Background: Brain-derived neurotrophic factor (BDNF) is an activity-dependent neurotrophin that mediates many aspects of brain plasticity. BDNF-deficiency is associated with numerous psychiatric conditions that feature altered social behavior. In rodents, BDNF reduction causes elevated aggression and is associated with impaired social function. BDNF is highly expressed in the hypothalamus, a region critical for the organization of social behaviors. Transcription of BDNF is controlled by several promoters, which drive expression of multiple transcripts encoding an identical protein. The existence of unique BDNF transcripts allows for precise control of BDNF production, but the functional consequences of multiple BDNF transcripts, and how they regulate circuits that control social behaviors are unknown.
Methods: We generated mice in which production of BDNF from promoters I, II, IV and VI is selectively disrupted (BDNF-e1, BDNF-e2, BDNF-e4, and BDNF-e6). We tested these animals on a battery of social behavior assays and used quantitative PCR, ELISA and single molecule in situ hybridization to analyze expression of BDNF transcripts and BDNF protein in cell-specific populations of the hypothalamus.
Results: Disruption of BDNF produced from promoters I and II, but not promoters IV and VI, resulted in abnormal social behaviors. BDNF-e1 and BDNF-e2 animals displayed decreased latency to attack, increased number of fights, and increased number of tail rattles compared to wild-type controls. BDNF-e1 females failed to nurse pups and BDNF-e1 and BDNF-e2 breeders showed significant mating impairments. BDNF-e1 males also attacked foreign pups and estrous females significantly more than wild-type males. BDNF-e4 and BDNF-e6 animals showed normal aggression, maternal care, and reproductive behaviors. Deficits in social behaviors were accompanied by significant decreases in BDNF in the hypothalamus, but not the prefrontal cortex, of BDNF-e1 and BDNF–e2 mice. We further identified exon-1 BDNF transcripts as highly expressed in Esr1-expressing neurons in the ventromedial hypothalamus (VMH), a cell population that is causally implicated in aggression and sex-specific social behaviors.
Conclusions: These data suggest that BDNF promoters I and II play a critical role in regulating social behaviors, likely through regulation of specific neuronal populations in the hypothalamus. Disruption of BDNF from promoter I causes decreased sociability and increased aggression towards other males, pups and females, suggesting that BDNF derived from this promoter plays an important role in regulating social interactions. These studies highlight BDNF as a key molecular player in modulating complex social behaviors such as aggression, reproduction, and parenting.
Disclosure: Nothing to Disclose.

38.4 Compromised Functional Integration and Segregation in Habenula and DMN Nodes in Human Reactive Aggression

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Background: Intermittent-explosive disorder (IED) is characterized by disproportionate reactive aggression. Previously, we have shown that a propensity for physical aggression in healthy adults is linked to heightened resting glucose metabolism in the default-mode network (DMN), which is active at rest. Abnormal resting-state functional connectivity (rsFC) in the default-mode network (DMN) has been suggested as a biomarker of neuropsychiatric disorders that are characterized by emotional instability (e.g., schizophrenia, bipolar disorder, ADHD). Until today it is unclear if rsFC is compromised in reactive aggressive individuals.
Methods: We applied graph theory to identify dysfunctional nodes in RA men ($n = 12$), reporting significant behavioral features of IED including elevated trait aggression and anger, compared to low-aggressive male controls ($n = 12$). All participants underwent a 5-minute resting-state fMRI scan. We assessed differences in complex network properties including (1) global efficiency, indicating functional integration/transfer of data information across the whole network, and (2) clustering coefficient, indicating functional segregation and network robustness of resting state networks by applying graph theory to a high-resolution anatomical template.
Results: Graph theory revealed significantly increased global efficiency in the left temporal pole, and a subcortical-prefrontal network including the right middle frontal gyrus, the right thalamus, and the right habenula in RA individuals compared to controls. Moreover, RA individuals exhibited significantly decreased clustering coefficient ($p = .01$) in the occipital cortex and DMN nodes including the precuneus, the dorsal anterior cingulate cortex, and the dorso-medial prefrontal cortex.
Conclusions: Our findings suggest that an imbalance between heightened functional integration in a subcortical-prefrontal network and diminished functional segregation in DMN nodes at rest may be a biomarker for reactive aggression. Interestingly, the habenula, which showed increased global efficiency in RA individuals, has recently been linked to the valence of aggressive behavior in mice as well as the likelihood of winning fights in zebrafish. Thus, our study provides first support for the role of the habenula in human reactive aggression. Further studies across species are needed to delineate the function of the habenula with respect to the motivation to engage in aggressive behavior.
Disclosure: Nothing to Disclose.

Study Group

39. The National Neuroscience Curriculum Initiative (NNCI) – An Update on New Ways to Communicate Neuroscience

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Study Group Summary: Over the past two decades, advances in neuroscience have dramatically enhanced our understanding of the brain and of the neurobiological basis of psychiatric illness. Yet teaching neuroscience remains fraught with challenges: the field is vast and constantly evolving; many programs lack access to faculty with content