Understanding the Influence of Sibling Support Group Facilitation on Mental Health Trainee Views and Skills of Family-Centered Care

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BACKGROUND

- Family-centered care is a core competency for psychiatric residency training programs, yet it is among the least taught [1, 2].
- Few programs expose trainees to the experiences of siblings of children with mental illness [3].

STUDY OBJECTIVE

- To evaluate whether a sibling support group led by Psychiatry, Psychology and Social Work trainees could promote family-centered care among trainees.

METHODS

- All trainees in Psychiatry, Psychology, and Social Work at Cambridge Health Alliance were invited to facilitate a sibling support group through the *Sibling Support Program: A Family-Centered Mental Health Initiative*, which was developed at the E.K. Shriver Center of UMass Medical School. The program serves families of child and adolescent patients admitted to the psychiatric inpatient units.
- Participant Trainees and Non-participant Trainees of the sibling support group were surveyed:

1. *Trainee Comparison Survey*: Assessed experiences of Participant Trainees vs Non-participant Trainees and their:
   - Exposure to family-centered care.
   - Comfort level in providing family-centered care.
   - Attitudes regarding the importance of family-centered care.
   - Desire to provide family-centered care in the future.

1. *Group Facilitator Survey*: Administered to Participant Trainees only to assess their perceptions of the sibling group leader experience.

RESULTS

***Table 1*. Number of trainees answering affirmatively on Trainee Comparison Survey questions that assess level of exposure to working with siblings during training.**

	Participant Trainees (N = 17)		Non-participant Trainees (N = 32)		p-value
I met with siblings of patients on the child and/or adolescent psychiatry inpatient units individually or in small groups.	17	100%	4	12.5%	<0.00001
I heard siblings share their stories about growing up with a brother/sister admitted to the child and/or adolescent psychiatry inpatient units.	17	100%	3	9.4%	<0.00001
I had direct experience helping siblings cope with their brother/sister's illness.	17	100%	5	15.6%	<0.00001
I participated in activities specifically focused on family-centered mental health care.	15	88.2%	16	50%	0.008225

***Table 2*. Trainee Comparison Survey likert scale questions on confidence and intention to practice family-centered care.** Values signify mean response (1=Strongly Disagree, 7=Strongly Agree).

	Participant Trainees (N = 17)	Non-participant Trainees (N = 32)	p-value
During my training, I increased my understanding of the impact of mental illness on siblings.	6.2	2.6	<0.00001
I am able to do the things expected of me according to a family-centered approach.	5.4	3.7	0.0007
I am confident that I am able to work with others in a family-centered way.	5.7	4.0	0.0001
I have the skills and abilities needed to participate in a family-centered approach to service.	5.5	4.0	0.001
I intend to participate in services in a family-centered way.	6.1	4.9	0.011
I plan to practice in an underserved area once I am done with my training.	5.9	6.1	0.702
I feel overwhelmed by the larger social conditions that impede the physical and emotional health of my patients and their families.	5.0	5.3	0.548

***Narrative Excerpts from Group Facilitator Survey*:**

"Siblings of patients in inpatient care need as much attention as patients in the hospital."

"I was surprised to learn how often siblings are given little to no information about what's going on … and how often they are asked not to talk about it with others by parents. It helped me appreciate the need for these groups!"

"I will definitely inquire about siblings of patients and if they are receiving enough support of their own."

DISCUSSION

- Participant Trainees were more likely to have responded that:
  - They had exposure to working with siblings during training (Table 1).
  - They had greater confidence in their family-centered care skills (Table 2).
  - They will practice in a family-centered way in the future (Table 2).
- Trainees who participated were overwhelmingly positive about their experience with the Sibling Support Program.
- Study limitations include rate of response, possible selection bias for Participant Trainees, and differences in training programs accounting for the difference in results.
- Future study should collect pre- and post-data on Participant Trainees to better determine whether it was participation in the sibling group itself that influenced the difference in results.

CONCLUSION

- The Sibling Support Program offers a unique training opportunity for mental health trainees to develop competency and gain confidence in providing family-centered care by facilitating a sibling support group.
- Other mental health training programs should consider implementing similar sibling support group programs to address the void in family-centered care opportunities for their trainees.

REFERENCES

1. Berman, Ellen, and Alison M. Heru. 2005. Family systems training in psychiatric residencies. *Family Process*. doi:10.1111/j.1545-5300.2005.00062.x.
2. Berman, Ellen M, Alison M Heru, Henry Grunebaum, John Rolland, Beatrice Wood, and Heidi Bruty. 2006. Family Skills for General Psychiatry Residents: Meeting ACGME Core Competency Requirements. *Academic Psychiatry* 30: 69–78. doi:10.1176/appi.ap.30.1.69.
3. Tudor, Megan E, and Matthew D Lerner. 2015. Intervention and support for siblings of youth with developmental disabilities: A systematic review. *Clinical Child and Family Psychology Review* 18. Springer: 1–23.

Feasibility and Acceptability of Group-Delivered Acceptance and Commitment Therapy (ACT) for Parents of Anxious Children

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Background

- Anxiety disorders affect as many as 1 in 4 youth and are among the most common childhood psychological problems (Costello et al., 2003).
- Anxiety disorders in youth are distressing and impairing for children and their families. They are also associated with risks that include social and academic challenges, adult anxiety, secondary mental health problems such as substance abuse, and major depression (Wood, 2006).
- Although cognitive-behavioral therapy (CBT) has been found to be an efficacious treatment for pediatric anxiety disorders, approximately 30-40% of children do not experience a meaningful reduction in anxiety symptoms in response to CBT (Kendall, Settipani, & Cummings, 2012).
- Caregiver behaviors such as *parent intrusiveness/lack of autonomy-granting* and *modeling of anxious responding* have been found to characterize parent behavior in pediatric anxiety disorders and may negatively affect the extent to which children benefit from CBT (Moore et al., 2004).
- Parent-focused interventions in CBT have been largely instructive regarding how best to change behavior to support the child's individual CBT work. There has been a lack of attention to internal parenting factors that may interfere with behavior change, particularly avoidance of uncomfortable emotions (**experiential avoidance**) and conviction in one's thoughts (**cognitive fusion**).
- **Acceptance and Commitment Therapy (ACT)** is a newer psychotherapeutic approach that targets problematic psychological processes, including experiential avoidance and cognitive fusion, to increase behavioral flexibility.
- Parent-focused ACT interventions have shown promise for changing parenting behaviors and improving well-being of parents and their children (Blackledge & Hayes, 2006; Coyne & Wilson, 2004).
- We conducted a pilot open trial of **ACT for Parents of Anxious Children (ACT-PAC),** a group-delivered caregiver treatment program for parents of youth with anxiety disorders. ACT-PAC focuses on reducing parent intrusiveness and modeling of anxious response. We examined the feasibility, acceptability, and clinical outcomes of ACT-PAC.

Method

Participants

- 23 parents (20 mothers, 3 fathers, mean age 45) of children ages 7-17 with a primary anxiety disorder diagnosis (14 males, 9 females; mean age 13) participated in the study. Most common diagnoses were generalized anxiety disorder, obsessive compulsive disorder, social phobia, and specific phobia.

Procedure

- This project took place within the Pediatric Anxiety Disorders Clinic, housed within the larger Child and Adolescent Neurodevelopmental Disorders (CANDO) Clinic at UMass Memorial Medical Center.
- Interested families were screed by phone, and those who appeared eligible participated in a comprehensive diagnostic assessment of their child's anxiety symptoms using the Anxiety Disorders Interview Schedule for DSM-IV: Child and Parent Version (ADIS-C/P).
- Eligible parents were invited to participate in a 6-week group treatment (1.5-hour weekly sessions) that followed the ACT-PAC protocol.
- Parents and their children completed pre- and post-ACT-PAC assessments.

Measures

- Parents' weekly attendance of group sessions was recorded and used to assess feasibility of ACT-PAC.
- Parents completed the Client Satisfaction Inventory (CSQ-8; McMurty & Hudson, 2000) and a qualitative feedback interview to assess acceptability of ACT-PAC.
- To evaluate changes in psychological flexibility, parents completed the Cognitive Fusion Questionnaire (CFQ; Gillanders et al., 2014) and Multidimensional Experiential Avoidance Questionnaire (MEAQ; Gámez et al., 2011)
- To evaluate youth symptoms, both parents and children reported on youth anxiety symptoms and psychosocial functioning by completing the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001) and the Screen for Child Anxiety Related Emotional Disorders (SCARED; Birmaher et al., 1999).

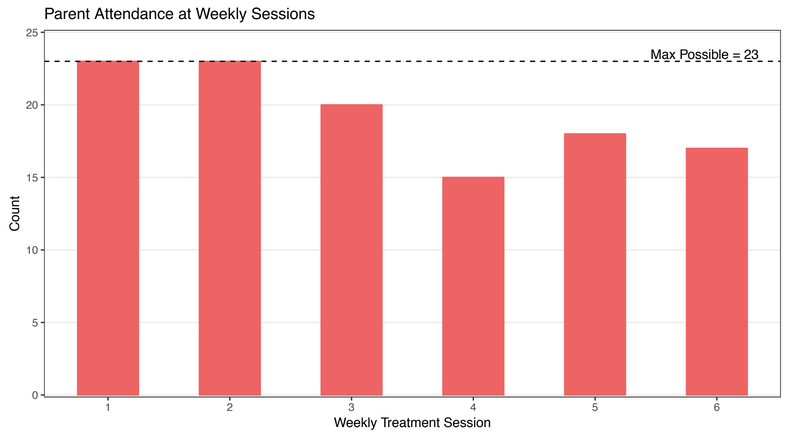
Intervention

ACT-PAC Components:

1. Mindfulness: Finding Stillness
2. Defusion: Weathering Thoughts & Feelings
3. The Matrix: Moving Towards vs. Moving Away
4. Valuing/Committed Action: Doing What Matters
5. Parenting Your Anxious Child
6. Self-Care: There's Only One You

Feasibility of ACT-PAC

The group intervention was shown to be feasible for parents to attend. Parents attended 5 of 6 weekly sessions on average, and 91% of parents attended 4 or more sessions.



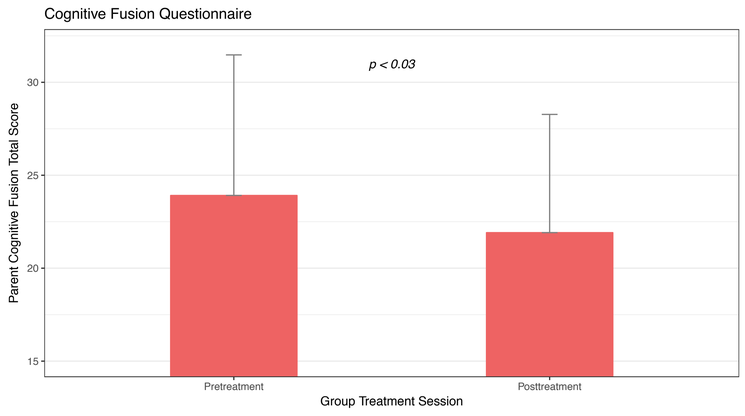
Acceptability of ACT-PAC

- Results indicate that parents found the experience of ACT-PAC to be beneficial, as reported on the Client Satisfaction Questionnaire (CSQ-8), M = 25.39, SD = 4.76 (scores range from 16 to 32).
- Qualitative feedback was generally positive about ACT-PAC, with the major themes being that parents appreciated that the group was non-judgmental, the group's focus on the needs of parents and how they can respond to their child, the focus on mindfulness, and the opportunity to connect with other parents experiencing similar difficulties with their child.
- "[It was a] nonjudgmental place…Some of the feelings you feel with children are hard, having feelings and thoughts that make you feel worse about yourself. [It was] comforting to know that I was not alone, and that didn't make me a bad parent."
- "It was a really good experience, and I learned a lot about myself in terms of how I'm reacting vs. what's going on with the child - very eye opening."

Results

Parent Psychological Flexibility:

Paired samples t-tests were conducted to compare parents' pre- and post-treatment CFQ and MEAQ scores. Parents' levels of self-reported cognitive fusion significantly decreased following ACT-PAC, $t(22) = -2.33$, $p < .05$.



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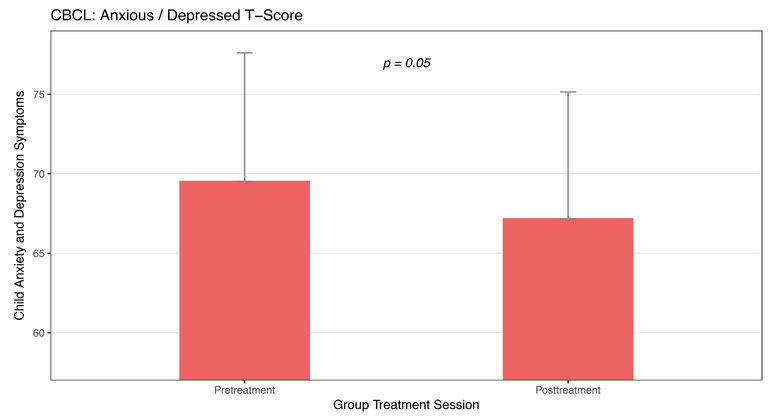
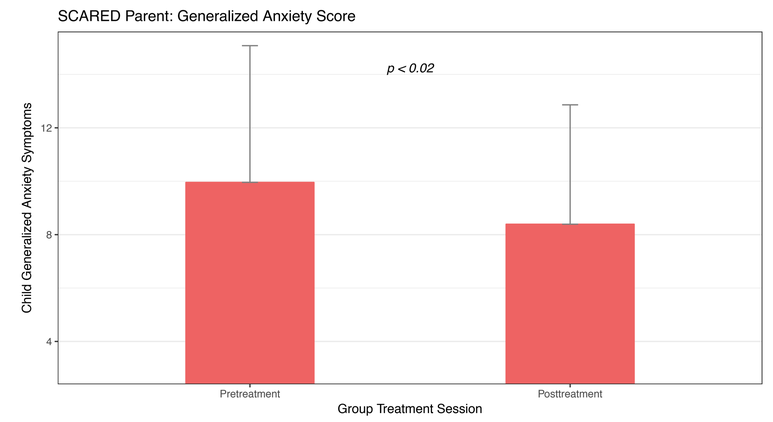
Results

Parent-Report of Youth Anxiety Symptoms and Psychosocial Functioning:

Parents' report of their children's anxiety and depression symptoms on the CBCL decreased significantly, $t(22) = -2.05$, $p = .05$.



Parents' report of their children's generalized anxiety symptoms on the SCARED decreased significantly, $t(22) = -2.54$, $p < .05$.



Discussion

Overall results suggest that ACT-PAC was mostly feasible for parents to attend, and the group intervention experience was generally acceptable to parents. Although results for clinical outcomes are preliminary and based on a small sample size, they point to the potential for ACT-PAC to decrease cognitive fusion in parents of youth with anxiety disorders, allowing them to approach their thoughts about their child's anxiety in a more psychologically flexible way. Results also suggest that ACT-PAC may help to reduce children's internalizing (anxiety and depression) and generalized anxiety symptoms by virtue of parents learning to think about and respond to their child's anxiety with increased autonomy-granting and decreased modeling of anxious responding.

Future Directions

- Increase sample diversity
- Assess anxiety disorders in parents
- Facilitate focus groups with ACT-PAC participating parents to discuss their experience in the study and parenting group and to receive feedback for improvement
- Assess change in parenting behaviors using observational measures
  - Collect a community-based control sample
- Examine change in weekly ACT-PAC measures
  - Cognitive Fusion Questionnaires
  - Self-reported parenting behavior and practice engagement
- Introduce mobile technology to help bring ACT-PAC strategies into daily life
- Evaluate the efficacy and clinical effectiveness of ACT-PAC using a well-designed randomized control trial. Continue to examine child symptom reduction and increased psychological flexibility in parents, as well as whether and how the parent intervention changes the way parents interact with their anxious children.

Rates of bipolar disorder screening and treatment among pregnant and postpartum women

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PRogram In Support of Moms PRISM

ABSTRACT

Objective: Bipolar disorder affects 2-8% of pregnant and postpartum women and untreated illness is associated with poor maternal and infant outcomes. The objectives of this study were to describe: (1) rates of women who screen positive for bipolar disorder in the obstetric setting; (2) their associated risk factors; and, (3) their participation in treatment.

Methods: Pregnant and postpartum women were recruited from 14 obstetric practices. Primary data were collected regarding obstetric and psychiatric care. Depression screenings were done with the Edinburgh Postnatal Depression Scale (EPDS), bipolar disorder screenings with the Mood Disorder Questionnaire (MDQ), and substance use screenings with the Parents, Partners, Past, and Pregnancy screen (4Ps).

Results: One-fifth (18.8%) of the total sample (n=575) screened positive for bipolar disorder. The likelihood of a positive screen was significantly increased amongst those who received prior pharmacotherapy and those who spoke with a provider about their mental health recently, but still felt they were not receiving adequate psychiatric help. Positive screens were significantly associated with positive substance abuse screens. Among those screened positive for bipolar disorder, 20.0% reported receiving psychiatric pharmacotherapy currently and 31.0% reported current psychotherapy participation.

Conclusion: Positive bipolar disorder screening rates were higher than found in prior studies. Despite being more than three times as likely to report feeling they needed psychiatric help, less than half of the sample that screened positive for bipolar disorder was receiving evidence-based treatment. Our data suggest that there is a gap in care that needs to be addressed to connect women who screen positive for bipolar disorder.

RISKS OF BIPOLAR DISORDER IN PREGNANCY AND POSTPARTUM

- Women are at their highest lifetime risk for new onset or recurrence of bipolar episodes during pregnancy and postpartum, especially if untreated
- Women suffering from untreated BD are more prone to adverse pregnancy outcomes:
  - Gestational hypertension, antepartum hemorrhage
  - Self-injury, substance abuse, suicide
  - Most important known risk factor for postpartum psychosis
- Infant outcomes are also compromised:
  - Preterm birth or small for gestational age, elevated levels of fetal stress hormones
  - Impaired mother-baby bonding

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DEMOGRAPHICS OF PARTICIPANTS

Characteristic	Positive MDQ (n = 108)	Negative MDQ (n = 467)	All participants (n = 575)
Portion of sample, %	18.8	81.2	100.0
Age* (mean, SE)	29.8 (0.5)	31.9 (0.2)	31.5 (0.2)
Education*,%			
Grade school/Some high school	5.9	2.2	2.8
HS diploma/GED equivalent	28.4	12.9	15.7
Some college or associate's degree	42.2	20.4	24.3
Bachelor's degree	14.7	26.8	24.7
Graduate degree	8.8	37.8	32.6
Race,%			
Black/African American	20.8	11.9	13.4
White	64.6	72.5	71.1
Asian	4.2	8.3	7.6
Other	2.1	0.9	1.1
More than one race	8.3	6.5	6.8
Ethnicity,%			
Hispanic/Latina	14.7	13.8	13.9
Primary source of medical payment for prenatal care*,%			
Private health insurance	37.6	71.2	65.3
MassHealth or Medicaid	60.4	27.7	33.5
Some other kind of insurance	2.0	1.1	1.2

MDQ was positive for bipolar disorder if patient reported 7 or more symptoms. *p-value < 0.001.

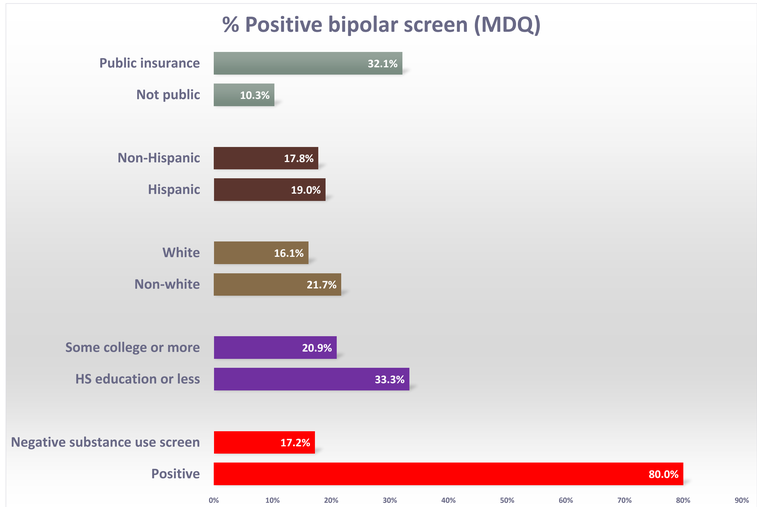
TREATMENT PATTERNS AND UTILIZATION, BY MDQ SCREEN

Characteristic	Rates (%)			Crude measures		Adjusted measures	
	Positive MDQ	Negative MDQ	All	OR	95% CI	aOR	95% CI
Patient diagnostics							
*Prior diagnosis of bipolar disorder**	33.3	2.6	8.4	18.9	9.4 - 38.1	14.4	6.2 - 33.2
*Positive substance abuse screen**	11.1	0.6	2.6	19.3	5.3 - 69.7	13.4	2.3 - 78.9
Interaction with healthcare regarding mental health							
*Spoke with professional about mental health**	54.0	22.2	27.9	4.1	2.6 - 6.5	4.3	2.6 - 7.2
*Offered medications/referred for mental health treatment**	28.0	8.3	11.8	4.3	2.5 - 7.5	3.3	1.8 - 6.2
*Felt needed psychiatric help but didn't receive it**	24.0	7.0	10.0	4.2	2.4 - 7.5	3.4	1.7 - 6.5
Psychiatric treatment							
*Any current treatment**	42.0	16.1	20.8	3.8	2.4 - 6.0	4.2	2.4 - 7.2
*Current treatment with psychiatric medications**	20.0	6.6	9.0	3.6	1.9 - 6.6	3.3	1.6 - 6.9
*Current treatment with psychotherapy**	31.0	10.9	14.5	3.7	2.2 - 6.1	4.0	2.2 - 7.4
Medication usage							
*Prescribed medications prior to pregnancy**	34.0	12.4	16.3	3.6	2.2 - 6.0	3.3	1.8 - 5.8
Stopped since learning pregnant	64.7	66.1	65.6	0.9	0.4 - 2.3	0.5	0.1 - 1.7

Breakdown of treatment patterns of participants in the study, based on screening results on the MDQ. Odds ratios show the likelihood of screening positive on the MDQ. MDQ was a positive screen for bipolar disorder if patient reported 7 or more symptoms; substance use screen was done using the 4Ps questionnaire.

*p-value < 0.001. CI = Confidence interval, OR = odds ratio, aOR = adjusted odds ratio. ORs are estimated using logistic regression, comparing perinatal women with and without positive MDQ, and adjusted for age, race, education, and insurance type.

BIPOLAR DISORDER SCREENS IN HEALTH DISPARATE GROUPS



CONCLUSIONS

- In comparison to previously published literature, positive bipolar disorder screening rates were higher than anticipated in our sample of pregnant women, especially in younger women and groups with known health disparities
- Less than half of our sample that screened positive for bipolar disorder was receiving evidence-based treatment
- Women with positive bipolar screens are much more likely to feel like they need psychiatric help but not getting it
- Women with positive bipolar screens have much higher rates of concurrent positive substance use screens
- Our data suggest that there is a gap in screening and care for perinatal bipolar disorder
- Screening must be increased, in accordance with many relevant professional society recommendations, but also done in conjunction with treatment planning and connection to care
- Important to screen for substance abuse in perinatal women that screen positive for bipolar disorder
- Implications for management in preconception planning and for women with existing bipolar diagnosis

REFERENCES

1. Byatt N, Pbert L, Hosein S, et al. PRogram in support of moms (PRISM): Development and beta testing. *Psychiatr Serv*. 2016;67(8):824-826. doi: 10.1176/appi.ps.201600049.
2. Byatt N, Moore Simas TA, Biebel K, et al. PRogram in support of moms (PRISM): A pilot group randomized controlled trial of two approaches to improving depression among perinatal women. *J Psychosom Obstet Gynaecol*. 2017:1-10. doi: 10.1080/0167482X.2017.1383380.
3. Rusner M, Berg M, Begley C. Bipolar disorder in pregnancy and childbirth: a systematic review of outcomes. BMC Pregnancy Childbirth. 2016;16(1):331.
4. Viguera AC WT, Baldessarini RJ, Newport DJ, Stowe Z, Reminick A, Zurick A, Cohen LS. Risk of Recurrence in Women With Bipolar Disorder During Pregnancy: Prospective Study of Mood Stabilizer Discontinuation. Am J Psychiatry. 2007;164:1817-1824
5. Jones I, Chandra PS, Dazzan P, Howard LM. Bipolar disorder, affective psychosis, and schizophrenia in pregnancy and the post-partum period. The Lancet. 2014;384(9956):1789-1799.
6. Freeman MP, Smith KW, Freeman SA, et al. The impact of reproductive events on the course of bipolar disorder in women. J Clin Psychiatry. 2002;63(4):284-287.
7. Vesga-Lopez O, Blanco C, Keyes K, Olfson M, Grant BF, Hasin DS. Psychiatric disorders in pregnant and postpartum women in the United States. Arch Gen Psychiatry. 2008;65(7):805-815.
8. Wisner KL, Sit DK, McShea MC, et al. Onset timing, thoughts of self-harm, and diagnoses in postpartum women with screen-positive depression findings. JAMA Psychiatry. 2013;70(5):490-498.
9. Kendig S, Keats JP, Hoffman MC, et al. Consensus Bundle on Maternal Mental Health: Perinatal Depression and Anxiety. J Midwifery Womens Health. 2017;62(2):232-239.
10. Byatt N, Biebel K, Moore Simas TA, et al. Improving perinatal depression care: the Massachusetts Child Psychiatry Access Project for Moms. Gen Hosp Psychiatry. 2016;40:12-17.
11. Frey BN, Simpson W, Wright L, Steiner M. Sensitivity and specificity of the Mood Disorder Questionnaire as a screening tool for bipolar disorder during pregnancy and the postpartum period. J Clin Psychiatry. 2012;73(11):1456-1461.

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The Child and Adolescent Service Intensity Instrument (CASII) and the Early Childhood Service Intensity Instrument (ECSII)

Peter Metz, MD; Ashley Green, LCSW; Fernando Valles, MPH

Introduction

CASII and ECSII are standardized instruments that support integrated care:

- Support treatment planning and assists in progress/outcomes measurement for children with mental health, medical, developmental and/or substance use conditions
- Consider environmental factors in addition to child factors that impact services needed
- Use field-tested algorithms to determine service intensity and guide beneficial interventions

Based on a System of Care Philosophy (SOC)

- Culturally sensitive, individualized, and strength-based
- Coordinated, using a team-based wraparound service planning process when indicated
- Provided in the least restrictive setting

Concept of Service Intensity vs Level of Care

- CASII/ECSII are "bricks and mortar" independent: they offer an alternative method of thinking about out of home placements and traditional service arrays, teams can work to provide comparable service intensity in home and community settings
- CASII/ECSII can be used within a traditional service array (OP, RTC, IP)

MN Dept of Human Services Experience with CASII

"We needed a standardized way of monitoring the clinical/functional status of all children receiving publicly funded mental health service system. The committee charged with finding an appropriate measure recommended the CASII. We conducted a two-year pilot study that resulted in a recommendation that this tool be used by all children's mental health providers serving children in our Minnesota Health Care Programs. ***The obvious benefit for us has been that we have a standardized mechanism for assessing the service intensity needs of children across the state. We have language that is familiar to everyone involved in treating these children.*** *We also have a standardized way to look at clinical/functional change over time.*

References

American Academy of Child and Adolescent Psychiatry Work Group on Systems of Care, *Child and Adolescent Service Intensity Instrument user's manual.* Washington, D.C.: American Academy of Child and Adolescent Psychiatry, 2007.

Daleiden, E. (2004) *Child status measurement: Operating characteristics of the CALOCUS and CAFAS*. State of Hawaii, Department of Health, Child and Adolescent Mental Health Division, 2004.

Daleiden, E & , Chorpita, B. From data to wisdom: Quality improvement strategies supporting large-scale implementation of evidence-based services *Child Adol Psychiat Clinics of North America 2005, 14,* 329– 349.

Fallon, T., Pumariega, A. J., Sowers, W., Klaehn, R., Huffine, C., Vaughan, T., Winters, N., Chenven, M., Marx, L., Zachik, A., Heffron, W., & Grimes, K. A (2006). Level of care Instrument for children's systems of care: Construction, reliability and validity. *J Child Fam Studies, 15*, 140-152.

Ono, Y., Pumariega, A.J., Yamamoto, A., Yoshida, K., Nakayama, H., Nakanishi, D, Aihara, K., Ichikawa, K., Hanafusa, M., Millsaps, U., CASII Development in Japan. New Research Poster. 56th Annual Meeting of the American Academy of Child and Adolescent Psychiatry, Honolulu, HI, October 28th, 2009.

Pumariega, A.J., Wade, P., Millsaps, U., Moser, M., & Clark, T. The Use of a Level of Care Measure in a Child Welfare Population. Paper Presentation. *Proceedings of the 18th Annual Research Conference: A System of Care for Children's Mental Health: Expanding the Research Base.* Tampa, Fla: Florida Mental Health Institute, 2006.

Pumariega, A.J., Millsaps, U., Moser, M., & Wade, P. Level of Care Determination in a Juvenile Justice Population. *Adolescent Psychiatry*. 4(4): 305-313, 2014.

Overview of CASII and ECSII

CASII's 6 Dimensions:

- ❑ Risk of Harm
- ❑ Functional Status
- ❑ Comorbid Conditions
  - ▪ Developmental, Medical, Substance Abuse, and Psychiatric
- ❑ Recovery Environment
  - ▪ Environmental Stress and Environmental Support
- ❑ Resiliency and/or Response to Services
- ❑ Involvement in Services

ECSII's 6 Domains: Focus on attachment and caregiving

- ❑ Degree of Safety
- ❑ Child-Caregiver Relationships
- ❑ Caregiving Environment
  - ▪ Strengths
  - ▪ Stressors
- ❑ Functional/Developmental Status
- ❑ Impact of the Child's Condition
- ❑ Services Profile
  - ▪ Caregiver/Child Involvement
  - ▪ Service Fit
  - ▪ Service Effectiveness

CASII/ECSII Scoring

Scoring for each Dimension/Domain requires adequate clinical information to locate correct anchor points, promoting a comprehensive biopsychosocial evaluation:

- Overall SI Level determined by the sum of scores for each dimension, although independent criteria can impact final SI Level (e.g. Risk of Harm at highest severity automatically determines higher SI level)
- Calculated SI scores correspond to defined levels of intensity to guide team planning
- Scoring can be done in ~ 10 to 15 minutes by trained providers when all information needed is available.

Service Planning

Instrument manuals contain guidance for specific resources that are indicated at a given SI level:

- Clinical Services
- Support Services (e.g. Care Coordination, after school programs, housing support, other natural supports)
- Crisis Stabilization and Prevention (availability of 24/7 crisis assessment in the community as well as ED)
- Care Environment (where services are provided and configuration of same, e.g. for level 6, IP care, "adequate temporary accommodations for family must be available")

How the CASII/ECSII can help your clients at the individual level

- Provides guidance for child or adolescent service plan
- Determines the SI score indicated for an anticipated care environment
- Assists community-based clinicians in obtaining adequate clinical information to inform the service plan
- Helps to focus interventions and supports on critical areas using Dimension Scores

How the CASII/ECSII can help your clients at the system level

- Advocates for services that are indicated by SI level but lacking in the service array, e.g. Intensive Care Coordination, In Home Therapy
- Monitors progress over time for populations of youth such as those in Residential and Inpatient settings, in foster care/CW custody, in JJ settings, medical home settings, etc. for quality improvement at the system level
- Promotes adherence to System of Care values and principles by child serving systems

What the CASII/ECSII are NOT

- Do not rigidly define the level of service intensity needed. Rather, they are guides that rely on clinical judgment
- Are not prescriptive about service planning: they recognize that available services and supports vary by location
- Family voice and choice drives planning process

Psychometrics of CASII/ECSII

CASII Reliability: 0.89-0.93 across a range of MH professionals, in a national study involving 614 youth from 4 sites, supported by SAMHSA, conducted by the American Institute for Research.

CASII Reliability and Validity also established in studies published studies on youth in Hawaii and Tennessee

ECSII Reliability: 0.675-0.829 over range of EC MH providers

ECSII inter-rater reliability: excellent, with correlation coefficients on Domains I-V (those used to derive the Service Intensity score) from 0.676-0.829

Construct validity: established by meeting a predicted criterion. Scores of the Oregon inter- rater reliability sample (52 clinicians) on 15 standardized vignettes were correlated with the "gold standard" ECSII scores on the same vignettes. This yielded an intra- class correlation coefficient of .9254

Concurrent validity: demonstrated statistically significant correlations between ECSII scores and CBCL and Parenting Stress Index scores

Users of CASII/ECSII

State Medicaid program; Commercial Insurance (Anthem BC/BS in CT); Sustained use in: AK, AZ, CT, DE, KY, MD, MT, ND, NV, OR, TN, WY

In-Person and Web-Based Training

In-person CASII and ECSII trainings are available

- Web-based training for CASII due to be released 09/2018
- Web-based training for ECSII due to be released 06/2019
- For information re: training, contact Fernando Valles, CASII/ECSII AACAP manager; fvalles@aacap.org

Hyperconnectivity of Key Cortical Regions Involved in Social Processing is Associated with Social Cognition Deficits in Adolescent ASD

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Background

Social Processing Cortical Regions in Autism Spectrum Disorder (ASD)

- Right posterior superior temporal gyrus (rpSTG) involved in language processing and social perception, particularly perception of biological motion[1]
- rpSTG is core area with observed differences between ASD and typically developing (TD) controls
- Resting state functional connectivity (rsFC) studies have shown both hyper- and hypo-connectivity of rpSTG in ASD with various brain regions associated with social cognition[2]
- Variation in study results may be due to small sample sizes, variability in methodologies, scanner differences, sample variability

Autism Brain Imaging Data Exchange (ABIDE):

- Grassroots consortium aggregating and openly sharing 1112 existing rsFC datasets with corresponding structural MRI and phenotypic information from 539 individuals with ASD and 573 age-matched controls (Age 7-64 years)[3]
- Allows for specific hypothesis testing based on careful selection of subjects

Hypothesis: Connectivity of rpSTG with other regions of social processing network is related to social cognition deficits in adolescent males, across wide range of social cognition including individuals with ASD and TD controls

Methods

We extracted data from ABIDE database for all males age 13-17 with verbal IQ in range of 85 to 115, to minimize confounding by differences associated with age, IQ, and gender. We limited our analysis to those subjects with documented total scores on the Social Responsiveness Scale (SRS). The final dataset included 29 subjects with ASD and 27 TD subjects (Table 1). Seed-to-voxel rsFC analyses were performed using the CONN-fMRI toolbox v18a and SPM12 with the rpSTG as defined by the FSL Harvard-Oxford Atlas used as the seed. Resting state analysis included motion correction (timepoints scrubbed if framewise displacement > 0.9mm), intensity normalization and band-pass temporal filtering (0.05-0.001 Hz), and regression of nuisance covariates. SRS scores were used as regressors in the analysis, controlling for age. A peak voxel threshold of p<0.001 and a cluster extent threshold of p<0.05 were set for positive and negative associations of connectivity (2-sided test), with significance defined as surviving family-wise error (FWE) correction at p<0.05. Identified regions with connectivities to rpSTG associated with SRS scores were then used in exploratory analysis as seeds to identify if connectivity association extended beyond the rpSTG.

Table 1: Subject Characteristics (reported as Mean(SD))

	ASD Group (n = 29)	TD Group (n = 27)
Age (years)	15.4 (1.5)	15.6 (1.3)
Verbal IQ	100.7 (9.5)	102.5 (8.6)
SRS T-score	90.1 (25.3)	20.7 (13.8)

REFERENCES
1. Saxe et al. Brain regions for perceiving and reasoning about other people in school-aged children. Child Dev. 2009; 80(4): 1197-1209.
2. Rane et al. Connectivity in autism: A review of MRI connectivity studies. Harv Rev Psychiatry 2015; 23(4): 223-244.
3. Di Martino et al. The autism brain imaging data exchange: towards a large-scale evaluation of the intrinsic brain architecture in autism. Mol Psychiatry 2014; 19(6): 659-667.
4. Knaus et al. Atypical PT anatomy in children with autism spectrum disorder with expressive language deficits. Brain Imaging Behav. 2017; doi: 10.1007/s11682-017-9795-7. [Epub ahead of print]
5. Kanwisher et al The fusiform face area: a module in human extrastriate cortex specialized for face perception. J Nuerosci. 1997; 5(4): 293-297.

Results

Increased Connectivity between Social Regions Associated with Social Cognition Deficits

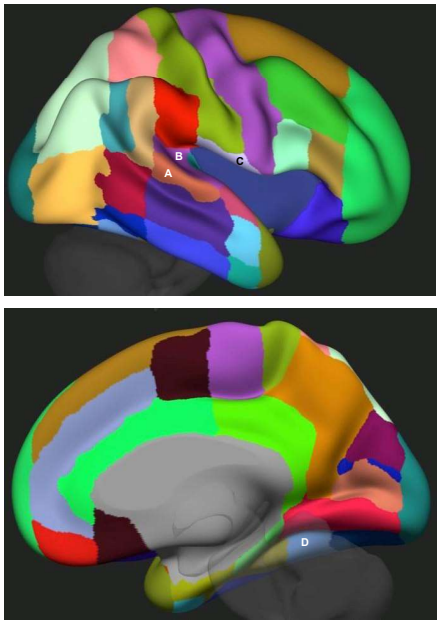
Figure 1. Harvard-Oxford atlas with regions pertinent to this analysis highlighted. Region A was the initial seed region selected for seed-to-voxel rsFC analysis.

Figure 2. Only one region was found to have its connectivity with the seed region significantly correlated with social cognition as measured by the Social Responsiveness Scale. This region included portions of the right cerebellum, and cortical regions were centered in the temporal occipital fusiform cortex (76 voxels covering 9% of region; see Region D in Figure 1),

Figure 3. Extended region of increased connectivity associated with SRS scores was identified using exploratory analysis with cluster identified in Figure 2 used as a seed for seed-to-voxel connectivity analysis. This extended region includes portions of the posterior superior temporal gyrus (43 voxels covering 10% of region; Region A in Figure 1), planum temporale (158 voxels covering 36% of region; Region B in Figure 1) and central opercular cortex (67 voxels covering 8% of region; Region C in Figure 1).

Figure 4: Graph of average connectivity between regions depicted in Figures 2 and 3 against SRS scores (Open circles = TD; Closed Circles = ASD).

Figure 1: Harvard-Oxford Atlas with Key Regions Labeled



A: Posterior Superior Temporal Sulcus (initial seed region)
B: Planum Temporale
C: Central Operculum
D: Temporal Occipital Fusiform Cortex

Figure 2: Region (in Yellow) with association between rpSTG connectivity and SRS scores

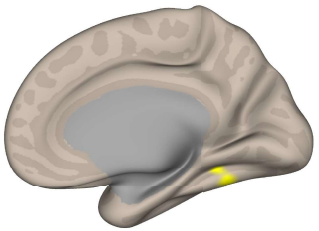
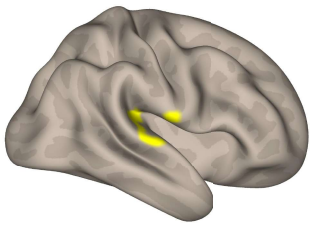
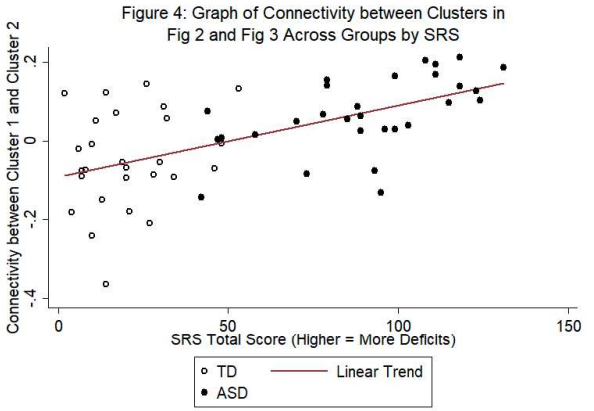


Figure 3: Extended Region (in Yellow) with association between connectivity with Fig 2 cluster and SRS scores





Conclusions

In addition to the role in interpretation of biological motion played by the rpSTG in social processing, the planum temporale is also associated with expressive language deficits in ASD[4]. In addition, the occipital fusiform cortex, also identified as the fusiform face area, is associated with face processing and plays an important role in social cognition.[5] All of these regions are intimately connected in the social brain network which is thought to be at the core of deficits in social cognition. Here, using a large database of imaging studies, we show that in higher functioning adolescent males with normal IQ, increased connectivity between these regions is associated with a greater degree of social cognition deficit across a population including individuals with ASD and TD controls. Further study is warranted to determine if these findings extend to females and lower functioning individuals.

Infants and Toddlers with Autism Spectrum Disorder Show Sexually Dimorphic Corpus Callosum Connectivity Similar to Typically Developing Counterparts

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all University of Massachusetts Medical School & Eunice Kennedy Shriver Center

Introduction

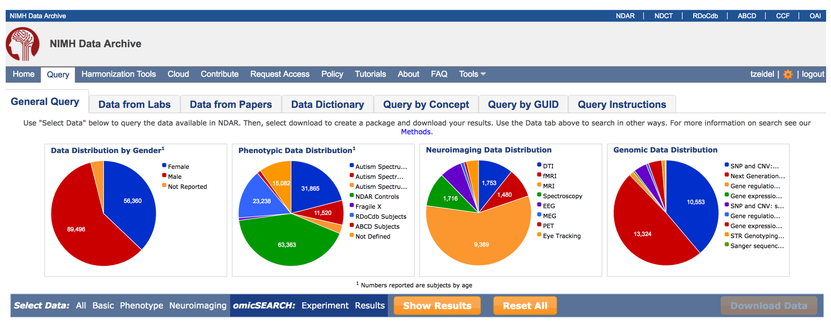
Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder that affects 1% of the world's population, and is characterized by difficulties in social interactions, as well as a repetitive and restricted behaviors[1,2].
There is a 4:1 ratio of diagnosed males to diagnosed females among individuals with ASD[1]. Girls and women with ASD are chronically under-studied, and exploring sex differences in ASD may lead to innovation in treatment for all people with ASD, as well as shed light on the biological and environmental etiology of ASD[1].

Aim

Assess the statistical relationship between sex, diagnostic group, and mean fractional anisotropy (FA) in the corpus callosum and thalamus of infants and toddlers ages 6-47 months using diffusion tensor imaging.

Methods

Clinical data and diffusion-weighted MRI scans from 184 subjects were obtained from the National Database for Autism Research (NDAR).
Subjects were assigned to four groups of 46 based on Autism Diagnostic Observation Schedule and sex (M with ASD,F with ASD, TD M, TD, F).
Some subjects in NDAR for whom a diffusion-weighted MRI scan was available were excluded from this analysis for a number of reasons. All potential typically developing (TD) controls were excluded if their data file showed a sibling with ASD, a prior language delay, or any other prior developmental delay.
Individuals who were not yet diagnosed with ASD at the time of the scan used in analysis were still assigned to the ASD group if their NDAR record showed they were diagnosed with ASD using the ADOS later in childhood.
Additionally, individuals with a medical diagnosis of pervasive developmental disorder-not otherwise specified (PDD-NOS) and an ADOS score designating ASD were included in this analysis as part of the ASD group.
A number of individuals had been diagnosed with ASD at the time of the scan available in NDAR, but for whom NDAR had record of sub-spectrum ADOS scores recorded later in childhood. These individuals were excluded from this analysis.
Groups were matched based on subject age, IQ, and symptom severity. A battery of t-tests and ANOVA tests were conducted in order to assure that there were no significant difference in mean age across all groups, as well as significant differences in IQ or symptom severity between the sexes within either diagnostic group. The typically developing group did have a significantly higher mean IQ than the ASD group.
Mean FA for the corpus callosum and the thalamus was obtained using diffusion-tensor processing of the diffusion-weighted MRI scans.
Multiway ANOVA was used to assess the effect of sex and group on mean FA in each region.



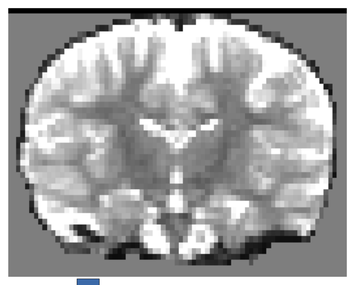
Pictured: NDAR data query user interface, courtesy of NDA

Data Use

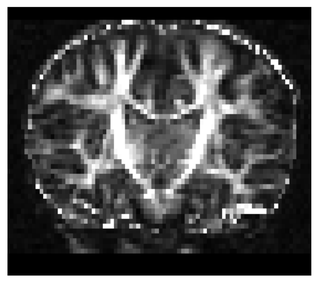
NDAR is an online repository of anthropometric, clinical, neuroimaging, and genomics data from more than 115,000 individuals with autism, healthy controls, and family members of individuals with autism. It is funded and administered by the National Institute of Mental Health (NIMH) Data Archive (NDA).
A certificate of data use agreement was granted by the NIH to the individuals involved in this analysis.
This analysis was determined to be not human subjects research by the National Institutes of Health and by the UMass Medical School Institutional Review Board due to the anonymous nature of the data.
Data was collected by the teams of Eric Courchesne, PhD and Karen Pierce, PhD at UC San Diego, and Joseph Piven, MD at UNC Chapel Hill.

MRI Scan Processing

Raw diffusion-weighted MRI files were obtained from NDAR. Files were converted to diffusion tensor images, from which regional FA values could be measured. A mean FA value was computed for each region within each subject, from which statistics by group could be analyzed.



Raw Diffusion MRI

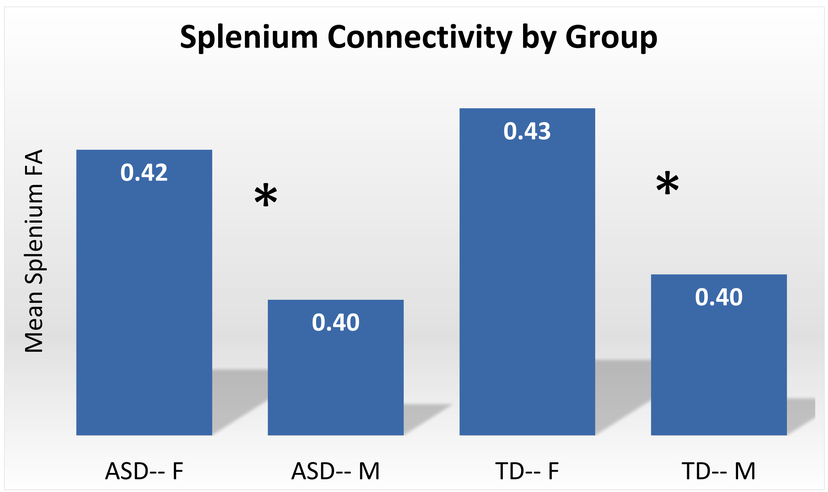


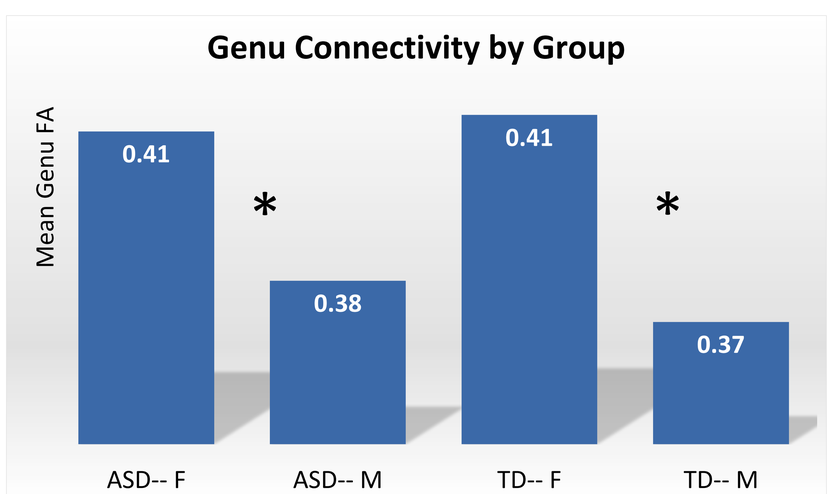
Fractional Anisotropy

Mean FA by Brain Region

Results

There was no effect of sex or group on thalamic connectivity or connectivity in the body of corpus callosum.
<u>There was a significant main effect of sex on connectivity in the genu and splenium of the corpus callosum, but no effect of diagnostic group.</u>
Additionally, there was no interaction effect of sex and diagnostic on any brain region analyzed in this study.





Conclusion

There was no interaction effect of group and sex on corpus callosum FA. Infants and toddlers with ASD show similar sexual dimorphism in corpus callosum connectivity to typically developing counter parts.

Limitations

Some demographic and past medical history data for participants in this analysis were missing from NDAR. As a result, the degree to which this sample is ethnically, racially, or socioeconomically representative of the American population is unknown. Also, groups could not be matched based on complete demographics. Furthermore, it is impossible to be certain that participants with potentially confounding medical comorbidities were excluded from this analysis.
It is also important to note that the presentation of autism, as well as gender identity are both aspects of individuality that exist on a spectrum. However, both presence of autism and sex/gender were treated as binary, categorical variables for the purpose of this analysis.

Discussion

Most neurodevelopment researchers agree that autism spectrum disorder is associated with lower brain white matter connectivity, particularly in the corpus callosum[3]. However, this conclusion may be biased by the lack of female subjects included in autism research.
Typically developing female toddlers do generally show higher connectivity, higher fiber density, and higher white matter volume in the corpus callosum when compared to their typically developing male counterparts[4,5].
Although adults with high-functioning autism show a decrease in white matter sexual dimorphism when compared to their typically developing counterparts[6], this analysis showed that infants and toddlers from a broad spectrum of autism symptom severity showed sexual dimorphism in the corpus callosum that was not dissimilar from their typically developing counterparts.
Furthermore, this analysis could not duplicate some recent preliminary findings that indicate there may be unilateral over-connectivity in the left thalamus of toddlers with autism[7].
Future DTI study of ASD gender differences must include measures to control for corpus callosum volume. Also, because handedness can confound laterality findings, children old enough to complete handedness assessments must be studied as well.
Another important future opportunity for increased nuance in the study of ASD and gender is a more open approach to gender identity. Preliminary surveys of sexuality and gender identity of adolescents and adults with ASD show that a greater proportion of people on the spectrum than of the general population report identifying with a gender non-conforming gender identity[8]. People with ASD that were assigned female sex at birth are more likely to report feelings of gender-nonconformity than are people with ASD that were assigned male at birth[8].
Gender identity may also have an effect on the specific presentation of autism. When a diverse group of people with ASD were asked to complete a detailed autism symptom inventory, transgender and non-binary individuals reported more severe cognitive symptoms, but less severe sensory symptoms than their cis-gender counterparts[9].
Complex integration of gender expression, autism symptom cluster analysis, and neuroimaging will hopefully contribute to a more robust understanding of gender, autism, and how both spectra interact to shape the developing brain.

Acknowledgements

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Ann Foley, MEd consulted on clinical instrument interpretation.

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References
1. Lai, M.-C., Lombardo, M. V., & Baron-Cohen, S. (2014). Autism. *The Lancet, 383*(9920), 896-910. https://doi.org/10.1016/S0140-6736(13)61539-1
2. American Psychiatric Association, *DSM-5*, 2013.
3. Rane, P., Cochran, D., Hodge, S. M., Haselgrove, C., Kennedy, D., & Frazier, J. A. (2015). Connectivity in Autism: A review of MRI connectivity studies. *Harvard Review of Psychiatry, 23*(4), 223–244. http://doi.org/10.1097/HRP.0000000000000072
4. Chaw-Liang, C., Nan-Chang, C., Yi-Chen, Y., Che-Sheng, H., & Kun-Long, H. (2018). Normal Development of the Corpus Callosum and Evolution of Corpus Callosum Sexual Dimorphism in Infancy. *Journal of Ultrasound in Medicine, 37(4), 869-877. doi:doi:10.1002/jum.14420*
5. Genc, S., Malpas, C. B., Ball, G., Silk, T. J., & Seal, M. L. (2018). Age, sex, and puberty related development of the corpus callosum: a multi-technique diffusion MRI study. *Brain Structure and Function, 223(6), 2753-2765. doi:10.1007/s00429-018-1658-5*
6. Beacher, F. D., Minati, L., Baron-Cohen, S., Lombardo, M. V., Lai, M.-C., Gray, M. A., & Critchley, H. D. (2012). Autism Attenuates Sex Differences in Brain Structure: A Combined Voxel-Based Morphometry and Diffusion Tensor Imaging Study. *American Journal of Neuroradiology, 33*(1), 83-89. doi:10.3174/ajnr.A2880
7. Qin, B., Wang, L., Zhang, Y., Cai, J., Chen, J., & Li, T. (2018). Enhanced Topological Network Efficiency in Preschool Autism Spectrum Disorder: A Diffusion Tensor Imaging Study. *Frontiers in Psychiatry, 9*, 278. http://doi.org/10.3389/fpsyt.2018.00278
8. Dewinter, J., De Graaf, H., & Begeer, S. (2017). Sexual Orientation, Gender Identity, and Romantic Relationships in Adolescents and Adults with Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders, 47(9): 2927-2934.* doi: 10.1007/s10803-017-3199-9.
9. Walsh, R.J., Krabbendam, L., Dewinter, J., & Begeer, S., (2018). Brief Report: Gender Identity Differences in Autistic Adults: Associations with Perceptual and Socio-cognitive Profiles. *Journal of Autism and Developmental Disorders, online only.* doi: 10.1007/s10803-018-3702-y.

A Review of Nitric Oxide Neurotransmission in Mood Disorders

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Abstract

Background: The biological basis of mood disorders (major depressive disorder and bipolar disorder) is framed in terms of biogenic amines (e.g. serotonin, dopamine, norepinephrine, glutamate) and even neurotrophic factors and inflammation. Intricately involved with all of the above is the less understood nitric oxide (NO) system.

Objective: Through a literature review, we summarize the current understanding of the NO system in context of mood disorders in order to identify underlying mechanisms.

Methods: We searched Pubmed through 2017 for animal models and limited human data on the following: mapping of the NO pathway; effects of inhibition of nitric oxide synthase (NOS) and soluble guanylyl cyclase (sGC) on depression, and indirectly in conjunction with traditional and untraditional antidepressants; and the effects of antidepressant and mood stabilizers on the NO system. The data is summarized in tables and graphs.

Results: The inhibition of NO (upstream via NMDA receptor antagonists, downstream via sGC inhibition, and the inhibition of NOS to synthesize NO) exerts antidepressant effects and also augments effects of antidepressant medications. In contrast, increasing NO levels (via direct NO donors, supplying the precursor L-arginine, or blocking the breakdown) prevents the beneficial effects of antidepressants. Finally, antidepressants and mood stabilizers led to an overall decrease of NO levels, but there was more variability in these results. Variability in results may arise in differences in agent, dose, duration, species, method of measurement, and location of measurement.

Conclusion: NO is strongly implicated in pathogenesis and treatment of mood disorders. A better understanding can lead to novel treatment options.

Tables

Substance	Effect	Model of Depression	Reference
L-NA (N^G-nitro-L-arginine)	Non-selective NOS inhibitor	mFST	(da Silva et al., 2000; Ergün and Ergün, 2007; Ergün et al., 2006; Harkin et al., 1999; Karolewicz et al., 2001)
		rFST	(Gigliucci et al., 2010; Harkin et al., 2003; Sherwin et al., 2017)
		mTST	(da Silva et al., 2000)
L-NAME (N^G-nitro-L-arginine methyl ester)	Non-selective NOS inhibitor	mFST	(Ghasemi et al., 2009a; Ghasemi et al., 2008; Ghasemi et al., 2009b; Harkin et al., 1999; Inan et al., 2004; Ostadhadi et al., 2016a; Ostadhadi et al., 2016b; Ostadhadi et al., 2016c; Ostadhadi et al., 2016d)
		rFST	(Jefferys and Funder, 1996; Sevgi et al., 2006; Spiacci Jr. et al., 2008)
		Learned helplessness model by tail shock	(Grahn et al., 2000)
		chronic unpredictable mild stress-induced depression in rat	(Lian and An, 2010)
L-NMMA (N^G-monomethyl-L-arginine)	Non-selective NOS inhibitor	mFST	(Harkin et al., 1999)
L-NPA (N^ω-propyl-L-arginine)	Selective nNOS inhibitor	mFST	(Ghasemi et al., 2008)
7-NI (7-nitroindazole)	Selective nNOS inhibitor	mFST	(Ostadhadi et al., 2016a; Ostadhadi et al., 2016b; Ostadhadi et al., 2016c; Ostadhadi et al., 2016d; Patil et al., 2005)
		rFST	(Harkin et al., 2003; Heiberg et al., 2002; Joca and Guimarães, 2006; Spiacci Jr. et al., 2008; Yildiz et al., 2000)
		mTST after chronic mild stress	(Zhou et al., 2007)
TRIM (1-[2-(trifluoromethyl) phenyl] imidazole)	Selective nNOS and iNOS inhibitor	rFST	(Sherwin et al., 2017; Ulak et al., 2008; Volke et al., 2003)
		Unpredictable chronic mild stress in mice	(Mutlu et al., 2009)
Aminoguanidine	Selective iNOS inhibitor	mFST	
		Chronic unexpected mild stress in mice	(Wang et al., 2008)
ODQ ([1H-163 [1,2,4]Oxadiazole[4,3-a]quinoxalin-1-one])	Selective guanylyl cyclase inhibitor	mFST	(Ergün and Ergün, 2007; Ghasemi et al., 2008)
		rFST	(Heiberg et al., 2002)
Methylene blue	Non-selective NOS inhbitor and guanylyl cyclase inhibitor	rFST	(Eroğlu and Çaglayan, 1997; Patil et al., 2005)
		mFST	(Ostadhadi et al., 2016a; Ostadhadi et al., 2016b)

Table 1. Antidepressant-like effects of several nitric oxide synthase (NOS) and soluble guanylyl cyclase (sGC) inhibitors in a variety of animal behavioral experiments.

Drug	NO/ cGMP modulator	Model of Depression	Result	Reference
Bupropion	Zinc chloride	mTST	augments	(Cunha et al., 2008)
	7-NI Methylene blue L-Arginine	mFST		(Dhir and Kulkarni, 2007)
	Sildenafil		prevents	
Citalopram	Zinc chloride	mFST	augments	(Szewczyk et al., 2002; Szewczyk et al., 2009)
	MK-801	rFST		(Maj et al., 1992b; Pruus et al., 2010)
	L-NA	mFST		(Harkin et al., 2004)
	TRIM	rFST		(Ulak et al., 2008)
Desipramine	Zinc chloride	mTST	augments	(Cunha et al., 2008)
	MK-801	rFST		(Pruus et al., 2010)
Fluoxetine	Zinc chloride	mFST		(Szewczyk et al., 2009)
		mTST		(Cunha et al., 2008)
	Amantadine Memantine Neramexane	rFST	augments	(Rogoz et al., 2002)
	MK-801			(Maj et al., 1992a; Pruus et al., 2010)
	L-NA			(Gigliucci et al., 2010; Harkin et al., 2004)
	7-NI			
	TRIM			(Ulak et al., 2008)
Fluvoxamine	Ketamine MK-801	Shock-induced depression in mice	augments	(Chaturvedi et al., 2001)
Imipramine	Zinc chloride	mFST	augments	(Szewczyk et al., 2002)
		mTST		(Cunha et al., 2008)
		Chronic unpredictable stress model in rats		(Cieslik et al., 2007)
	Amantadine Memantine Neramexane	rFST		(Maj and Rogoz, 2000; Reus et al., 2010; Rogoz et al., 2004; Rogoz et al., 2002)
	MK-801			(Maj et al., 1992b)
	L-NA	mFST		(Harkin et al., 2004)
	7-NI			
	L-Arginine		prevents	(Harkin et al., 1999)
Mianserin	MK-801	rFST	augments	(Maj et al., 1992b)
Oxaprotiline	MK-801	rFST	augments	(Maj et al., 1992a)
Paroxetine	Zinc chloride	mTST	augments	(Cunha et al., 2008)
	MK-801 Ifenprodil L-NAME	mFST	augments	(Ghasemi et al., 2009a)
	L-Arginine	mFST	prevents	
Reboxetine	Zinc chloride	mFST	without synergistic effect	(Szewczyk et al., 2009)
	L-NA			(Harkin et al., 2004)
	TRIM	rFST		(Ulak et al., 2008)
Sertraline	L-NA	mFST	augments	(Harkin et al., 2004)
Tianeptine	TRIM	rFST	augments	(Ulak et al., 2008)
Venlafaxine	Amantadine Memantine Neramexane	rFST	augments	(Rogoz et al., 2002)
	L-NAME Methylene blue L-Arginine	Chronic behavior despair in mice	augments prevents	(Kumar et al., 2010)

Table 2. NMDA receptor/nitric oxide synthase (NOS)/soluble guanylyl cyclse (sGC) modulators affects antidepressant-like effects of conventional antidepressants in a variety of animal behavioral experiments.

Substance	Treatment: Dose	Treatment: Duration	Species	Measurement	Region/ Cells	Result	Reference
Amitriptyline	0.3, 1 & 3 µg/µl	72 h	Human	Nitrite and nitrate levels	Synovial cells	↓	(Yaron et al., 1999)
Citalopram	20-40 mg/day	12 w	MDD patients with CAD	Total NO level	Plasma	↑	(van Zyl et al., 2009)
	15 mg/kg	2 w	Rat	Conversion of L-[^{3}H]arginine to L-[^{3}H]citrulline	Cortex, Hippocampus, Cerebellum	⇔	(Jopek et al., 1999)
	20 mg/kg/24h	3 w					(Wegener et al., 2004)
	5 mg/kg	2 h					
	1 µM	15 min	Rat	NMDA receptor-mediated depolarization-evoked increase of cGMP	Cerebellar slices	↓	(Raiteri et al., 1991)
	1 & 100 µM (via the microdialysis probe)	3 h	Rat	Conversion of L-[^{3}H]arginine to L-[^{3}H]citrulline	Hippocampus	↓	(Wegener et al., 2003)
Clomipramine	10-20 µM	24 h	Mouse	Nitrite levels after LPS stimulation	Microglia and astrocytes cultures	↓	(Hwang et al., 2008)
				iNOS mRNA expression			
Desipramine	1 & 5 µM	4 h	-	Absorbance at wavelength of 530 nm resulting from the conversion of L-arginine to NO	PC12 cells	↓	(Li et al., 2006)
Escitalopram	2.5 and 5 mg/kg	3 w	Rat	Immunohistochemical NOS Staining	Hippocampus, Cortex, Striatum	↓	(Saglam et al., 2008)
Fluoxetine	1 µM	0.5-6 h	Mouse	iNOS mRNA expression	BV2 microglial cells	↑	(Ha et al., 2006)
				Nitrite level			
	0.3, 1 & 3 µg/µl	72 h	Human	Nitrite and nitrate level	Synovial cells	↓	(Yaron et al., 1999)
	1.8 mg/kg	3 w	CMS rat	NADPH-diaphorase staining	Hippocampus (CA1 / CA2-3)		(Luo and Tan, 2001)
	10 mg/kg	3 and 7 d	Mouse	nNOS immunoblotting	Hippocampus		(Zhang et al., 2010)
	20 mg/kg	90 min	Rat	Differential pulse voltammetry and amperometry	Striatum		(Crespi, 2010)
	1 and 5 µM	4 h	-	Absorbance at wavelength of 530 nm resulting from the conversion of L-arginine to NO	PC12 cells		(Li et al., 2006)
Fluvoxamine	50 mg/kg	2 w	Rat	iNOS mRNA expression	Hippothalamus, Hippocampus, Frontal cortex, Brain stem, Cerebellum	↑	(Suzuki et al., 2002)
Imipramine	5-15 µM	24 h	Mouse	Nitrite levels after LPS stimulation	Microglia and astrocytes cultures	↓	(Hwang et al., 2008)
				iNOS mRNA expression			
	15 mg/kg	3 w	Rat	Conversion of L-[^{3}H]arginine to L-[^{3}H]citrulline	Hippocampus		(Harvey et al., 2006)
	20 µM (via the microdialysis probe)	3 h					(Wegener et al., 2003)
	10 & 20 mg/kg	30 min prior 6 h acute immobilization stress	Mouse	Nitrite level	Brain		(Kumar et al., 2009)
	20 mg/kg	20-60 min	Rat	NOx level	Amygdala		(Maruta et al., 2005)
	50 mg/kg	4 w	Rat	Nitrate level	Hippothalamus, Hippocampus, Cerebral cortex, Brain stem, Cerebellum	↑	(Suzuki et al., 2003)
				iNOS mRNA expression			
	15 mg/kg	2 w	Rat	Conversion of L-[^{3}H]arginine to L-[^{3}H]citrulline	Cortex, Hippocampus, Cerebellum	⇔	(Jopek et al., 1999)
Maprotiline	50 mg/kg	2 w	Rat	iNOS mRNA expression	Hippothalamus, Hippocampus, Frontal cortex, Brain stem, Cerebellum	↑	(Suzuki et al., 2002)
Milnacipran	10 mg/kg	2 w	Mouse	Conversion of L-[^{3}H]arginine to L-[^{3}H]citrulline	Cerebral cortex	↓	(Ikenouchi-Sugita et al., 2009)
				Nitrite level	Cerebral cortex, Hippocampus		
					Midbrain	⇔	
Moclobemide	2.5 & 10 µM	4 h	-	Absorbance at wavelength of 530 nm resulting from the conversion of L-arginine to NO	PC12 cells	↓	(Li et al., 2006)
Paroxetine	10 mg/kg	30 min	Mouse	Nitrate level	Brain		(Umathe et al., 2009)
		Acute or 2 w	Rat	Nitrite and nitrate level	Serum	↓	(Angulo et al., 2001)
				nNOS protein expression	Corpus cavernosum		
	2 µM (via the microdialysis probe)	3 h		Conversion of L-[^{3}H]arginine to L-[^{3}H]citrulline	hippocampus		(Wegener et al., 2003)
Tianeptine	2 µM (via the microdialysis probe)	3 h	Rat	Conversion of L-[^{3}H]arginine to L-[^{3}H]citrulline	hippocampus	↓	(Wegener et al., 2003)
Venlafaxine	20 mg/kg	4 w	CMS rat	Nitrite level	Cortex	↓	(Eren et al., 2007)
	2.5-10 mg/kg	5 d	Sleep-deprivated rat		Brain		(Kumar and Garg, 2008)
	5 & 10 mg/kg	7 d	Mouse with chronic behavior despair				(Kumar et al., 2010)
		30 min prior 6 h acute immobilization stress	Mouse				(Kumar et al., 2009)
Venlafaxine plus Gingo biloba	15 & 40 mg/kg	2-3 w	CMS Rat	Immunohistochemistry for nNOS protein	Hippocampus (CA3)	↓	(Qin et al., 2005)

Table 3. Effect of antidepressants on nitric oxide synthase and NO levels.

Figures

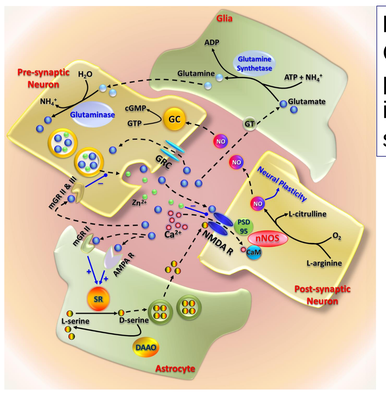

Figure 1. Glutamatergic/ NO pathway in the central nerves system.

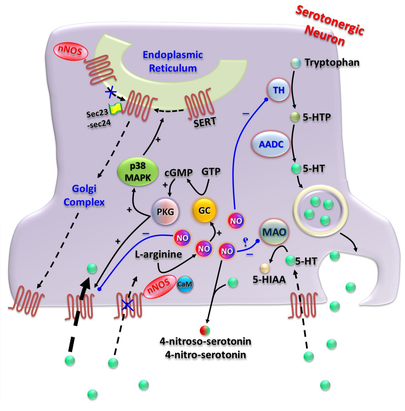

Figure 2. Multi-dimensional modulation of pre-synaptic serotonin transmission by nitric oxide (NO)

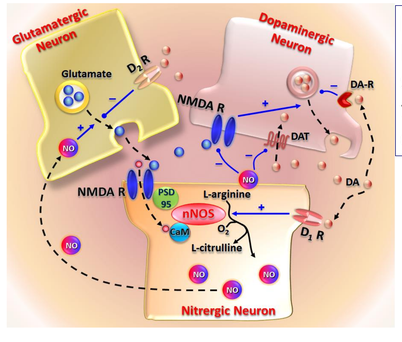

Figure 3. Regulation of tonic striatal dopaminergic transmission by nitric oxide (NO)

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Perceptions of Addiction by Individuals Mandated to Substance Use Treatment

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Introduction

Addiction disproportionately impacts criminal justice populations[1].

- Up to 65% of current or past offenders are estimated to meet criteria for substance use disorders (SUDs)[2]. Yet, most offenders fail to receive addictions treatment during or post incarceration[3].
- Nationwide, individuals recently released from prison (within two months of discharge) are 12.7 times more likely to die of a drug overdose than community members[5]. In MA, they are 55 times more likely to die within 2 months[6].
- Even when former inmates are provided with SUD treatment, including pharmacotherapy at low or no cost, most fail to remain in treatment[7].
- **Accordingly, it is critical to <u>engage and retain</u> individuals in treatment who have criminal justice involvement .**

Drug Treatment Courts (DTC) are specialty courts that mandate SUD treatment in exchange for a reduced sentence or probation

- There are more than 3,000 DTCs nationwide[8].
- Completion of DTC programs decreases drug and alcohol relapses, overdoses, and re-offense rates[9-11].
- However, dropout from DTCs can be as high as 75%, with only 49% on average completing the program[10,11].
- Those who fail to complete DTCs are usually re-incarcerated and have higher rates of drug and alcohol relapses and criminal re-offending[7-9].
- **To reduce relapses and overdoses in offenders with SUDs, we need to understand what factors contributes to dropout from DTC.**

Understanding how offenders perceive their own addiction may help to develop ways of improving retention in DTCs and treatment more broadly.

- No research to date has examined how individuals with SUDs perceive addiction.
- Existing literature looked at treatment providers, correctional personnel, and the general public perceive addiction[10-12]. This work served to improve access to treatment, reduce stigma, and engage individuals with SUDs in treatment.
- However, it may be just as critical to understand how individuals with SUDs perceive their own addictions. This can help us match individuals to treatments that are consistent with their beliefs about nature of addiction. For instance, those who believe that addiction is a disorder, might be more willing to initiate and remain in pharmacotherapy than those who perceive it as a choice.

Research Aims

To examine how probationers in DTCs perceive addiction, with the ultimate goal of developing a line of research that examines the relationship between perceptions of addiction and engagement in and retention in SUD treatment.

Methods

Methods
Participants (N=47) were recruited from 8 DTC within 4 months of enrolling. Recruitment is ongoing, with aim of 75 participants by April, 2019.

Participants complete 1) semi-structured interview and 2) self-report measures, including demographic questionnaire.

Demographics (to date):

- Male: 74.5% (n=35) Female: 25.5% (n=12)
- White: 60.9% (n=28), Black or African American 17.4% (n=8), Hispanic, 4.3% (n=2), Other 17.4% (n=8)
- Drug that caused the most harm (from TCUDS-V):
  - Heroin/opioid pain reliever – 64.4% (n=29)
  - Crack/cocaine – 20.0% (n=9)
  - Alcohol – 8.9% (n=4)
  - None reported – 4.4% (n=2)
  - Depressant medications – 2.2% (n=1)

Results

1. Preliminary findings produced the following themes about perceptions of addiction.

1. Addiction <u>is a disease or a chronic condition</u> that is a hereditary and biologically based with physical symptoms.

"You have the genes and you start using... I feel like I would like it more than someone who doesn't [have the genes]" (#07)

"It's not a choice because … you're getting physically sick" (#12)

"It rewires certain nerve ending in your brain... I've found myself wondering why I'm doing it and telling myself a million times that I'm not gonna do it, and I still end up feeling it [cravings]" (#16)

2. Addiction <u>is a choice</u>, especially relative to diseases like cancer.

"You don't have a choice of having cancer or diabetes… You have a choice to pick up a needle" (#14)

"If you're a drug addict, like a heroin addict, …you put heroin in your body the first time, and it's your decision to keep on doing it…I know it sucks, it's hard to stop …but it's not a disease... Like if you got cancer you can't say, 'Alright I don't want it anymore...'" (#23)

"My dad's a heroin addict, so I think that it's all what you choose to do with it, because my brother and sister aren't" (#17)

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Results continued

3. Addiction is influenced by <u>the environment</u>.

"It all depends on the environment you're around when you grow up. If your parents are addicts or they're just always around liquor, it gets…in your mind that it's normal." (#28)

"I wasn't born an addict, I didn't start doing heroin 'till I was 26 years old in jail… And the only reason why I did was because everybody else was doing it." (#05)

4. Addiction is <u>socially constructed</u>.

"If it was a disease how [can] they lock you up in jail?" (#21)

"I hate to even say this but do you know how much money is in addiction facilities? …Sober houses, halfway houses, it's a [expletive] market, okay? They're making more money putting us through this program than they are keeping us in jail… Realistically it's all about money and it's put as a disease to make money." (#25)

5. Addiction is a <u>weakness</u>.

"Well a lot of people are just weak minded or whatever, they just don't… If you want it bad enough, you don't wanna get high no more, you do things like groups, meetings, stuff like that, you do enough stuff to work on your addiction, you can get over it… (#05)

2. Many individuals described addiction using multiple themes, including as something that is situation dependent.

Addiction starts out as a <u>choice and then becomes a disease</u>.

"At first, if you're abstinent from drugs and alcohol, absolutely it comes down to a choice. But I feel like once you take that choice away… For me, if I put a drink or a drug in my system, that choice is gone…" (#18)

"…It's a disease to a point…the way I look at it is the second you stop using, it's choice go back out there"(#03)

Discussion

- Probationers in DTCs perceive addiction in a variety of ways, including often using multiple themes that may shift over time.
- These preliminary findings identify a range of perspectives, and highlight the potential need to match treatment to individuals' perspectives. It may be especially important to understand perspectives on addiction with populations that are mandated to treatment because they may have fewer options about the types of treatments they receive.
- Additional research, including longitudinal study, is necessary to understand how perspectives on addiction influence enrollment in and retention in treatment.
- Limitations include reliance on participant self-report, self-selected sample of probationers interested in participating in research, and generalizability of findings to other probationers and individuals with SUDs.

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Extreme Weather Events & the Onset of Psychotic Depression

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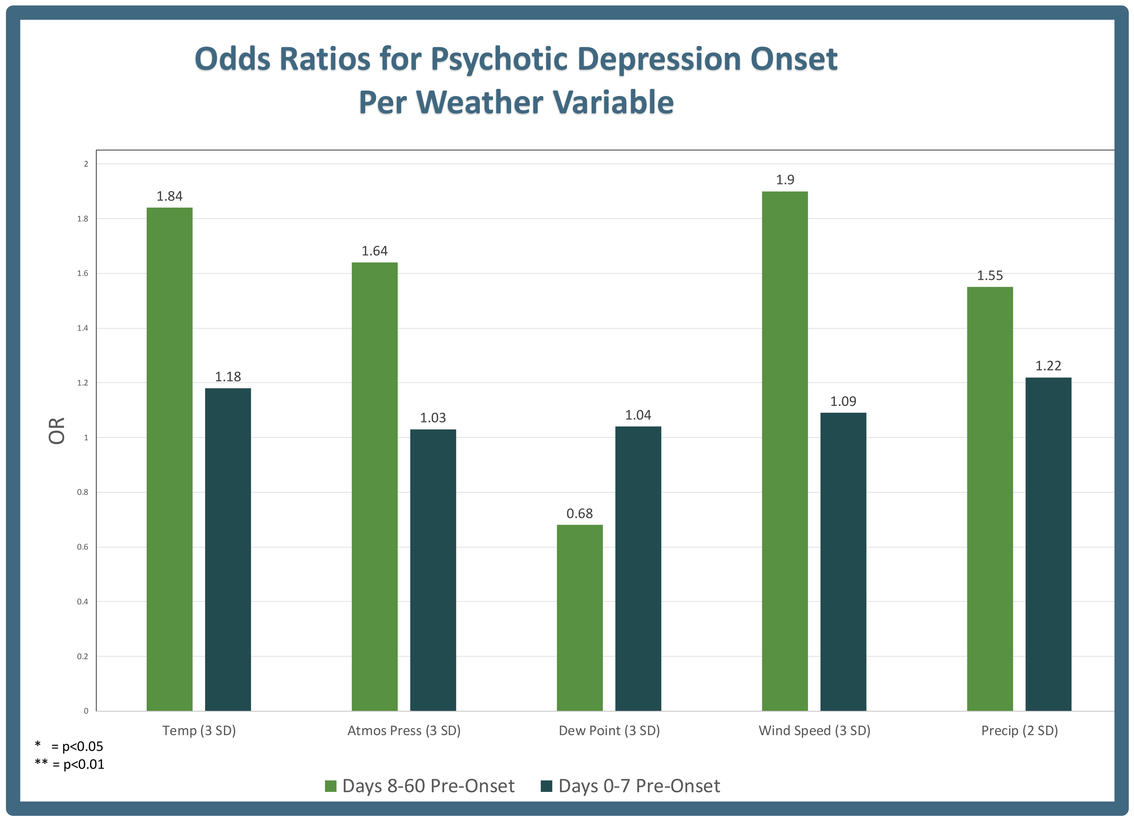
Introduction

Weather parameters are known to influence mood, behavior, and symptom severity in various disease states. Seasonal Affective Disorder is a well-established phenomenon. Additionally, a small number of investigators have found that admission rates for bipolar disorder (Shapira, 2004, *Bipolar Dis* 6:1) and suicide frequency (Maes,1994, *Acta Psych Scand* 90:5) both positively correlate with ambient temperature, while violent acts and emergency psychiatric visits both correlate with lowered barometric pressure as seen in advancing storm fronts (Schory, 2003, *Can J of Psych* 48:9.) A single European investigator found an association between lowered barometric pressure and the incidence of psychotic depression, a severe form of depression with psychotic symptoms present during the period of mood disturbance. (Radua, 2010, *Psych Res* 175:3.) The purpose of this study is to evaluate further the effects of various changing weather parameters on the onset of psychotic depression.

Methods

- Study Sample: 259 subjects with psychotic depression who participated in the National Institute of Mental Health STOP-PD (The Study of Pharmacotherapy of Psychotic Depression) between December 2002 and June 2007. Weather events were examined in relation to these subjects' onset dates.
- Weather data was obtained from the National Oceanic and Atmospheric Administration (NOAA).
- Daily mean weather variables (temperature, dew point, barometric pressure, wind speed, precipitation) were calculated for each of the 60 days prior to a patient's onset.
- Extreme weather events (defined as 2 or 3 standard deviations from the daily historical mean (from 1980-1999) to control for seasonality and patient acclimatization) were then tabulated for each patient's pre-onset period.
- Longitudinal logistic regression models, implemented with general estimating equations (GEE), were used to determine the effect of a specific weather predictor event (such as local temperature exceeding the average temperature by 3 standard deviations on a particular day) on the outcome (episode onset), separating (through interaction terms) the effects of the weather predictor event during a longer term period (8 to 60 days before the depressive episode) and the effects of the occurrence of the weather predictor event in the immediate seven days before episode onset.
- Odds ratios were calculated from the GEE model parameter estimates to represent the effect of the weather events on the outcome.
- SAS 9.4 (SAS Institute, Cary, NC) was used for all analyses.

Results



	OR	p-Value
Temperature		
8-60d Pre-Onset	1.84	0.0038
0-7d Pre-Onset	1.18	0.0881
Atmosph. Pressure		
8-60d Pre-Onset	1.64	0.0287
0-7d Pre-Onset	1.03	0.7276
Dew Point		
8-60d Pre-Onset	0.68	0.2438
0-7d Pre-Onset	1.04	0.8305
Wind Speed		
8-60d Pre-Onset	1.90	0.0004
0-7d Pre-Onset	1.09	0.2698
Precipitation		
8-60d Pre-Onset	1.55	0.0157
0-7d Pre-Onset	1.22	0.0276

Results are expressed as odds ratios for onset of psychotic depressive episodes when proceeded by the occurrence of extremes in five weather variables (temperature, atmospheric pressure, dew point/humidity, wind speed, and precipitation.) The weather variables were classified as 2, 3, or 4 standard deviations (SD) above/below a historical average. Light green denotes the exposure period of 8 days prior to 60 days prior to onset. Dark green denotes the exposure period of 1 week prior to onset. Note that ORs are smaller and p values are larger for the dark green exposure period due to fewer extreme weather events during this shorter period. ***The longer pre-onset time models for temperature (3 SD), atmospheric pressure (3 SD), wind speed (3 SD), and precipitation (2 SD) all showed that the condition deviation from average had a subsequent effect of increasing the probability of an episode significantly. In addition, a 2 SD from the average in precipitation during the week prior also significantly increased the probability of an episode.***

Discussion

Understanding the mechanism of how weather parameters influence psychotic depression in particular and psychiatric conditions in general may provide clues regarding the underlying pathophysiology of these conditions.

Of note, weather parameters are also known to influence onset and symptom severity in various neurological conditions. For example, increased ambient temperature is a common trigger for many ailments, including those psychiatric, in multiple sclerosis and other neuroinflammatory conditions. This is thought to be due to Uhthoff's Phenomenon, the observation that heat decreases the speed of nerve conduction, especially in areas of demyelination (Frohman 2013, *Nature Rev Neuro* 9:9.) Low barometric pressure also induces migraines in susceptible individuals (Kimoto 2011, *Int Med* 5:18.) While a pressure mechanism is far from clear, it is known that healthy individuals such as pilots, climbers and divers exposed to pressure extremes may experience a wide array of neuropsychiatric symptoms (Blanchet 1997, *Stress Med* 13; Etzion 1999, *Euro J Physio* 437; Rostain 1975, *Physio & Med of Diving*.) As such, the role of barometric pressure in this study and elsewhere should not come as a complete surprise. While there is little scientific evidence to support a wind speed effect, many cultures use conditions of high winds to explain unusual behavior, eg the Sirocco Winds of Italy & the Santa Ana "Devil Winds" of Southern California.

Further directions for this research are many:

- Determining directionality of weather parameters.
- Exploring different time periods of susceptibility.
- Analyzing how weather affects remission status, need for hospitalization, and whether suicide was attempted or completed, all of which are surrogates for severity of psychotic depression.
- Investigating effects of age and gender.
- Considering synergistic effects between variables which may help to identify a perfect storm that pushes an otherwise susceptible brain into psychosis and depression.

Potential limitations of these analyses include relying on patients' reported onset dates, lack of directionality regarding the change in weather parameter, a wide pre-onset period of susceptibility, and failure of statistical models to produce meaningful results for rapid changes in weather parameters, which are likely to play a role.

Conclusions

Psychiatric disorders are known to be multifactorial. These results demonstrate that extreme weather events are a factor in the onset of psychotic depression. In particular, an individual is 1.84 times more likely to experience a psychotic depression if he or she is exposed to a 3 SD temperature event in the time period of 8 to 60 days prior to onset. Similarly, during this same time period, an individual is 1.64 times more likely to experience an episode if exposed to a 3 SD barometric pressure event, 1.9 times more likely to experience an episode if exposed to a 3 SD wind speed event, and 1.55 times more likely to experience an episode if exposed to a 2 SD precipitation event. Additionally, an individual is 1.22 times more likely to experience an episode if exposed to a 2 SD precipitation event during the week prior to onset.

While the mechanism at this point is largely speculative and the implications for the treatment of psychiatric illness require further research, the present results support the role of environmental factors in the onset of psychiatric illness. Given the known role of temperature in nerve conduction and the variety of neuropsychiatric symptoms seen at pressure extremes, these results also support a physiological, neurological and neuroinflammatory basis for psychotic depression.

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