Research Statement

Overview

My work is centered on the mechanisms that support the development and maintenance of internalizing disorders and substance abuse in the first three decades of life. Our work is supported by the NIMH (R01-MH107444, 2016-21) and NIDA (R21-DA040717, 2016-18) and has led to 60 chapters and papers in *PNAS*, *Nature Reviews Neurosci*, *Psychol Bull*, *Molecular Psychiatry*, *Psychol Sci*, and elsewhere (*h*-index: 29). Much of our work is focused on understanding the distributed neural circuits underlying fearful and anxious states and traits—anxious temperament, behavioral inhibition, neuroticism, trait anxiety, and so on. This extended family of traits—or what I have termed *dispositional negativity*—confer increased risk for a range of common, debilitating, and treatment-resistant mental illnesses and other kinds of adverse outcomes, from divorce to premature death (A. J. Shackman, Kaplan, et al., 2016; A. J. Shackman, Tromp, et al., 2016). To understand the origins and course of this liability, we use a broad spectrum of tools—including multimodal neuroimaging (MRI, PET), peripheral physiological measures, ecological momentary assessment (EMA), semi-structured clinical and life-stress interviews, acute alcohol manipulations, machine-learning, and genetic analyses—in a variety of populations—child and adolescent anxiety patients, young adults, community-dwelling smokers, and monkeys—working closely with collaborators in North America, Israel, Korea, and Germany. Clinically, our work promises to enhance our understanding of how fearful and anxious states and traits contribute to a range of psychiatric disorders, facilitate the discovery of novel intermediate phenotypes and biomarkers, and set the stage for developing more effective transdiagnostic interventions. From a basic psychological science perspective, our work begins to address fundamental questions about the nature and origins of temperament and the interplay of emotion and cognition—questions that often cannot be addressed using traditional behavioral or psychometric measures.

Dispositional Negativity and the Central Extended Amygdala (EAc)

Work by my group demonstrates that core features of the dispositional negativity phenotype—including heightened behavioral inhibition and elevated cortisol—can be successfully modeled in nonhuman primates (Oler, Fox, Shackman, & Kalin, 2016; A. J. Shackman et al., 2017). Monkeys provide a particularly useful model of extreme early-life anxiety; children and monkeys share similar genes, homologous brains, and a similar repertoire of defensive responses to novelty and potential threat, increasing the likelihood of successful translation to human disease. Work that I began as a postdoctoral fellow and have continued with collaborators at the Wisconsin and California National Primates Centers provides compelling evidence that trait-like individual differences in dispositional anxiety reflect heightened threat-related activity in a neural system centered on the central extended amygdala (EAc), including the central nucleus of the amygdala (Ce) and neighboring bed nucleus of the stria terminalis (BST) (Fox et al., 2015). Some parts of this circuitry—such as the Ce (chemoarchitectonically identified using an *in vivo* PET measure of serotonin transporter binding)—are commonly recruited by individuals with profoundly different manifestations of their extreme disposition (e.g., those who selectively respond to threat with increased behavioral inhibition and low levels of neuroendocrine activity or *vice versa*), reinforcing the possibility of developing 'broad-spectrum' treatments for patients with different clinical presentations of their pathological anxiety (A. J. Shackman et al., 2013). Leveraging 'resting-state' fMRI, other work highlights the importance of functional connections between the prefrontal cortex (PFC) and the EAc (Birn et al., 2014a). For example, monkeys with an anxious disposition and children with anxiety disorders show a strikingly similar pattern of reduced connectivity between the Ce and prefrontal regions implicated in the top-down regulation of emotion, highlighting the importance of this evolutionarily conserved circuit for extreme early-life anxiety. More broadly, this observation teaches us that core features of temperament can be discerned in the spontaneous, on-going activity of the brain in the absence of trait-relevant challenges (A. J. Shackman, Tromp, et al., 2016). More recently, we have begun to identify the molecular (Roseboom et al., 2014) and genetic mechanisms (Fox et al., 2015) governing trait-like individual differences in the activity and connectivity of these key regions. Leveraging the fact that all of the 592 monkeys that we have

phenotyped are members of an extended pedigree of nearly 2,000 individuals, we used FDG-PET and voxelwise genetic correlation analyses to fractionate, for the first time, the neural system underlying trait-like individual differences in the risk-conferring anxious phenotype into genetically and environmentally sensitive subdivisions, with some regions (such as the BST) mediating the heritable transmission of anxiety from parents to their offspring and other regions (such as the Ce) mediating differences in anxiety associated with experience (e.g., stress, poor parenting). More recently, we have extended this approach to fMRI-based measures of functional connectivity (which can perhaps more easily be translated to humans than FDG-PET), demonstrating that individual differences in Ce-BST connectivity also contribute to the genetic transmission of dispositional anxiety (Fox, Oler, et al., *in prep*).

This body of research has produced a number of high-profile empirical reports—with several selected for special recognition (Birn et al., 2014b) or accompanying commentaries (Roseboom et al., 2014). More recently, my work prompted an invitation from *J Neurosci* to contribute a review focused on the neurobiology of fear and anxiety (A. J. Shackman & Fox, 2016). There, my close collaborator, Drew Fox (California National Primate Center), and I challenged the widely held view—indeed, it is so pervasive that it is literally baked into RDoC—that "*the amygdala mediates fear, the BST mediates anxiety.*" On the basis of anatomical and physiological work in rodents, primates, and humans, we argued that, while the Ce and BST are certainly not interchangeable, they are more alike than different, and that both regions are critically involved in orchestrating phasic ('fearful') and sustained ('anxious') responses to a wide range of threat-related cues and contexts (see also A. J. Shackman, Tromp, et al., 2016). In the 15 months since publication, the review has proven impactful—already it has been incorporated into the writings of prominent emotion theorists—and generative, guiding the interpretation of mechanistic studies in rodents and the analysis and interpretation of imaging research in humans. An updated and refined version of our model was recently accepted for publication as part of a special issue of *Neurosci Letters* organized by Tor Wager (Fox & Shackman, *in press*). As yet, Bruce Cuthbert is not budging on RDoC. Sad!

Collectively, this corpus of work provides a strong theoretical and methodological foundation for recent and on-going work by my group. For example, we have used 3T and 7T fMRI (with NIMH collaborators) to trace the functional connectivity of the EAc in humans (Gorka, Torrisi, Shackman, Grillon, & Ernst, *in press;* Tillman et al., *accepted pending minor revisions*). As part of a NIMH-funded R01, now in its second year, we are investigating whether individual differences in threat-related EAc function prospectively predict the onset or recurrence of internalizing symptoms in young adults, particularly those exposed to significant stressors during the 30-month follow-up period (https://tinyurl.com/ShackmanR01). The overall design of this longitudinal study builds on work that I performed as a graduate student with Richie Davidson, Robin Nusslock, Jim Coan, Lyn Abramson, Lauren Alloy (Temple), and Marika Kovacs (Western Psychiatric) (Heller et al., 2009; Nusslock et al., 2011; Nusslock et al., *in press*). Through collaborations with Luiz Pessoa (Maryland) and Matthias Gamer (Würzburg), this project will also afford important opportunities to assess the value of network (i.e., graph-theoretic) models of functional connectivity and to determine the EAc's role in directing attention to threat-related social cues (A. J. Shackman, Kaplan, et al., 2016; Stout, Shackman, Pedersen, Miskovich, & Larson, 2017).

As part of a collaboration with John Curtin and Megan Piper (Wisconsin), we are testing—for the first time in humans—whether the EAc is sensitized by acute withdrawal in chronic tobacco smokers (https://tinyurl.com/ShackmanR21), as predicted by prominent models of addiction derived from rodent models, in particular, that developed by George Koob (NIAAA Director). Building on fear-potentiated startle research by Curtin's group, a related project is focused on testing whether the anxiolyic effects of acute alcohol administration reflect dampening of threat-related activity in the EAc. As part of a collaboration with Andy De Los Reyes (Maryland) and Talma Hendler (Tel Aviv), we are testing whether the EAc is sensitized among adolescents suffering from social anxiety disorder. Aside from their scientific and pedagogical utility, the data and publications arising from the tobacco, alcohol, and teen anxiety projects will support for other planned applications for extramural funding and set the stage for developing bidirectional translational models of fearful and anxious states and traits, a critical avenue for future research (Fox & Shackman, *in press;* A. J. Shackman & Fox, 2016).

Dispositional Negativity in the Wild: Ecological Momentary Assessment (EMA)

Functional imaging studies of fearful and anxious states and traits tend to rely on a limited number of well-controlled, but highly artificial manipulations—fearful and angry faces, aversive sounds and images, electric shocks, and so on—collected under unnatural conditions. Such manipulations are only mildly distressing and vulnerable to self-selection biases (A. J. Shackman & Lapate, *in press-b;* A. J. Shackman et al., 2006). Structural imaging studies, of course, simply do not permit direct inferences about functional significance. As a consequence, the real-world significance of neural systems identified in the laboratory is typically unclear. Given the limitations of ambulatory measures of brain activity—there is no 'fMRI helmet' as yet—addressing this fundamental question requires the integration of imaging assays with measures of negative affect, stress, and motivated behavior collected in the field. Using a combination of structural imaging and ecological momentary assessment (EMA) data, we recently demonstrated that individual differences in BST volume (voxelwise Jacobian determinant) positively predict negative affect in daily life—across days, context, and momentary challenges—some four years later (Fox, Shackman, et al., *in prep*). This observation reinforces our hypothesis (A. J. Shackman, Tromp, et al., 2016), that the BST helps govern the experience of trait-like differences in dispositional negativity in the real world, close to clinically important end-points, and underscores the value of this multi-method approach for identifying the neural systems associated with naturalistic variation in mood and behavior, a central goal of psychology, psychiatry, and the behavioral neurosciences. More practically, it sets the stage for analyses linking EMA to fMRI-based measures of EAc activity and connectivity using data collected as part of our on-going NIMH R01 and NIDA R21 projects. The former project is particularly interesting because it incorporates 4 waves of EMA data collection over a 30-month span—positioning us to partition trait and state variance, examine latent trajectory-based groups, assess prospective relations with internalizing symptoms, and so forth.

In collaboration with Ed Lemay (Maryland) and Todd Kashdan (George Mason), we have also used EMA and hierarchical linear modeling (HLM) techniques to identify the situational factors that govern the experience of dispositional negativity in the wild. For example, we found that individuals with a more negative disposition derive greater emotional benefits (e.g., decreased negative affect, increased positive affect) from the presence of close companions, motivating the hypothesis that friends, romantic partners, and family members serve as a regulatory 'prosthesis' for dispositionally negative individuals (A. J. Shackman et al., *in press*). In more recent work, including data collected during the first year of our NIMH R01 (n=117 usable/complete datasets: MRI + EMA + SCID5-RV + Cambridge Life Stress Interview + Psychometric Battery), we have extended our model of dispositional negativity (A. J. Shackman, Tromp, et al., 2016) in several important ways, showing that: (a) dispositionally negative individuals are exposed to fewer positive events in their daily lives; (b) dispositionally negative individuals are more reactive to positive daily events (after controlling for differences in exposure) or what Jonathan Rottenberg recently described as a 'counterintuitive mood brightening' effect (*Ann Rev Clin Psychol* 2017); and (c) socially anxious individuals are also hyper-reactive to positive daily events (Barstead, DeYoung, Anderson, & Shackman, *in prep;* Doorley, Shackman, & Kashdan, *in prep*). These results set the stage for developing targeted, scalable, low-cost psychosocial or e-Health/mHealth intervention strategies. More broadly, they begin to address fundamental questions about the interaction of emotional traits and situations (cf. Caspi et al. *Ann Rev Psychol* 2005).

Dispositional Negativity and Working Memory

Like many patients with anxiety disorders, individuals with a negative disposition are prone to pervasive distress and intrusive thoughts in the absence of immediate threat (A. J. Shackman, Tromp, et al., 2016). Building on work that I performed as a graduate student (A. J. Shackman, Maxwell, McMenamin, Greischar, & Davidson, 2011; A. J. Shackman et al., 2006; J. E. Shackman, Shackman, & Pollak, 2007), recent behavioral and electrophysiological work suggests that these symptoms may be rooted in the mis-allocation of working resources to threat-related cues (Stout, Shackman, Johnson, & Larson, 2014; Stout, Shackman, & Larson, 2013). Like selective attention, working memory is a limited-capacity workspace where information is transiently

stored and used to guide goal-directed cognition. Once lodged in working memory, threat-related information is poised to bias thoughts, feelings, and behavior when it is no longer present in the external world, promoting pervasive distress. As part of a longstanding collaboration with Chris Larson's group (UW—Milwaukee), we recently used fMRI and a well-established emotional change-detection task to show that individuals with a more negative disposition show exaggerated mis-allocation of domain-specific (fusiform) and domain-general (frontoparietal) resources to threat-related face distracters and that this mnemonic bias is mediated by heightened amygdala reactivity to task-irrelevant threat, consistent with our previously published hypothesis (Stout et al., 2013). These observations provide a novel framework for understanding the neurocognitive processes underlying dispositional risk for anxiety disorders and depression.

Dispositional Negativity and the Mid-Cingulate Cortex (MCC)

Like many anxiety patients, individuals with extreme dispositional negativity are marked by an inhibited, threat-avoidant profile of choices and behaviors, but the neural mechanisms underlying heightened instrumental avoidance in humans or other primates has only recently begun to come into focus. Work by my group, Greg Hajcak, and others suggests that it reflects alterations in a distributed circuit centered on the mid-cingulate cortex (MCC). In a highly cited recent report, Jim Cavanagh (New Mexico) and I showed that control-sensitive electrophysiological signals generated in the MCC (ERN, FRN, No-Go N2) are exaggerated in individuals with a more negative disposition—*that is, measures of cognitive control and trait negative affect show functional convergence*—and prospectively predict heightened behavioral inhibition and instrumental avoidance (Cavanagh & Shackman, 2015). In related work, I showed that negative affect, pain (which elicits robust negative affect), and cognitive control consistently recruit an overlapping territory in the MCC (A. J. Shackman, Salomons, et al., 2011). As part of an on-going collaboration with Luiz Pessoa and Dave Seminowicz (Maryland), Tor Wager (Boulder), and Wani Woo (Sungkyunkwan University, Korea), we have replicated this pattern using different meta-analytic study databases and more recently developed analytic tools (NeuroSynth vs. BrainMap/GingerALE) (A. J. Shackman et al., *in prep*). Furthermore, the same pattern emerged in a sample of subjects that alternated between negative affect (i.e., shock-threat), thermal pain, and cognitive control tasks in a single fMRI session, ruling out the possibility that the observed 3-way overlap is an artifact of the spatial blurring inherent to brain imaging meta-analyses. Remarkably, this overlap was apparent even when we assessed spatially unsmoothed fMRI data in individual subjects. In short, negative affect, pain, and cognitive control are anatomically co-localized in the MCC. Of course, we want to infer that neural overlaps provides evidence of mental overlap—that negative affect, pain, and cognitive control reflect a shared psychological process, such as salience, arousal, or adaptive control (A. J. Shackman, Salomons, et al., 2011). But this is by no means guaranteed; it could be that negative affect, pain, and cognitive control engage fundamentally different processes that are encoded in distinct (albeit overlapping) patterns of MCC activation (cf. Zaki et al. *Trends Cog Sci* 2016). To address this, we used machine learning techniques (SVM/Lasso PCR) to show that 'brain signatures' (multi-voxel pattern-based classifiers) trained on each of the tasks exhibit robust cross-classification performance (Cohen's d = 0.80-2.39; leave-one-out). Using the same data, we also developed a successful domain-general signature, providing additional evidence of representational similarity. Collectively, these observations provide compelling new evidence that negative affect, pain, and cognitive control are anatomically co-localized and functionally integrated in the MCC, enabling us to decisively reject claims that the 'dorsal ACC' is specialized for cognition (Bush et al. *Trends Cog Sci* 2000) or selective for pain (Lieberman & Eisenberger *PNAS* 2015).

Based on these and other observations, I proposed and have continued to refine *The Adaptive Control Hypothesis* (TACH), which suggests that MCC is a hub, where punishment-relevant signals are integrated and used to optimally regulate regions involved in expressing fear and anxiety, executing aversively-motivated behavior, and tuning attention, and bias reinforcement learning in the face of action-outcome uncertainty (Cavanagh & Shackman, 2015; A. J. Shackman et al., *in prep;* A. J. Shackman, Salomons, et al., 2011). This work provides a neurobiologically-grounded framework for understanding the mechanisms underlying exaggerated avoidance and aberrant punishment learning in dispositionally at-risk individuals and internalizing patients. More

broadly, these observations teach us that that emotion and cognition are assembled from partially overlapping neural 'ingredients' and, hence, should not be conceptualized as fundamentally different mental kinds or faculties (Fox, Lapate, Davidson, & Shackman, *in press;* Okon-Singer, Hendler, Pessoa, & Shackman, 2015; Okon-Singer et al., *in press;* A. J. Shackman, Fox, & Seminowicz, 2015; A. J. Shackman & Lapate, *in press-a*).

The *Nature Reviews* paper first describing TACH has been cited more than 1,000 times. It was prominently featured in recent books by Joe LeDoux and Luiz Pessoa as well as high-profile reviews by clinical and cognitive neuroscientists. It has informed the design and analysis of empirical work as well as public debates over the interpretation of those results (Wager et al. *PNAS* 2016; Lieberman et al. *PNAS* 2016; https://tinyurl.com/CingulateGate).

Development and Dissemination of Improved Methods

In support of our substantive scientific goals, my group has developed improved methods and supported their adoption by investigators at Maryland and other institutions. For example:

- Developed several fMRI-optimized paradigms for rigorously manipulating certain and uncertain threat
- Established eye-tracking at the Maryland Neuroimaging Center
- Piloted, implemented, and shared enhanced methods for fMRI data collection and processing, including multiband fMRI, improved field-map correction, high-resolution boundary-based registration and diffeomorphic spatial normalization techniques) (Smith, Hur, Kaplan, DeYoung, & Shackman, *in prep;* Tillman et al., *accepted pending minor revisions*)
- Supported the development (Fox, Shackman, et al., *in prep;* A. J. Shackman & Fox, 2016; Tillman et al., *accepted pending minor revisions*) and subsequent dissemination (Klumpers et al. *J Neurosci* in press; Najafi, Kinnison & Pessoa *bioRxiv* 2017) of improved tools and practices for identifying the major subdivisions of the extended amygdala
- Established novel methods for acute alcohol administration in the MRI environment (Hur et al., *in prep*)
- Developed and shared methods for EMA data collection (Barstead et al., *in prep;* Doorley et al., *in prep;* A. J. Shackman et al., *in press*)
- With guidance from Rick Zinbarg (Northwestern), modified the SCID5-RV to enable dimensional symptom ratings

Rigorous, Reproducible, and Transparent Science

Understanding the nature of fear and anxiety demands reproducible research. Yet, the actual reproducibility of published research in the social and biomedical sciences is alarmingly low (cf. Munafò et al. *Nature Hum Behav* 2017). The resulting 'replication crisis' provides an important opportunity for reform and my group has begun to embrace several of the most important recommendations (Fox et al., *in press*). We strive to completely and transparently describe our methods, enabling other researchers to fairly evaluate the merits and limitations of our work. Public repositories and other new tools make it easy to go a step further and directly share data and results. My lab is committed to sharing our published imaging results using NeuroVault.org and, as part of our on-going NIMH-funded work, are sharing all of our raw data (data-archive.nimh.nih.gov), enabling other researchers to combine and reuse them in novel ways. Performing studies with inadequate statistical power—which increase the likelihood of null results and false discoveries and lead to overly rosy effect-size estimates—represents another danger to reproducible science. This challenge can be challenging to surmount, given the high cost of imaging research ($600/hour at Maryland) and associated 'opportunity costs' (i.e., fewer publications), but we do our best. In some cases, this has involved *ad hoc* mini-consortia. Adopting these kinds of best practices promises to increase efficiency, enhance reproducibility, and accelerate our understanding of the nature and origins of fearful and anxious states, traits, and disorders.

REFERENCES

Barstead, M. G., DeYoung, K. A., Anderson, A. S., & Shackman, A. J. (*in prep*). Dispositional negativity in the wild: Exposure and reactivity to daily negative events.

Birn, R. M., Shackman, A. J., Oler, J. A., Williams, L. E., McFarlin, D. R., Rogers, G. M., . . . Kalin, N. H. (2014a). Evolutionarily conserved dysfunction of prefrontal-amygdalar connectivity in early-life anxiety. *Molecular Psychiatry, 19*, 915-922.

Birn, R. M., Shackman, A. J., Oler, J. A., Williams, L. E., McFarlin, D. R., Rogers, G. M., . . . Kalin, N. H. (2014b). Extreme early-life anxiety is associated with an evolutionarily conserved reduction in the strength of intrinsic functional connectivity between the dorsolateral prefrontal cortex and the central nucleus of the amygdala. *Molecular Psychiatry, 19*, 853.

Cavanagh, J. F., & Shackman, A. J. (2015). Frontal midline theta reflects anxiety and cognitive control: Meta-analytic evidence. *Journal of Physiology, Paris, 109*, 3-15.

Doorley, J., Shackman, A. J., & Kashdan, T. B. (*in prep*). Socially anxious adults are hyper-responsive to positive daily events.

Fox, A. S., Lapate, R. C., Davidson, R. J., & Shackman, A. J. (*in press*). The nature of emotion: A research agenda for the 21st century. In A. S. Fox, R. C. Lapate, A. J. Shackman, & R. J. Davidson (Eds.), *The nature of emotion. Fundamental questions* (2nd ed., pp. [http://shackmanlab.org/wp-content/uploads/2017/2007/fox_shackman_NoE_Epilogue_070917Final.pdf]). New York: Oxford University Press.

Fox, A. S., Oler, J. A., Birn, R. M., Shackman, A. J., Alexander, A. L., Rogers, J., & Kalin, N. H. (*in prep*). Functional connectivity within the primate extended amygdala predicts anxiety and is heritable.

Fox, A. S., Oler, J. A., Shackman, A. J., Shelton, S. E., Raveendran, M., McKay, D. R., . . . Kalin, N. H. (2015). Intergenerational neural mediators of early-life anxious temperament. *Proceedings of the National Academy of Sciences USA, 112*, 9118-9122.

Fox, A. S., & Shackman, A. J. (*in press*). The central extended amygdala in fear and anxiety: Closing the gap between mechanistic and neuroimaging research. *Neuroscience Letters*.

Fox, A. S., Shackman, A. J., Vack, N. J., Rosenkranz, M. A., MacCoon, D. S., Lutz, A., & Davidson, R. J. (*in prep*). Extended amygdala volume is associated with the real-world experience of dispositional negativity 4 years later.

Gorka, A. X., Torrisi, S., Shackman, A. J., Grillon, C., & Ernst, M. (*in press*). Intrinsic functional connectivity of the central nucleus of the amygdala and bed nucleus of the stria terminalis. *Neuroimage*.

Heller, A. S., Johnstone, T., Shackman, A. J., Light, S., Peterson, M. J., Kolden, G. G., . . . Davidson, R. J. (2009). Reduced capacity to sustain positive emotion in major depression reflects diminished maintenance of fronto-striatal brain activation. *Proceedings of the National Academy of Sciences USA, 106*, 22445-22450.

Hur, J., Kaplan, C. M., Bradford, D. E., Curtin, J. J., Smith, J. F., & Shackman, A. J. (*in prep*). Acute alcohol administration dampens threat-related activation in the central extended amygdala.

Nusslock, R., Shackman, A. J., Harmon-Jones, E., Alloy, L. B., Coan, J. A., & Abramson, L. Y. (2011). Cognitive vulnerability and frontal brain asymmetry: common predictors of first prospective depressive episode. *Journal of Abnormal Psychology, 120*, 497-503.

Nusslock, R., Shackman, A. J., McMenamin, B. W., Greischar, L. L., Davidson, R. J., & Kovacs, M. (*in press*). Comorbid anxiety moderates the relationship between depression history and prefrontal EEG asymmetry. *Psychophysiology*.

Okon-Singer, H., Hendler, T., Pessoa, L., & Shackman, A. J. (2015). The neurobiology of emotion-cognition interactions: Fundamental questions and strategies for future research. *Frontiers in Human Neuroscience, 9*.

Okon-Singer, H., Stout, D. M., Stockbridge, M. D., Gamer, M., Fox, A. S., & Shackman, A. J. (*in press*). The interplay of emotion and cognition. In A. S. Fox, R. C. Lapate, A. J. Shackman, & R. J. Davidson (Eds.), *The nature of emotion. Fundamental questions* (2nd ed.). NY: Oxford University Press.

Oler, J. A., Fox, A. S., Shackman, A. J., & Kalin, N. H. (2016). The central nucleus of the amygdala is a critical substrate for individual differences in anxiety. In D. G. Amaral & R. Adolphs (Eds.), *Living without an amygdala*. NY: Guilford.

Roseboom, P. H., Nanda, S. A., Fox, A. S., Oler, J. A., Shackman, A. J., Shelton, S. E., . . . Kalin, N. H. (2014). Neuropeptide Y receptor gene expression in the primate amygdala predicts anxious temperament and brain metabolism. *Biological Psychiatry, 76*, 850-857.

Shackman, A. J., & Fox, A. S. (2016). Contributions of the central extended amygdala to fear and anxiety. *Journal of Neuroscience, 36*, 8050-8063.

Shackman, A. J., Fox, A. S., Oler, J. A., Shelton, S. E., Davidson, R. J., & Kalin, N. H. (2013). Neural mechanisms underlying heterogeneity in the presentation of anxious temperament. *Proceedings of the National Academy of Sciences of the United States of America, 110*, 6145-6150.

Shackman, A. J., Fox, A. S., Oler, J. A., Shelton, S. E., Oakes, T. R., Davidson, R. J., & Kalin, N. H. (2017). Heightened extended amygdala metabolism following threat characterizes the early phenotypic risk to develop anxiety-related psychopathology. *Molecular Psychiatry, 22*, 724-732.

Shackman, A. J., Fox, A. S., & Seminowicz, D. A. (2015). The cognitive-emotional brain: Opportunities and challenges for understanding neuropsychiatric disorders. *Behavioral and Brain Sciences, 38*, e86.

Shackman, A. J., Furman, A. J., Keaser, M. L., Payano Sosa, J. S., Stockbridge, M. D., Padmala, S., . . . Seminowicz, D. A. (*in prep*). The integration of negative affect, pain and cognitive control in the midcingulate cortex.

Shackman, A. J., Kaplan, C. M., Stockbridge, M. D., Tillman, R. M., Tromp, D. P. M., Fox, A. S., & Gamer, M. (2016). The neurobiology of anxiety and attentional biases to threat: Implications for understanding anxiety disorders in adults and youth. *Journal of Experimental Psychopathology, 7*, 311-342.

Shackman, A. J., & Lapate, R. C. (*in press-a*). How do emotion and cognition interact? In A. S. Fox, R. C. Lapate, A. J. Shackman, & R. J. Davidson (Eds.), *The nature of emotion. Fundamental questions* (2nd ed.). New York, NY: Oxford University Press.

Shackman, A. J., & Lapate, R. C. (*in press-b*). What is the added value of studying the brain for understanding emotion? In A. S. Fox, R. C. Lapate, A. J. Shackman, & R. J. Davidson (Eds.), *The nature of emotion. Fundamental questions* (2nd ed.). New York, NY: Oxford University Press.

Shackman, A. J., Maxwell, J. S., McMenamin, B. W., Greischar, L. L., & Davidson, R. J. (2011). Stress potentiates early and attenuates late stages of visual processing. *Journal of Neuroscience, 31*, 1156-1161.

Shackman, A. J., Salomons, T. V., Slagter, H. A., Fox, A. S., Winter, J. J., & Davidson, R. J. (2011). The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nature Reviews. Neuroscience, 12*, 154-167.

Shackman, A. J., Sarinopoulos, I., Maxwell, J. S., Pizzagalli, D. A., Lavric, A., & Davidson, R. J. (2006). Anxiety selectively disrupts visuospatial working memory. *Emotion, 6*, 40-61.

Shackman, A. J., Tromp, D. P. M., Stockbridge, M. D., Kaplan, C. M., Tillman, R. M., & Fox, A. S. (2016). Dispositional negativity: An integrative psychological and neurobiological perspective. *Psychological Bulletin, 142*, 1275-1314.

Shackman, A. J., Weinstein, J. S., Hudja, S. N., Bloomer, C. D., Barstead, M. G., Fox, A. S., & Lemay, E. P. (*in press*). Dispositional negativity in the wild: Social environment governs momentary emotional experience. *Emotion*.

Shackman, J. E., Shackman, A. J., & Pollak, S. D. (2007). Physical abuse amplifies attention to threat and increases anxiety in children. *Emotion, 7*, 838-852.

Smith, J. F., Hur, J., Kaplan, C. M., DeYoung, K. A., & Shackman, A. J. (*in prep*). A practical suite of approaches for high-precision normalization of magnetic resonance imaging data.

Stout, D. M., Shackman, A. J., Johnson, J. S., & Larson, C. L. (2014). Worry is associated with impaired gating of threat from working memory. *Emotion, 15*, 6-11.

Stout, D. M., Shackman, A. J., & Larson, C. L. (2013). Failure to filter: Anxious individuals show inefficient gating of threat from working memory. *Frontiers in Human Neuroscience, 7*, doi: 10.3389/fnhum.2013.00058.

Stout, D. M., Shackman, A. J., Pedersen, W. S., Miskovich, T. A., & Larson, C. L. (2017). Neural circuitry governing anxious individuals' mis-allocation of working memory to threat. *Scientific Reports, 7*, 8742.

Tillman, R. M., Stockbridge, M. D., Nacewicz, B. M., Torrisi, S., Fox, A. S., Smith, J. F., & Shackman, A. J. (*accepted pending minor revisions*). Intrinsic functional connectivity of the central extended amygdala. *Human Brain Mapping*.