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Research Statement

Development is a period of remarkable plasticity when the environment has a profound influence on our brains, minds, and behavior. Our interactions with the environment sculpt development from basic sensation and perception to higher-order affective and cognitive functions like self-regulation and language. This experience-driven development confers both great opportunity and vulnerability for brain and cognitive health. Under typical conditions, developmental plasticity enables us to learn and adapt to our environment. However, atypical experiences or plasticity may divert development towards a range of negative health outcomes.

I study *how and when developmental plasticity interacts with environmental experiences to construct brain function, cognition, and behavior*. My research program informs typical experience-driven development, and tests how disrupted experiences (e.g. adversity) or disrupted plasticity (e.g. developmental disorders) alter development. My ongoing and future research seeks to identify how positive factors like exercise and sleep promote typical or resilient brain plasticity and health in development, and to predict individual mental health trajectories to facilitate interventions in at-risk populations. I integrate behavioral paradigms with physiology, neuroimaging, and original methodological approaches (e.g. Gabard-Durnam et al., 2018 *Brain Img. Methods*) to provide a mechanistic account of development. By investigating questions across affective and cognitive domains, my research aims to provide insight into fundamental principles of brain and behavior development.

Typical Experience-Driven Development

My first research area demonstrates how normative, day-to-day experiences shape self-regulation development. Learning to regulate emotions is a hallmark of healthy development, and emotion regulation deficits occur across diverse forms of psychopathology. Identifying windows of plasticity when experiences most heavily impact emotion regulation development is critical for both understanding and effectively intervening in mental health trajectories. However, these windows have been difficult to detect because the core brain substrates of emotion regulation, especially the prefrontal cortex, undergo prolonged development over decades (Tottenham & Gabard-Durnam, 2017 *Curr. Opin. Psychol.*). Therefore, I first sought to identify when emotion regulation brain circuitry may be most plastic across this long timeframe. I have used a resting-state functional magnetic resonance imaging (fMRI) approach that measures ongoing brain activity in the absence of specific tasks, as this signal is sensitive to changes in brain plasticity. By examining the development of resting-state fMRI in emotion regulation circuitry from infancy through adulthood, I have shown a qualitative shift in this circuit's activity between childhood and adolescence, consistent with increased plasticity before adolescence (Gabard-Durnam et al., 2014 *NeuroImage*; Gabard-Durnam, et al., 2018 *Dev. Cog. Neuro.*).

To directly compare how childhood and adolescent experiences sculpt self-regulation circuitry and behavior, I have leveraged music as an emotional experience (Gabard-Durnam et al., under review, *Science*). Analyses of adult music preferences have revealed that developmental timing of the first exposure to songs matters, such that musical tastes are set in adolescence. However, familiar music is also a powerful modulator of emotions, regardless of musical taste, and engages the prefrontal cortex. Pop songs provide age-specific music experiences to test, as they are very salient within discrete time windows (e.g. when they are heavily played on the radio). Using pop songs that adults heard first during preschool, childhood, or adolescence, I have found that under stress, adults show a selective preference for music from their childhoods relative to other periods. Only music introduced in childhood regulates adult emotion and autonomic function, via unique enhancement of adult prefrontal cortex activity. My results indicate that childhood is a period of peak plasticity when music can enduringly influence emotion regulation neurobiology and behavior. They show how and why we turn to music from childhood as a salve to relieve distress.

Identifying this sensitive window in emotion regulation development raises the question of how childhood emotional experiences become embedded in the underlying brain circuitry with persistent behavioral consequences. I have shown that over the course of childhood, affective stimuli elicit activity that gradually shapes the resting-state activity maintained years afterwards in emotion regulation circuitry (Gabard-Durnam, et al., 2016 *J. Neurosci.*). However, responses to affective stimuli in adolescence no longer

shape subsequent resting-state activity. That is, when the brain is highly plastic, brain responses to experiences becomes incorporated into the ongoing brain activity preserved in adulthood. This phenomenon in brain function development is akin to the adage "fire together, wire together" about brain structure development. Beyond informing development, these findings address an important open debate in cognitive neuroscience about how to interpret resting-state activity. These results provide empirical evidence that adult brain activity reflects one's history of developmental experiences.

Sequelae of Disrupted Experiences

Heightened plasticity in development also confers increased vulnerability to adverse experiences, which can have lasting impacts (reviewed in Gabard-Durnam & McLaughlin, 2019 *Biol. Psychiatry*). In particular, early caregiving experiences are critical to healthy affective development. For example, caregivers are important external regulators of emotion in children while their ability to self-regulate is still developing. I have found that caregiver presence elicits regulation-related brain activity, and more successful emotion regulation behavior in children (Gee*, Gabard-Durnam*, et al. 2015 *Psych. Science*). How do disrupted early caregiving experiences alter affective development? My second research area has shown that caregiving disruptions in early life can shift the timetables for developing emotion regulation behavior.

Specifically, in animal models, disrupted caregiving accelerates affective development. I have found initial behavioral evidence for the same effect in humans. Adults with early-life caregiving disruption (e.g. parental death) prefer music from an earlier preschool period, and show emotion regulation benefits from this preschool music compared to adults without this adversity (Gabard-Durnam et al., under review, *Science*). That is, early caregiving disruption appears to accelerate the developmental timing when familiar music regulates emotions. However, early caregiving adversity is also associated with higher rates of disordered emotion regulation (e.g. depression, anxiety). To test whether accelerated emotion regulation development is adaptive among those with early adversity, I have examined how caregiving disruption (e.g. orphanage care) interacts with genetic profiles (i.e. BDNF) that affect brain plasticity levels (Gabard-Durnam et al., in prep). Among youth with prior caregiver disruption, I find that individuals with genetic profiles for high brain plasticity show brain activity consistent with accelerated emotion regulation development and have reduced anxiety and depression symptoms. In contrast, youth with genetic profiles for low plasticity have aberrant brain activity and more severe symptoms. These findings show how brain plasticity facilitates adversity-accelerated development to offer short-term resilience for self-regulation behavior. Whether accelerated development confers long-term protection or mental health risk is an open question for my future research.

Sequelae of Disrupted Neuroplasticity

The typical course of experience-driven development may be altered not only when experience is disrupted, but also when experience occurs appropriately in the context of disrupted plasticity. Thus, my third research area focuses on how atypical brain plasticity affects learning from experiences and contributes to disordered development. Altered brain plasticity occurs in a range of disorders, suggesting disrupted experience-driven development is a core feature of psychopathology. In particular, atypical brain plasticity is thought to occur in neurodevelopmental disorders like Autism Spectrum Disorder. For example, electroencephalography (EEG) oscillations capture brain plasticity changes, and I have previously observed disrupted development of EEG oscillations in infants at high-risk for autism (e.g., Gabard-Durnam et al., 2015 *J. Autism Dev Disord.*). Moreover, I have taken a data-driven approach to show that altered EEG oscillations associated with brain plasticity robustly discriminate future autism diagnoses (Gabard-Durnam et al., 2019 *Nature Commun.*). By comparing EEGs over the first 3 years of life, I find that EEG oscillations within the first year already identify infants with later autism diagnoses, before behavioral symptoms largely emerge. These findings suggest that early brain plasticity measures may help expedite detection and treatment of disorders like autism compared to evaluations based solely on behavior.

To explicitly test how disrupted plasticity in autism affects learning from experiences, I have focused on early language learning as a model case. Language acquisition is an essential experience-driven process that is often disrupted in individuals with autism. These language difficulties are thought to reflect delayed plasticity windows when language components are learned. However, empirical measurements of this plasticity delay

have remained elusive. I have addressed this challenge by translating a brain plasticity measure from computational models into human EEG (Gabard-Durnam et al., in prep). I have shown that in typical development, windows of brain plasticity for learning language are initiated by changes in the brain's signal-to-noise ratio. That is, brain responses to external language "signals" are amplified relative to ongoing internal "noise" to sculpt brain function. Infants with future autism diagnoses show delayed changes in this signal-to-noise ratio, indicating delayed plasticity for learning language sounds. Moreover, the degree of signal-to-noise change predicts future language skill, illustrating how disrupted plasticity translates into disrupted cognition and behavior. My ongoing research explores how these early plasticity dynamics affect subsequent higher-order language learning functions like audiovisual integration in typical and atypical development.

Future Directions

In these ways, my research program shows how normative experiences become embedded in brain function during windows of plasticity to sculpt healthy development and impact adult behavior. Disruptions to expected experiences or plasticity may shift the timing of this experience-driven development with both adaptive and maladaptive consequences. Fundamental questions remain about how plasticity interacts with experience to shape typical and atypical development that complement my current research. I will continue to use model cases in cognitive and affective domains that enable me to best address the following aims.

First, while my ongoing research examines negative factors affecting experience-driven development, my future research *will incorporate positive factors that promote typical and resilient experience-driven development*. For example, developmental plasticity is enriched through physical activity and sleep in animal models. I have begun examining how these plasticity-promoting factors buffer against negative effects of disrupted plasticity in language learning. I am collecting pilot data on infant motor activity and sleep levels with EEGs across the window for learning language sounds in both typically developing infants and infants with medication-induced plasticity disruptions. Plasticity in emotion regulation circuitry like the prefrontal cortex is also highly sensitive to exercise and sleep in animal models. Therefore, I will test how these factors buffer against negative effects of adverse experiences in emotion regulation development. Specifically, I will conduct studies in youth with and without caregiving adversity to test how experiences get embedded in the brain to shape self-regulation behavior, and how sleep and exercise factors influence this experience-driven development. Thus, targeting plasticity enhancers across typical and at-risk populations may inform developmental interventions to promote resilient brain and cognitive health.

Second, my future research will *integrate computational approaches with empirical measures to inform experience-driven development and predict health outcomes*. I have begun to translate measures (e.g. signal-to-noise ratios) between computational models and neuroimaging data in the context of plasticity in autism. My future research will examine both computational measures and modeling frameworks across populations. For example, animal model research suggests that Bayesian model frameworks may be especially useful to parse features of experience-driven development. These measures and models combined with my empirical measures can inform new principles of experience-driven development across domains. Computational approaches will also facilitate *predictions* in development. Specifically, across individuals with prior adversity or disrupted plasticity, outcomes vary widely from resilient behavior to poor physical and mental health. The ability to accurately predict which individuals are on trajectories to negative outcomes would facilitate early interventions when there is time to redirect development. Therefore, my research will incorporate data-driven, machine-learning approaches that make individual predictions from measures of experience and developmental plasticity to identify negative outcomes. Accordingly, I have begun analyses with support vector machine-learning methods to test how early plasticity-related EEG measures in infants predict subsequent diagnostic outcomes. I would also apply these approaches to understand affective development in at-risk populations with prior adversity. Integrating computational approaches will thus facilitate explaining and predicting brain and cognitive health in development.

In these ways, I eagerly anticipate elucidating experience-driven development across brain, cognition, and behavior in my own laboratory.