including left caudal anterior cingulate cortex and Beck Depressive Inventory (BDI-2, *r*=-.44, *p* =.087) and the left rostral anterior cingulate cortex was positively correlated with peripheral serotonin levels (*r*=.510, *p*=.052).

Functional Connectivity between Brain Regions (Resting-State Functional MRI; rsfMRI)

Resting-state fMRI (rsfMRI) is a brain imaging technique used to assess functional connectivity between brain regions by measuring inter-correlation of time courses of blood-oxygen-level dependent (BOLD) signals when the participant is not engaged in any task other than being restfully awake. The standard method for constructing a functional network is a seed-based approach where a region of interest (ROI) is selected as the *seed*. The averaged time courses of BOLD signals on voxels within the seed are used as a regressor to identify other brain regions with significant resting-state functional connectivity (rs-FC) with the seed. Using this technique, rs-FC in some brain networks have been found to be of considerable interest for understanding neuropsychiatric syndromes. The rs-FC in a so-called default mode network (DMN)[125]—encompassing precuneus (PrC), rACC, dorsomedial prefrontal cortex (dmPFC) and adjacent regions (the hot-color regions in the left panel of FIGURE)—is found to be altered in both ASD[64,65,126,129] and MDD.[66] ASD is associated with altered rs-FC related to PrC and dmPFC, and the alterations are related to the deficits in social functions.[93]

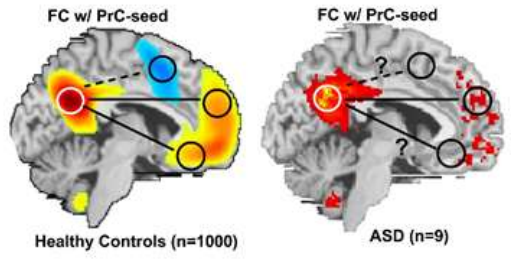


Fig. 8: rs-FC with PrC in TD (left) and ASD/HFA (right)

<u>HFA vs. typically developing</u>. Preliminary analyses involving a subsample participants suggest that the rs-FC with PrC is diminished in rACC and supplementary motor area (SMA) in our sample of HFA (*n*=9), as compared to the positive coupling between PrC-rACC (hot color) and negative coupling in PrC-SMA (cold color) in a large sample of TD controls (*n*=1000), available publicly on Neurosynth.org (FIGURE 8).

<u>HFA and the default mode network</u>. Because a meta-analysis in 187 neuroimaging studies of ASD implicated the dorsomedial prefrontal cortex (dmPFC) as a hotspot commonly reported to be altered in ASD (http://www.neurosynth.org/analyses/terms/autism), we examined the rs-FC with this ASD-hotspot.

Our preliminary analyses suggest that the rs-FC with the dmPFC is diminished in SMA in our ASD sample (*n*=9), as compared to the negative coupling in dmPFC-SMA in the sample of TD controls (n=1000) (FIGURE 9).

Further, the dmPFC-SMA and dmPFC-rACC rs-FC were inversely associated with social anhedonia scores (p=0.002 & p<0.001). Because the rACC mediates hedonic responses, and the SMA mediates cognitive monitoring of reality, and dmPFC, rACC, SMA, and PrC are all closely related to social cognition,[94] these findings have important implications for ASD. For example, the extant research indicates altered functional connectivity between brain regions in the DMN appears to be diagnosis-specific.

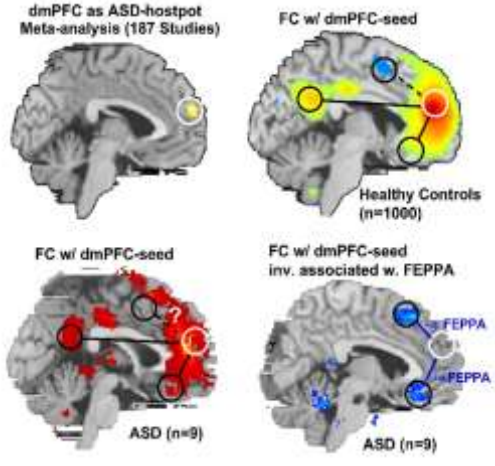
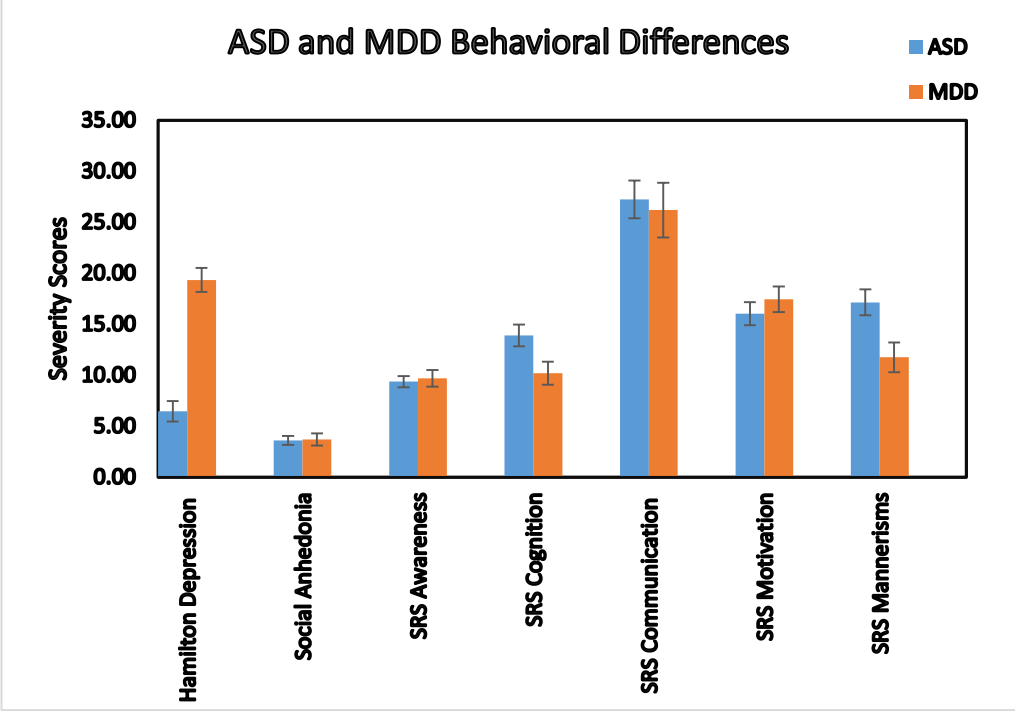


Fig. 9: rs-FC with dmPFC. The dmPFC as the seed (upper left). rs-FC in TD (upper right) and ASD/HFA (lower left). Inverse association w. FEPPA.

COMPARISON OF ASD AND MDD SAMPLES

As indicated in our grant proposal, one of the advantages of conducting this study at Stony Brook University was the opportunity to collaborate with other labs and in so going gain access to data from other relevant samples. This this end, we were able to compare our HFA sample with Dr. Christine DeLorenzo's sample of adults with diagnosed major depressive disorder (MDD) who were participating in an NIMH-funded treatment study (*Advancing Personalized Antidepressant Treatment Using PET/MRI*) and who were undergoing brain scan on the same MRI scanner using some of the same brain sequences (MRS, ASL). A total of 18 adult males between the ages of 18 and 45 years have participated in Dr. Lorenzo's study to date, all of whom meet SCID diagnoses for MDD. By design, the MDD sample was assessed with the Social Responsiveness Scale (SRS-2) of autism symptoms, Revised Social Anhedonia Scale (RSAS), and Hamilton Depression Scale (HAM-D) (Table 3).

Behavioral Measures



Our preliminary indicate that the HFA sample exhibited more severe ASD symptomatology than the MDD sample for two SRS-2 subscales: Cognition (t=2.30, p=.026) and Mannerisms (t=2.64, p=.011) (FIGURE). Interestingly, both samples were not dissimilar on any other subscales or for the SRS-2 Total score (p=.324). As expected, the MDD sample exhibited more severe depression (HAM-D) than the HFA group (t=-8.33, p=.000). It is noteworthy that both groups exhibited comparable levels of social anhedonia as assessed with the RSAS (t=-0.19, p=.853). ***We consider this to be an important finding that has considerable implications for understanding the differential validity of MDD and social anhedonia as behavioral phenotypes among HFA***.

Magnetic Resonance Spectroscopy (MRS)

MRS data for Glx and GABA were available for both HFA and MDD samples. In the full sample of HFA and MDD, there were higher levels of Glx in the HFA sample (t=3.43, p=.002) than the MDD group, raising the possibility of differential levels in HFA+D vs. HFA/-D**.** This will be a topic of future analyses. Our model posits lower levels of glutamate in HFA than TD, suggesting that the glutamate suppression effect may be greater in MDD than HFA, raising the possibility of differential levels in HFA+D vs. HFA/-D. There were no significant HFA-MDD group differences among the full sample for GABA (p=.169).

Arterial Spin Labeling

Our preliminary analyses for subsamples of HFA and MDD found significantly lower CBF in our HFA (*n*=8) versus MDD (*n*=7) samples for several brain regions including the cingulate (*p*=.03) and the dorsolateral

prefrontal cortex (*p*=.009).

Diffusion MRI Connectometry (Using Diffusion Spectrum Imaging)

Diffusion MRI data were acquired using the same diffusion spectrum imaging protocol: bmax = 4000, 4 spherical b shells, spatial resolution = 2x2x2 mm^3. Diffusion MRI connectometry (Yeh et al., NeuroImage 125 (2016): 162-171) was used to study the diffusion difference between the ASD group and the MDD group. A multiple regression model was used to consider, group, age, and Ham-D score in a total of 22 subjects. A T-score threshold of 3 was assigned to select local connectomes, and the local connectomes were tracked using a deterministic fiber tracking algorithm (Yeh et al., PLOS One (8(11):e80713, 2013). The tracking algorithm used right ACC as the region of interest. The connectometry analysis identified decreased connectivity in ASD group in the corpus callosum, right cingulum, and right cortico striatal pathway (FDR=0.012) (FIGURE).

Using a whole brain analysis with the same data, the connectometry analysis identified decreased connectivity in the ASD group in the corpus callosum, right corticothalamic pathway, right cortico striatal pathway, left corticothalamic pathway, and left corticothalamic pathway (FDR=0.014).

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Table 1: Descriptive Characteristics of Phase 1 Study Sample

Characteristic	ASD (*n*=31)
DEMOGRAPHICS	
Age (*M*/*SD*)	25.2 (6.9)
Gender (*Males*; F/%)	31 (100%)
Ethnicity (*White/Caucasian*; F/%)	27 (87.1%)
Level of education	
Some High School (F/%)	2 (6.5)
High school diploma (F/%)	4 (12.9%)
Some college (F/%)	13 (41.9%)
College degree (F/%)	11 (35.5%)
Master's degree (F/%)	1 (3.2%)
COGNITIVE	
IQ (KBIT)	
Verbal (*M/SD*)	107 (16.1)
Non-Verbal (*M/SD*)	105.9 (14.1)
Composite (*M/SD*)	107.3 (16)
Trail Making (M/SD)	
Item 1 (*M/SD*)	28.9 (16.3)
Item 2 (*M/SD*)	61.7 (41.4)
Item 1: Faster than average (F/%)	20 (66.7%)
Item 1: Slower than average (F/%)	10 (33.3%)
Item 2: Faster than average (F/%)	22 (75.9%)
Item 2: Slower than average (F/%)	7 (24.1%)
ASD	
ADOS-2	
ADOS-2 Dx (Yes; F/%)	31 (100%)
ADOS-2 SA (*M*/SD)	10 (2.6)
ADOS-2 RRB (M/SD)	3.3 (1.5)
ADOS-2 Total (M/SD)	13.3 (3.5)
ADOS2-CSS (M/SD)	7.2 (1.9)
ADOS-2 CSS Level	
CSS Low (F/%)	3 (9.7%)
CSS Moderate (F/%)	14 (45.2%)
CSS High (F/%)	14 (45.2%)
SRS	
Total score (M/SD)	83.7 (28.3)

LAB MEASURES	
TSH	
TSH	1.8 (.8)
TSH-T4	1.2 (.2)
TSH/TSH-T4 (M/SD)	.8 (.4)
Creatine (M/SD)	.8 (.1)
Prolactin (M/SD)	9.5 (4.5)
C Reative Protein (M/SD)	4.5 (7.6)
Serotonin (whole blood; M/SD)	111 (88.8)
Drug screen positive (*Yes;* F/%)	2 (6.5%)
PSTCHIATRIC SYMPTOMS	
HAM-D (M/MD)	6.45 (4.7)
BDI-II (M/MD)	14.1 (9.9)
Rumination (M/SD)	48.5 (11.5)
Social Anhedonia Scale Rev. (M/SD)	3.6 (2.5)
HAM-A	7.18 (5.5)
State Trait Anxiety Inventory (M/SD)	86.3 (21.8)

Table 2: Number (%) With T Score >70 and above Impairment Cutoff for the Adult Self Report Inventory-4R

Characteristic	T>70 (*n*=30)	Impairment (*n*=30)
Generalized anxiety disorder (F/%)	7 (23.3%)	9 (30%)
Social phobia	9 (30%)	8 (26.7%)
Schizoid personality	10 (33%)	6 (20%)
Somatosensory	0 (0%)	1 (3.3%)
Post-Traumatic Stress Disorder	6 (20%)	2 (6.7%)
Anorexia	5 (16.7%)	0 (0%)
Bulimia	3 (10%)	1 (3.4%)
Depression		9 (30%)
Major Depressive Disorder	12 (40%)	
Dysthymic disorder	14 (46.7%)	
Manic episode	4 (13.3%)	4 (13.8%)
ADHD	10 (33.3%)	11 (36.7%)
Inattention	9 (30%)	
Hyper-impulsivity	5 (16.7%)	
Oppositional defiant disorder	4 (13.3%)	6 (20%)
Conduct Disorder and AntiSoc	0 (0%)	0 (0%)
Conduct Disorder	0 (0%)	0 (0%)
Antisocial personality	0 (0%)	0 (0%)
Schizophrenia	4 (13.3%)	3 (10%)
Substance abuse	1 (3.3%)	1 (3.4%)
Disassociation	4 (13.3%)	
Borderline personality	3 (10%)	3 (11.5%)

Table 3: Descriptive Characteristics of ASD and MDD Study Samples

Characteristic	ASD (*n*=30)	**MDD (*n*=18)**	**Statistic**	*p*	ES
DEMOGRAPHICS					
Age (*M*/*SD*)	25.35 (6.94)	**27.22 (8.14)**	-.848[a]	.401	.24d
Gender (*Males*; F/%)	30 (100%)	18 (100%)			
ASD					
SRS (all scales)					
SRS Awareness (*M*/*SD*)	9.37 (3.06)	9.69 (3.28)	-.331[a]	.743	.10d
SRS Cognition (*M*/*SD*)	13.9 (5.8)	10.19 (4.52)	2.22a	.032*	.71d
SRS Communication (*M*/*SD*)	27.23 (10.09)	26.19 (10.75)	.327a	.745	.10d
SRS Motivation (*M*/*SD*)	16.03 (6.13)	17.44 (5.03)	-.785a	.437	.25d
SRS Mannerisms (*M*/*SD*)	17.13 (6.96)	11.75 (5.86)	2.63a	.012*	.84d
SRS total (*M*/*SD*)	83.67 (28.39)	75.65 (23.82)	.984a	.330	.30d
HAM-D (*M*/*SD*)	6.45 (4.74)	19.33 (4.97)	-8.37a	.000***	2.64[d]
Rev. Social Anhedonia (*M*/*SD*)	3.6 (2.46)	3.69 (2.39)	-.116a	.908	.04d
MRS					
GABA	1.83 (.78)	1.49 (.63)	1.41a	.169	.48d
Glx	11.25 (2.52)	8.53 (2.11)	3.43a	.002	1.17 d

NOTE: $p < .05$*, $p < .01$**, $p < .001$***.

[a] *t* test

What opportunities for training and professional development has the project provided?

- PI Dr. Gadow and Co-I Dr. Lerner have each mentored Coordinator Rebecca Weber one-on-one in data management and analytic techniques.
- Coordinator Rebecca Weber and Co-I Dr. Lerner's Clinical Psychology PhD students have participated in weekly training for the Structured Clinical Interview for DSM IV to be administered in Phase 1, for which weekly clinical supervision is ongoing (since 9/2014).
- Co-I Dr. Lerner's 2nd year Clinical Psychology PhD students have participated in ADOS-2 Introductory Clinical Training and ADOS-2 Advanced/Research Training by New York Presbyterian Center for the Developing Brain (CADS), Weill Cornell Medical College, & Columbia University Medical Center (7/2014) and successfully undergone review to be certified (12/2014, 7/2015) as research-reliable examiners for this gold-standard ASD diagnostic assessment (Autism Diagnostic Observation Schedule, 2nd edition), to be administered in Phase 1.
- Likewise, Co-I Dr. Lerner's 1st year Clinical Psychology PhD has participated in ADOS-2 Introductory Clinical Training by New York University Child Study Center (8/2015) and ADOS-2 Advanced/Research Training by Weill Cornell Medical College & CADB (10/2015), and is currently completing steps toward reliability review.

- Co-l Dr. Lerner has trained Coordinator Rebecca Weber and his Clinical Psychology PhD students in administration of the Kaufman Brief Intelligence Test, 2nd edition, to be administered in Phase 1 (7/2014).
- Coordinator Rebecca Weber has completed training and certification in Phlebotomy for Research (Adults) at Stony Brook University Hospital, which consisted of 3 hours of classroom instruction (9/2014) and 20 hours of practicum with adult inpatients and outpatients under direct supervision of Stony Brook University Hospital Phlebotomy staff (11/2014). Coordinator will be responsible for Phase 1 blood draws.

How were the results disseminated to communities of interest?

To date our research team has presented on poster and a second poster is currently under review at IMFAR. As our last participant was only scanned in August 2018, there has been limited opportunity to present our findings. This will, however, be corrected in the near future.

1. Garman, H., Whitaker-Azmitia, P.M., Gadow, K.D. Biomarkers of co-morbid anxiety and depression in Autism Spectrum Disorders. Poster presented at Society for Neuroscience Meeting. Washington DC, MD. (Nov., 2017).

2. Joseph Giacomantonio, Monika Batra, Heather Garman, Alex Mulhall, Russell Vogel, Ken Wagner, Xiang He, Kenneth D. Gadow. (Submitted November 2018). Association of Choline Levels on the Severity of Social Anhedonia in Adults with Autism Spectrum Disorder. IMFAR.

What do you plan to do during the next reporting period to accomplish the goals?

As this is the Final Report there will be no next reporting period. However, as noted above, the grant submission and publication process will continue in full swing.

4. IMPACT:

What \Vas the impact on the development of the principal discipline(s) of the project?

Nothing to Report.

What \Vas the impact on other disciplines?

Nothing to Report.

What was the impact on technology transfer?

Nothing to Report.

What was the impact on society beyond science and technology?

Nothing to Report.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change: Nothing to Report. Study has been completed.

Actual or anticipated problems or delays and actions or plans to resolve them: In Year 4 of the study a flood in the radio-chemistry laboratory and a snow storm that resulted in cancelation of a key IRB meeting delayed recruitment from January to late spring. Both issues were successfully resolved.

Changes that had a significant impact on expenditures: Nothing to Report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents: Nothing to Report.

6. PRODUCTS:

- Publications, conference papers, and presentations. The research team has presented one poster in 2017 and another poster is under review at IMFAR. However, as we have previously started, data analyses are moving forward in earnest, and there will be many products in the near future. We have submitted one grant application and one LoL based in part on our preliminary findings.

- Journal publications. Nothing to Report.

- Books or other non-periodical, one-time publications. Nothing to Report.

- Other publications, conference papers, and presentations. Nothing to Report.

- Website(s) or other Internet site(s) Nothing to Report.

- Technologies or techniques Nothing to Report.

- Inventions, patent applications, and/or licenses Nothing to Report.

- Other Products Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

1.	Name: Contribution to Project:	Kenneth D. Gadow, PhD No change.
2.	Name: Contribution to Project:	Ramin Parsey, MD, PhD No change.
3.	Name: Contribution to Project:	Christine DeLorenzo, PhD No change.
4.	Name: Contribution to Project:	Matthew Lerner, PhD No change.
5.	Name: Contribution to Project:	Patricia Whitaker-Azmitia, PhD No change.
6.	Name: Contribution to Project:	Jie Yang, PhD No change.
7.	Name: Project Role: Person months worked: Contribution to Project: Funding Support:	Glenda Trujillo, PhD Co-Investigator 0.02 Dr. Trujillo made recommendations for the assays to be used for analysis of immunologic markers in Phase 1 blood samples, for the collection of these samples, and for the Coordinator's phlebotomy training to be tailored to the needs of this protocol. Dr. Trujillo's salary support at 2% effort has ended due to her resignation, effective 11/14/2014.
8.	Name: Project Role: Person months worked: Contribution to Project:	Joyce Sprafkin, PhD Co-Investigator None Clinician. Dr. Sprafkin retired, effective April 2015.
9.	Name: Project Role: Contribution to Project:	Rebecca Weber, BA Coordinator Position termed 9-30-16
10.	Name: Project Role: Contribution to Project:	Heather Garman, MS Coordinator Position started 10-01-16

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Kenneth D.Gadow, PhD
No change.

Ramin Parsey, MD, PhD
ACTIVE SUPPORT:

Advancing Personalized Antidepressant Treatment Using PETIMRI; NIMH; PI: DeLorenzo. R01 MH104512; 5/1/15- 4/30/19; Goals/Aims: To predict response to antidepressant treatment and develop non-invasive techniques for PET imaging; Role: Co-I. CM:.24. Agency Contracting/Grants Officer: Dr. Judith M. Rumsey. *This project has no financial or substantive overlap with AR130397.* Active support not yet pending at last submission.

Biosignatures of Treatment Remission in Major Depression; NIMH; PI's: Weissman, Parsey, McGrath. 5U01 MH092250-04; 07/01/10- 06/30/16; Goals/Aims: This multi-site study will compare a serotonin selective reuptake inhibitor and placebo and assess a comprehensive array of clinical and biological moderators and mediators of outcome. Using innovative statistical approaches, the identified moderators and mediators will then be used to develop a differential depression treatment response index as a first step to developing personalized medication treatment of major depression disorder. Role: Co-PI. CM:.6. *This project has no financial or substantive overlap with AR130397.*
No change.

Lithium's Molecular Mechanism of Action and the Pathology of Bipolar Disorders; NIMH. 1 R01 MH090276-01A1; 06/01/12-05/31/16; Goals/Aims: This project will utilize MRI and PET imaging techniques to investigate the molecular mechanisms of lithium in a bipolar patient population compared to healthy controls. This work will further develop our understanding of the pathology of bipolar, and will contribute to our understanding of personal diagnosis and treatment. Role: PI. CM:4. *This project has no financial or substantive overlap with AR130397.* No change.

Understanding the Molecular Mechanism of Action of Electroconvulsive Therapy in vivo Using Positron Emission Tomography; Brain & Behavior Research Foundation. 08/01/12- 07/31/16; Goals/Aims: This study will use positron emission tomography to provide data essential for the understanding of the role of the 5-HT1A receptor in major depressive disorder and specifically electroconvulsive therapy's antidepressant mechanism of action. By understanding the neurochemical mechanisms involved not only in the pathophysiology of major depressive disorder but also the therapeutic action of ECT, significantly improved therapies can be developed. Role: PI. CM:.24. *This project has no financial or substantive overlap with AR130397.*
No change.

Characterizing Placebo Response; NIH; PI: Petkova. 1 R01 MH99003-01; 12/01/13- 11/30/15; Goals/Aims: Clinical expertise will be provided to guide methodology development, interpret results, and real-data validation of project's models. Role: Co-I. CM:.54. *This project has no financial or substantive overlap with AR130397.*
No change.

PREVIOUS SUPPORT:

Understanding the Mechanism of Action of Lithium and the Pathophysiology of Bipolar Disorder with Molecular Imaging of the Serotonin System; The DANA Foundation. 08/01/13- 07/30/13; Goals/Aims: Examination of the effects of lithium of the serotonin transporter and 1A receptor; Role: PI. CM:O. *This project has no financial or substantive overlap with AR130397.*
Now completed support, active at last submission.

Christine Delorenzo, PhD
ACTIVE SUPPORT:
Advancing Personalized Antidepressant Treatment Using PETIMRI; NIMH. R01MH104512; 5/1/15- 4/30/19; Goals/Aims: To predict response to antidepressant treatment and develop non-invasive techniques for PET imaging; Role: Pl. 25o/o effort. Agency Contracting/Grants Officer: Dr. Judith M. Rumsey. *This project* has *no financial or substantive overlap with AR130397.*
Active support not yet pending at last submission.

Uncovering an Image-Based Biomarker of Depression; Stony Brook University. Fusion Seed Grant; 8/2015 – 6/2017; Goals/Aims: The goal of this grant is to develop an image-based biomarker of depression; Role: PI (no salary support). Agency Contracting/Grants Officer: Dr. Una M Obeid. *This project has no financial or substantive overlap with AR130397.*
Active support not yet pending at last submission.

Prediction of Antidepressant Treatment Response Using Magnetic Resonance Imaging (MRI); Dana Foundation. David Mahoney Neuroimaging Grant; 10/2015- 9/2018; Goals/Aims: To develop a high resolution diffusion imaging sequence to assess the health of white matter tracts prior to antidepressant treatment for the purposes of prediction; Role: PI (no salary support). Agency Contracting/Grants Officer: Kevin Aguirre. *This project* has *no financial or substantive overlap with AR130397.*
Active support not yet pending at last submission.

Personality Development and Vulnerability to First-Episode Depression; NIMH; Supplement to R01MH093479; 2014- 2017; Goals/Aims: In this project, we examine personality development, alongside other vulnerabilities, as a risk factor for first onset of depression. These vulnerabilities are related to structural and functional neuroimaging; Role: Co-I. 20o/o effort year 2. Agency Contracting/Grants Officer: Dr. Mercedes Rubio. *This project has no financial or substantive overlap with AR130397.*
No change.

Cognitive Impairment in MS Linked to Structural and Functional Connectivity; Department of Defense; PI Dr. Lauren Krupp. MS130103; 2014- 2016; Goals/Aims: To use brain imaging to understand how the MS disease process causes cognitive impairment; Role: Co-I. 16% effort. Agency Contracting/Grants Officer: Peggi Lesnow. *This study involves many of the* same *types of imaging* as *the current proposal. However it* is *significantly different in that it* is *focused only on Multiple Sclerosis.*
No change.

PREVIOUS SUPPORT:
Characterization of a *New Metabotropic Glutamate Receptor Subtype 5 PET Ligand;* NIMH. 5K01MH091354-01; 5/1/11 – 4/30/15; Goals/Aims: To characterize the PET ligand [^{11}C]ABP688 for use in studies of depression and other mood disorders; Role: Pl. 75°/o effort. Agency Contracting/Grants Officer: Dr. Christine Wise Clarkson. *This project* has *no financial or substantive overlap with AR130397.*
Now completed support, active at last submission.

Uncovering Biomarkers of Major Depressive Disorder Using Multimodallmaging; Irving Institute for Clinical and Translational Research Grant, Columbia University; 03/01/12 – 2/28/14; Goals/Aims: To combine several imaging modalities, using advanced machine learning and

statistical classification techniques that have been successful in integrating large amounts of information in other fields; Role: Pl. Agency Contracting/Grants Officer: Michelle A. McClave. *This study involved many of the same types of imaging as the current proposal. However it was significantly different in that (1) It is focused only on depression (and not autism), (2) The imaging did not involve the highest resolution options or the simultaneous PETIMRI scanner, and (3) it was focused on methodology.*
Now completed support, active at last submission.

Fronto-striatal circuitry in Parkinson's Disease; Hartman Foundation; PI Hoi-Chung Leung; 2013 – 2014; Goals/Aims: To develop neuroimaging experiments to examine functional and anatomical connectivity changes in patients in early stages of Parkinson's Disease; Role: Co-I. 2o/o effort. Agency Contracting/Grants Officer: Catherine Costanzo. *This project has no financial or substantive overlap with AR130397.*
Now completed support, active at last submission.

Recruitment of Women in Biomedical Engineering (BME) through Mentored Internships in Neuroimaging; Presidential Mini-Grants for Departmental Diversity Initiative; 9/1/2013-06/30/2014; Goals/Aims: This funding is used to establish a pilot program providing medical imaging internships to undergraduate women throughout the academic year. Through guided research in state-of-the-art biomedical engineering (neuroimaging) techniques within a supportive and encouraging community, this highly technical and multidisciplinary field will be both accessible and enjoyable to participants. This will encourage women to major in engineering disciplines; Role: Pl. Agency Contracting/Grants Officer: Barbara Doran-Lubitz. *This project has no financial or substantive overlap with AR130397.*
Now completed support, active at last submission.

Matthew Lerner, PhD
ACTIVE SUPPORT:
A Web-Based Tool to Assess Social Cognition in ASD; Simons Foundation. Explorer Award; 11/2015 -11/2016; Aims: 1) To evaluate the internal consistency of SELweb module scores. 2) To assess criterion validity of SELweb in comparison with existing social cognitive measures. 3) To evaluate SELweb performance in comparison to established normative data from general education youth; Role: Pl. CM:1.0. *This project has no financial or substantive overlap with AR130397.*
Active support not yet pending at last submission.

Effects of Active Emotion Identification; Alan Aida Fund for Communication. 05/2015 – 05/2016; Aims: 1) To assess whether AEI relates to specific psychophysiological mechanisms of social perception and cognition. 2) To determine if engagement in AEI relates to sustained changes social perception, cognition, and behavior across levels of analysis. 3) To ascertain whether effects on social perception, cognition, and behavior are evident in a "high need" population of young adults with ASD; Role: Pl. CM:1.0. *This project has no financial or substantive overlap with AR130397.*
Active support not yet pending at last submission.

Theater in School to Promote Youth with ASD - Pilot Study; Arts Connection. 10/2015 – 06/2017; Aims: 1) To identify and isolate elements of a school-based theater arts program (STAARS) thought to be related to social and academic outcomes in the special population of children with ASD by consulting stakeholders and observing students. 2) To determine whether the elements identified relate to changes in children's social, language, planning and attention

skills, and creativity; Role: Co-Pl. CM:1.5. *This project has no financial or substantive overlap with AR130397.*
Active support not yet pending at last submission.

Improving Effectiveness of Behavior Management Strategies at Maryhaven; Maryhaven Center of Hope. 8/15/15- 12/15/16; Goal/Aims: To identify factors associated with increased IISCIP-R gradienf' and injuries employing a comprehensive dataset obtained at Maryhaven during the 2014 calendar year; Role: Pl. CM:.28. *This project has no financial or substantive overlap with AR130397.*
Active support not yet pending at last submission.

Consortium on Autism & Sign Language; American Academy of Arts & Sciences. Exploratory Fund; 03/2015- 03/2016; Goals/Aims: We will hold a two-day symposium of Academy Fellows as well as nationally known researchers in two areas: sign language linguistics and the study of social communication among individuals with autism spectrum disorders (ASD). The symposium will be held at the Norton Woods Conference Center at the House of the Academy in Cambridge in mid-December 2015; Role: Co-Pl. CM:1.0. *This project has no financial or substantive overlap with AR130397.*
Active support not yet pending at last submission.

Electrophysiological Effects of Social Performance-based Intervention for Autism Spectrum Disorder: A Randomized Controlled Trial; Stony Brook University, Department of Psychiatry. Pilot Grants Program; 07/2015- 07/2016; Aims: 1) Does SDARI affect neural mechanisms of social perception and cognition? 2) Do baseline characteristics predict response to SDARI?; Role: Pl. CM:1.0. *This project has no financial or substantive overlap with AR130397.*
Active support not yet pending at last submission.

Cognitive Consequences of Emotion; National Science Foundation; PI: Gerald Clore, PhD, University of Virginia. 1252079; 2013- 2016; Aims: 1) To understand effects of emotional states on perception, memory, and creativity. 2) To assess the affect-as-information hypothesis on judgments in individuals with and without a predisposition towards a local processing focus; Role: Co-l. CM:.25. *This project has no financial or substantive overlap with AR130397.*
Active support not yet pending at last submission.

Consortium on Autism & Sign Language; Nancy Lurie Marks Family Foundation. Sponsored Symposium Grant; 2014- 2015; Goals/Aims: Same as American Academy of Arts & Sciences, above; Role: Pl. CM:.6. *This project has no financial or substantive overlap with AR130397.* Active support not yet pending at last submission.

PREVIOUS SUPPORT:
No change.

Patricia Whitaker-Azmitia, PhD
No change.

Jie Yang, PhD
Jie Yang, PhD

ACTIVE SUPPORT:

ME/CFS: Activity Patterns and Autonomic Dysfunction. 1R01NR016227-01 Friedberg (PI) 04/01/2016-03/31/2020. Goal:1) To assess the relation between non-improvement and prospectively assessed activity patterns and life events; 2) To assess the relation between improvement and prospectively assessed activity patterns and life events.; 3) To assess the relation between activity patterns and symptoms. *This project has no financial or substantive overlap with AR130397.*

No change

Advancing Virtual Colonoscopy for Early Cancer Screening. 1R01CA206171-01A1 Liang (PI) 06/03/2016-05/31/2021. Goal: 1*)* To develop and evaluate adaptive image reconstruction and image processing algorithms to retain image textures for polyp detection and characterization with as low as achievable CT radiation;2) To explore and evaluate texture features as imaging biomarkers to detect polyps and characterize polyp Subtypes. *This project has no financial or substantive overlap with AR130397.*

No change

P13K Signaling and Channelopathies in the Heart. 1R01DK108989 Lin (PI) 07/01/2016-06/30/2020. Goal: to examine how PI3K/Akt regulates the function of Nav1.5 and HCN2 channels and investigates the effects of insulin resistance on I_{NaP} and I_h. *This project has no financial or substantive overlap with AR130397.*

No change

Sphingolipids in Cancer Therapy and Biology. 2P01CA09713211A1 Hannun (PI) 09/02/2014-

08/30/2019. Goal: To investigate the role of sphingolipids in tumor initiation and differentiation, growth and death of tumor cells, tumor cell invasiveness and metastasis and tumor senescence. Role: Lead Biostatistician. 20°/o effort. *This project has no financial or substantive overlap with AR130397.*

No change.

PREVIOUS SUPPORT:

Targeted Approach for Prevention and Therapy of Colorectal Cancer. 1R01CA17211301A1

Yang (PI) 07/01/2013-06/30/2017. Goal: To evaluate a novel compound which potently and selectively inhibits KLF5 as a therapeutic candidate for colorectal cancer. Role: Co-l. 1.5°/o effort. *This project has no financial or substantive overlap with AR130397.*

No change.

Plasticity-based, adaptive, computerized cognitive remediation treatment (PACR) for adults with

Multiple Sclerosis (MS). RG 4808A8/1 Krupp (PI) 04/03/2013-03/31/2016. Goals: 1) To evaluate the effect of plasticity-based, adaptive, computerized cognitive remediation ("PACR") on generalized cognitive and functional performance, 2) To identify specific predictors of response to guide future use; Role: Co-l. 4.5°/o effort for year 1-2; 9% effort for year 3. *This project has no financial or substantive overlap with AR130397.*

Now completed support, active at last submission.

Cognitive Impairment in MS Linked to Structural and Functional Connectivity Effect.
W81XWH1410248 Krupp (PI) 9/29/2014-9/28/2016. Goals: 1) To measure cognitive Intra Individual Variability (IIV) in multiple Scerloris MS and healthy control participants to serve as an index of cognitive impairment and measure structural, functional and metabolic imaging markers to serve as indices of MS disease pathology, 2) To link these measures to identify the biological basis of cognitive impairment in MS. Role: Co-l. 10°/o effort. *This project has no financial or substantive overlap with AR130397.*

Now completed support, active at last submission.

A Pilot Study of Regional Cerebral Oxygen Saturation (rS02) Monitoring in Predicting Neurological and Survival Outcomes. 13CRP17440000 Parnia (PI) 07/01/2013-06/30/2015. Goals: To measure the level of rS02 achieved during CPR and in the first 24 hours of the post resuscitation period in cardiac arrest patients to investigate the level of rS02 and optimal read out signal that is associated with survival, neurological and functional outcomes at discharge, and 30 days following cardiac arrest. Role: Co-I. 1°/o effort. *This project has no financial or substantive overlap with AR130397.*

Now completed support, active at last submission.

Screening Lung Cancer by Ultra Low-Dose Computed Tomography. 5R01CA143111 Liang (PI)

07/01/2010-04/30/2015. Goal: To reduce the X-ray exposure risk by lowering the mAs value as low as achievable, while retaining the image quality suitable to the clinical task. Role: Co-I.

3.2o/o effort. *This project has no financial or substantive overlap with AR130397.*

Now completed support, active at last submission.

Now completed support, active at last submission.

What other organizations were involved as partners? Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS: None.

9. APPENDICES:

Revised SOW

YEAR 1

Aim #1: Obtain Institution Review Board (IRB) approval for DOD application
1a.Task: Obtain IRB approval
Responsible personnel: Dr. Gadow
Milestone: IRB approval secured
Timeline: Prior to award Week 0 (9/30/2014)

1b.Task: Submit IRB DOD amendment to existing IRB approval
Responsible personnel: Dr. Gadow
Milestone: Complete and submit IRB amendment
Timeline: Weeks 1-4 (10/7/2014 – 10/28/2014)

1c.Task: Obtain IRB amendment approval
Responsible personnel: Dr. Gadow
Milestone: Complete and submit revised IRB forms
Timeline: Weeks 4-6 (10/28/2014 – 11/11/2014)

Aim #2: Prepare for subject recruitment
2. Task: Prepare subject recruitment materials
Responsible personnel: Dr. Gadow, Coordinator
Milestones: Solicitation lists, advertisements
Timeline: Weeks 6-11 (11/11/2014 – 12/16/2014)

Aim # 3: Prepare for Phase 1 and Phase 2 data collection
3a. Task: Prepare for data collection
Responsible personnel: Dr. Gadow, Coordinator
Milestone: Pilot test fMRI task and conduct Phase 2 wet runs
Timeline: Weeks 12-52 (12/23/2014 – 9/30/2015)

YEAR 2

Aim # 3: Recruitment, data collection, and data processing for Phase 1
3a. Task: Recruitment of first block of 10 Phase 1 participants
Responsible personnel: Dr. Gadow, Coordinator
Milestone: Continue participant solicitation
Timeline: Weeks 1-34 (10/1/2015 – 6/1/2016)

3b. Task: Collect psychosocial data
Responsible personnel: Dr. Gadow, Coordinator
Milestones: Administer diagnostic and psychosocial measures, collect blood samples
Timeline: Weeks 34-52 (6/1/2016 – 9/30/2016)

3c. Task: Record and enter diagnostic and psychosocial data
Responsible personnel: Dr. Gadow, Coordinator
Milestones: Score assessment measures and enter data for analyses
Timeline: Weeks 34-52 (6/1/2016 – 9/30/2016)

3d. Task: Collecting and storing Phase 1 immunologic data
Responsible personnel: Dr. Gadow, Coordinator
Milestones: Collect and properly store blood samples
Timeline: Weeks 34-52 (6/1/2016 – 9/30/2016)

Aim # 4: Recruitment, data collection, and data processing for Phase 2
4a. Task: Recruitment of first block of 3 Phase 2 participants
Responsible personnel: Dr. Gadow, Dr. DeLorenzo, Coordinator
Milestone: Initiate participant solicitation
Timeline: Weeks 39-52 (7/1/2015 – 9/30/2016)

4b. Task: Conduct fMRI
Responsible personnel: Dr. Gadow, Dr. DeLorenzo, Coordinator
Milestone: Conduct fMRIs
Timeline: Weeks 39-52 (7/1/2015 – 9/30/2016)

4c. Task: Storing and processing Phase 2 fMRI data
Responsible personnel: Dr. DeLorenzo
Milestones and timeline: Storing and initial processing fMRI data Weeks 39-52 (7/1/2015-9/30/2016)

YEAR 3

Aim # 3: Recruitment, data collection, and data processing for Phase 1
3a.Task: Recruitment of first block of Phase 1 participants
Responsible personnel: Dr. Gadow, Coordinator
MilestoneS: Continue participant solicitation
Timeline: Weeks 1-34 (10/1/2016 – 6/1/2017)

3b. Task: Collect psychosocial data
Responsible personnel: Dr. Gadow, Coordinator
Milestones: Administer diagnostic and psychosocial measures, collect blood samples
Timeline: Weeks 34-52 (6/1/2017 – 9/30/2017)

3c. Task: Record and enter diagnostic and psychosocial data
Responsible personnel: Dr. Gadow, Coordinator
MilestoneS: Score assessment measures and enter data for analyses
Timeline: Weeks 34-52 (6/1/2017 – 9/30/2017)

3d. Task: Collecting and storing Phase 1 immunologic data
Responsible personnel: Dr. Gadow, Coordinator
Milestones: Collect and properly store blood samples
Timeline: Weeks 34-52 (6/1/2017 – 9/30/2017)

Aim # 4: Recruitment, data collection, and data processing for Phase 2
4a. Task: Recruitment of first block of 3 Phase 2 participants
Responsible personnel: Dr. Gadow, Dr. DeLorenzo, Coordinator
Milestone: Initiate participant solicitation
Timeline: Weeks 39-52 (7/1/2016 – 9/30/2017)

4b. Task: Conduct fMRI
Responsible personnel: Dr. Gadow, Dr. DeLorenzo, Coordinator

Milestone: Conduct fMRIs
Timeline: Weeks 39-52 (7/1/2016 – 9/30/2017)

4c. Task: Storing and processing Phase 2 fMRI data
Responsible personnel: Dr. DeLorenzo
Milestones and timeline: Storing and initial processing fMRI data Weeks 39-52 (7/1/2016-9/30/2017)

YEAR 4

Aim #5: Completed Aim #5.

Aim #6: Analyze the data with regard to the stated hypotheses of the study
6. Task: Conduct data analyses
Responsible personnel: Dr. Yang, Dr. Gadow, Dr. DeLorenzo,
Milestones: Data analyses are being conducted using SPSS
Timeline: Weeks 46-52 (10/1/18 – to present)

Aim #7: Prepare abstracts, presentations, and manuscripts
7. Responsible personnel: Dr. Gadow, Dr. Parsey, Dr. DeLorenzo, Dr. Yang, Dr. Whitaker-Azmitia
Milestones: Submit proposals to present at national or international meetings and prepare for submission manuscripts to peer-reviewed journals
Timeline: Weeks 46-52 (10/1/18 – to present)

	Year 2				Year 3				Year 4			
Target Enrollment (per quarter)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Phase 1			4	2	2	3	1	9	4	2	4	3
Phase 2			0	1	2	1	2	3	2	2	3	3
Target Enrollment (cumulative)												
Phase 1			4	6	8	11	12	21	25	27	31	34
Phase 2			0	1	3	4	6	9	11	13	16	19