Heterogeneity in Neurodevelopmental Disorders: Identification, Nosology, and Intervention

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Symposium

Traditional psychiatric nosology categorizes individuals into distinct groups based on set criteria taken from the Diagnostic and Statistical Manual of Mental Disorders (DSM). Relatively recently, the Research Domain Criteria (RDoC) initiative within the National Institute of Mental Health has emerged from an appreciation that heterogeneity within DSM-defined diagnostic categories precludes the ability to use diagnosis to inform and improve targeted treatments. The RDoC framework has led to important research investigating continuous instead of categorical measures of symptom burden across many levels of inquiry (genomics, neural circuits, behavior, self-reports). We propose that an understanding of heterogeneity within and across diagnostic boundaries will improve characterization of the neural and behavioral features of typical and atypical development, ultimately allowing for improved outcome prediction and individually-targeted treatments. Talks in this symposium will address a range of timely and relevant issues, including heterogeneity within and across highly comorbid neurodevelopmental disorders (ADHD and autism spectrum disorder), transdiagnostic risk factors for suicidal ideation and behaviors, and leveraging heterogeneity to shed light on differing response to treatment for ADHD and for reading intervention. By the end of this symposium, it is hoped that attendees will appreciate the importance of characterizing brain function and dysfunction related to cognitive and clinical heterogeneity so as to better understand the mechanisms underlying such heterogeneity, and the promise this approach has for the development of personalized treatment strategies. This line of research contributes important insights to the recent push for personalized treatments and deep phenotyping in research, medicine, and education, and is thus highly relevant and addresses a topic currently under debate.

Objective

Learning objectives for this symposium include: 1) to gain knowledge about methods via which to study individual differences relevant to cognitive and clinical heterogeneity; 2) to understand how a dimensional approach to studying typical and atypical development can lead to a richer understanding of heterogeneity within and across diagnostic categories; and 3) to learn about the benefits and shortcomings of both current nosology and of efforts toward implementing personalized medicine.

Target Audience

The target audience for this symposium includes researchers who are working with special populations or groups that differ on various factors (e.g., age, academic ability), who are interested in better understanding heterogeneity within populations, and who wish to understand the pros and cons of categorical versus

dimensional approaches in translational research. We also aim to pitch our symposium towards young investigators and trainees.

Presentations

Parsing heterogeneity in prevalent neurodevelopmental disorders using executive function profiles and individual connectome mapping

Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are characterized by considerable phenotypic heterogeneity and comorbidity. Traditional diagnostic classification schemes are increasingly recognized as imperfect predictors of etiology and treatment response. Alternative systems such as the Research Domain Criteria (RDoC) focus on the full range of variation in behavior across clinical and non-clinical populations. As neurodevelopmental disorders are often accompanied by executive function (EF) deficits (Dajani & Uddin, 2015), we focus on this set of abilities in the current work. In a latent profile analysis including behavioral measures of EF collected from children with ASD, ADHD, ASD + ADHD, and typically developing (TD) children, we found evidence for three classes of children exhibiting "above average", "average", and "impaired" EF abilities. These EF classes did not strictly reproduce diagnostic categories, indicating that current diagnostic labels may not map neatly onto distinct behavioral profiles (Dajani et al., 2016). We replicated this finding of three EF classes in an independent sample (Baez et al., 2019). A natural question is whether children falling within the three behavioral EF classes exhibit differences at the neural level. Surprisingly, we found that subgroups of children identified by EF ability irrespective of diagnostic label did not exhibit differences in functional connectivity metrics (Dajani et al., 2019a). This work suggests that neither traditional diagnostic categories nor subgroups derived from behavioral profiles clearly define neurobiologically separable groups. Finally, we attempted to parse heterogeneity in this mixed sample using individual connectome mapping including brain regions critical for EF (Dajani et al., Under Revision). We did not find evidence for stable or valid subgroups based on these brain connectivity metrics (Dajani et al., 2019b). Taken together, these studies highlight the difficulties associated with parsing heterogeneity in prevalent neurodevelopmental disorders, and suggest that novel data-driven approaches must be developed to inform a revised diagnostic nosology. References: 1) Baez AC, Dajani DR, Voorhies W, Parlade MV, Alessandri M, Britton JC, Llabre MM, Uddin LQ (2019). Parsing heterogeneity of executive function in typically and atypically developing children: A conceptual replication and exploration of social function. Journal of Autism and Developmental Disorders, Epub Ahead of Print. 2) Dajani DR, Burrows CA, Nebel MB, Mostofsky SH, Gates KM, Uddin LQ (2019b). Parsing heterogeneity in autism and attention-deficit/hyperactivity disorder with individual connectome mapping. Brain Connectivity, In Press. 3) Dajani DR, Burrows CA, Odriozola P, Baez A, Nebel MB, Mostofsky SH, Uddin LQ (2019a). Investigating functional brain network integrity using a traditional and novel categorical scheme for neurodevelopmental disorders. Neuroimage: Clinical, 21: 101678. 4) Dajani DR, Llabre M, Nebel MB, Mostofsky SH, Uddin LQ (2016). Heterogeneity of executive functions among comorbid neurodevelopmental disorders. Scientific Reports, 6:36566. 5) Dajani DR, Odriozola P, Winters M, Voorhies W, Marcano S, Baez A, Gates KM, Dick AS, Uddin LQ. Cognitive flexibility: From task adaptation to individual connectome mapping. Journal of Cognitive Neuroscience, Under Revision. 6) Dajani DR, Uddin LQ (2015). Demystifying cognitive flexibility: Implications for clinical and developmental neuroscience. Trends in Neurosciences, 38(9): 571-578.

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Can within-person models help improve our understanding of risk for suicidal ideation and behavior?

Suicidal ideation and behaviors (STBs) among youth represent a substantial public health problem, and death by suicide is the second leading cause of death for youth worldwide (Mokdad et al., 2016). Youth STBs cut across nearly all DSM disorders, yet are difficult to predict due to high heterogeneity between individuals. Beginning at the transition to adolescence, rates of STBs increase exponentially (Curtin et al., 2016, Glenn et al., 2017). Neural mechanisms offer great promise in finding pathways to STBs. In particular, a greater understanding of neural responses to acute, emotional stressors may help identify periods of enhanced risk for suicide (Miller & Prinstein, 2019). In a promising initial study, we have found that youth with suicidal ideation histories differentially recruit prefrontal regions, particularly the dorsolateral prefrontal cortex (dlPFC), during an emotion reactivity task (Miller et al., 2018). We have recently extended this finding in a larger sample (N = 123), demonstrating that neural mechanisms underlying emotional reactivity, including the dlPFC, may longitudinally predict suicidal ideation severity (Miller et al., in prep). A promising future direction is combining these neuroimaging techniques with within-person modeling to identify person specific risk models (Miller & Eisenlohr-Moul, in press). In a series of studies using within-person models, we find that STB risk is not captured within diagnostic bounds but is better predicted by within-person processes, such as facing higher-than-usual stress (Miller et al., 2017, Miller et al., 2019). Together, this line of research demonstrates that transdiagnostic mechanisms, such as emotion reactivity, may help us improve our understanding of suicide risk, particularly when paired with within-person modeling techniques. References: 1) Curtin S, Warner M, Hedegaard H. 2016. Increase in suicide in the United States, 1999–2014. NCHS Data Brief. 241, National Center for Health Statistics, Hyattsville, MD. 2) Glenn CR, Lanzillo EC, Esposito EC, Santee AC, Nock MK, Auerbach RP. 2017. Examining the Course of Suicidal and Nonsuicidal Self-Injurious Thoughts and Behaviors in Outpatient and Inpatient Adolescents. J. Abnorm. Child Psychol. 45(5):971–83. 3) Miller, A. B. & Prinstein, M. J. (2019). Adolescent Suicide as a Failure of Acute Stress Response Systems. Annual Review of Clinical Psychology. 15:425–50. 4) Miller AB, McLaughlin KA, Busso DS, Brueck S, Peverill M, Sheridan MA. 2018. Neural Correlates of Emotion Regulation and Adolescent Suicidal Ideation. Biol. Psychiatry Cogn. Neurosci. Neuroimaging. 3(2):125–32. 5) Miller, A. B., & Eisenlohr-Moul, T. A. (in press). Biological stress systems and suicide: A review and opportunitites for methodological innovation. Current Behavioral Neuroscience Reports. 6) Miller, A. B., Eisenlohr-Moul, T. A., Glenn, C., Turner, B., Chapman, A., Nock, M. K., & Prinstein, M. J. (2019) Does higher-than-usual stress predict non-suicidal self-injury? Evidence from two prospective studies in adolescent girls and emerging adult females. Journal of Child Psychology and Psychiatry. 60(10): 1076–84. 7) Miller, A. B., Eisenlohr-Moul, T., Giletta, M. Hastings, P. D., Rudolph, K. D., Nock, M. K., & Prinstein, M. J. (2017). A within-person approach to risk for suicidal ideation and suicidal behavior: Examining the roles of depression, stress, and abuse exposure. Journal of Consulting and Clinical Psychology, 85(7), 712-722. 8) Miller, A. B., Jenness, J.J., Sambrook, K. A., Sheridan, M. A., & McLaughlin, K. A. (in prep) Child abuse, neural markers of emotion reactivity and regulation, and adolescent suicidal ideation: A preliminary, prospective study. 9) Mokdad AH, Forouzanfar MH, Daoud F, Mokdad AA, Bcheraoui CE, et al. 2016. Global burden of diseases, injuries, and risk factors for young people's health during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet. 387(10036):2383–2401.

Presenter

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Heterogeneity in functional brain network reconfiguration after methylphenidate administration underlies individual differences in improvements in response control

Youth with ADHD exhibit substantial heterogeneity in their clinical, cognitive, and neural profiles, a feature that likely contributes to inconsistent treatment response to drugs such as methylphenidate on the individual level. In order to better target treatments to individuals, it is important to understand how these drugs exert their effects. In addition to improving symptoms in many individuals with ADHD, methylphenidate has been shown to normalize functional connectivity strength between pairs of brain regions during cognitive tasks. Despite evidence that ADHD is characterized by distributed disruptions in the functional connectome, extant research has not investigated how large-scale changes in brain organization after administration of methylphenidate may relate to improvements in behavior, nor how heterogeneity in neural response to methylphenidate may underlie heterogeneity in alleviation of clinical symptoms or cognitive deficits. Thus, in a double-blind, randomized, placebo-controlled, crossover study we conducted fMRI scans in medication-naïve children with ADHD after administration of methylphenidate and of placebo. We then compared functional brain network organization with a focus on participation coefficient, a measure of integration across distinct networks, to that of typically developing (TD) children. We additionally related change in participation coefficient to improvement in response control on a go/no-go task. We found varied neural responses to methylphenidate in the participants with ADHD, with some exhibiting little change in brain network integration and others exhibiting large changes. Critically, participants whose network integration changed the most after methylphenidate improved the most on the go/no-go task. These results indicate that there is heterogeneity within ADHD regarding how methylphenidate reconfigures brain network organization, and this heterogeneity can explain the variable treatment response observed in ADHD after methylphenidate administration.

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Dichotomous vs. continuous approaches for studying learning difficulties, ADHD, and predicting intervention response

Whether and how we may label children as needing extra assistance, through either educational or clinical assessment, varies for a myriad of reasons. For example, there are substantial disparities in access to quality health care and education, as well as variability in awareness of mental health problems and learning disabilities, creating both false positive and false negative cases. Further, there is heterogeneity of response across individuals to any intervention, be it clinical or educational. Some proportion of children in every intervention fail to respond. One challenge education and clinical researchers face is to determine how to define the struggling group at the front end: diagnosis label, symptom median-splits, cut-score thresholds, and continuous approaches will all be discussed. A second challenge researchers must address is how to define improvement over time: participants may improve on one behavioral or neuropsychological measure but not another. We summarize our experiences with pre/post neuroimaging of youth receiving in-school reading interventions (Roe et al. 2018; Nugiel et al. 2019) and studies of continuous vs. diagnosis label comparisons in a diverse sample of children with ADHD and comorbidities (Nugiel et al. under review). First, we compare continuous vs. group approaches for understanding reading ability and brain control engagement in 4th grade children before and after an in-school intervention. Across our recent studies of struggling readers, we find that different group definitions yield some overlapping

results, but also some unique results related to use of continuous rather than dichotomous measures. When determining intervention response, we discuss using a relative gain approach rather than median-split or score threshold. We also compare analyses in children with and without ADHD via diagnosis-based vs. continuous rating scale score comparisons. We find that many non-diagnosed children from the community have high parent-reported attention problems, and that a continuous rating scale approach is more sensitive for finding differences related to attention problems than a diagnostic group assignment. References: 1) Nugiel T., Roe M.A., Taylor W.P., Cirino P.T., Vaughn S.R., Fletcher J.M., Juranek J., Church J.A. (2019). Brain activity before intervention relates to future reading gains. Cortex, 111, 286-302. 2) Nugiel T, Roe MA, Engelhard LE, Mitchell ME, Zheng A, Church JA. Pediatric ADHD symptom burden relates to distinct neural activity across executive function domains (under review). 3) Roe M.A., Martinez J.E., Mumford J.A., Taylor W.P., Cirino P.T., Fletcher J.M., Juranek J., Church J.A. (2018). Control engagement during sentence and inhibition fMRI tasks in children with reading difficulties. Cerebral Cortex, 28(10), 3697-3710.

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