The Interplay of Emotion and Cognition

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Until the 20th century, the study of emotion and cognition was largely a philosophical matter. Although contemporary theoretical perspectives on the mind and its disorders remain heavily influenced by the introspective measures that defined this earlier era of scholarship, the last several decades have witnessed the emergence of powerful new tools for objectively assaying emotion and brain function, which have yielded new insights into the interplay of emotion and cognition. Here, we consider ways in which this rapidly growing body of research begins to address more specific questions about how emotional and cognitive processes interact, how they are integrated in the brain, and the implications for understanding neuropsychiatric disease.

EMOTION INFLUENCES COGNITION

Emotion—including emotional cues, emotional states, and emotional traits—can profoundly influence key elements of cognition in both adaptive and maladaptive ways.

Emotional Stimuli Grab Attention

Emotionally-salient cues—snakes, spiders, angry faces, and erotica, to name a few—strongly influence attention. Attention is a fundamental property of perception and cognition. "Attention is necessary because…the environment presents far more perceptual information than can be effectively processed, one's memory contains more competing traces than can be recalled, and the available choices, tasks, or motor responses are far greater than one can handle" (Chun, Golomb, & Turk-Browne, 2011, p. 75). Attentional mechanisms select the most relevant sources of information while inhibiting or ignoring potential distractions and competing courses of action (Desimone & Duncan, 1995). Once a target is selected from competing options, attention determines how deeply it is processed, how quickly and accurately a response is executed, and how well it is later remembered.

Remarkably, emotion influences all of these processes. Across a range of tasks, emotionally-salient stimuli are more likely to be detected, to capture attention, and to be remembered (Carretie, 2014; Markovic, Anderson, & Todd, 2014; Pool, Brosch, Delplanque, & Sander, 2016). Emotional stimuli are associated with enhanced processing in sensory regions of the brain and amplified processing is associated with faster and more accurate performance (Carretie, 2014; Kouider, Eger, Dolan, & Henson, 2009; Lim, Padmala, & Pessoa, 2009; Pourtois, Schettino, & Vuilleumier, 2013; Vuilleumier et al., 2002).

Individuals show marked differences in the amount of attention they allocate to emotionally salient information. Such attentional biases are intimately related to emotional traits and disorders. Hyper-vigilance for threat is a core component of both dispositional and pathological anxiety (Grupe & Nitschke, 2013). Children and adults with a more anxious disposition, like many patients with anxiety disorders, tend to allocate excess attention to threat-related cues when they are present in the environment, even when they are irrelevant to the task at hand (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007; Dudeney, Sharpe, & Hunt, 2015; Okon-Singer, Alyagon, Kofman, Tzelgov, & Henik, 2011; Van Bockstaele et al., 2014). On average, anxious individuals are more likely to initially orient their gaze towards threat in free-viewing tasks; they are quicker to fixate threat-related targets in visual search tasks; and they show difficulty disengaging from threat-related distractors in spatial cueing, visual search, and dot-probe tasks (Armstrong & Olatunji, 2012; Aue & Okon-Singer, 2015; Cisler & Koster, 2010; Rudaizky, Basanovic, & MacLeod, 2014). In some cases, more complex patterns of initial vigilance followed by avoidance have been reported (Armstrong & Olatunji, 2012; Aue & Okon-Singer, 2015; Di Simplicio et al., 2014; Mogg & Bradley, 2016; Onnis, Dadds, & Bryant, 2011; Weierich, Treat, & Hollingworth, 2008; Zvielli, Bernstein, & Koster, 2014).

There is compelling evidence that attentional biases to threat causally contribute to the development and maintenance of extreme anxiety (Shackman, Kaplan, et al., 2016). Attentional biases to threat can promote inflated estimates of threat intensity or likelihood (Aue & Okon-Singer, 2015), a key feature of the anxious phenotype (Grupe & Nitschke, 2013). Furthermore, interventions targeting the attentional bias to threat have been shown to reduce distress, behavioral signs of anxiety, and intrusive thoughts elicited during subsequent exposure to cognitive stressors, public speaking challenges, and worry inductions in non-clinical samples (Dennis & O'Toole, 2014; MacLeod & Mathews, 2012). Consistent, medium-to-small treatment effects have also been found in clinical samples (Heeren, Mogoase, Philippot, & McNally, 2015; Linetzky, Pergamin-Hight, Pine, & Bar-Haim, 2015; MacLeod & Clarke, 2015).

The impact of emotion on attention reflects the coordinated activity of multiple cortical and subcortical brain regions (Arend, Henik, & Okon-Singer, 2015; Pessoa & Adolphs, 2010). Here, we focus on the role of the amygdala, a heterogeneous collection of nuclei buried beneath the temporal lobe (Fox & Kalin, 2014; Freese & Amaral, 2009). Imaging and single unit studies performed in humans and monkeys demonstrate that the amygdala is sensitive to a broad range of emotionally and motivationally significant stimuli, including emotional faces and images, erotica, food, and substance cues (Chase, Eickhoff, Laird, & Hogarth, 2011; Costafreda, Brammer, David, & Fu, 2008; Fried, MacDonald, & Wilson, 1997; Fusar-Poli et al., 2009; Gothard, Battaglia, Erickson, Spitler, & Amaral, 2007; Hoffman, Gothard, Schmid, & Logothetis, 2007; Kirby & Robinson, *in press;* Kuhn & Gallinat, 2011; Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012; Sabatinelli et al., 2011; Sergerie, Chochol, & Armony, 2008; Sescousse, Caldu, Segura, & Dreher, 2013; Tang, Fellows, Small, & Dagher, 2012; Wang et al., 2014). Mechanistic studies in animals and anatomical tracing studies in nonhuman primates suggest that the amygdala can prioritize the processing of emotional stimuli via at least two mechanisms: directly, via excitatory projections to relevant areas of sensory cortex (e.g., fusiform face area) and indirectly, via projections to ascending neurotransmitter systems in the basal forebrain and brainstem that, in turn, modulate sensory cortex (i.e., increase the neuronal signal-to-noise ratio; Davis & Whalen, 2001; Freese & Amaral, 2009). Imaging research shows that variation in amygdala activation predicts whether degraded emotional stimuli are detected and that this association with performance is mediated by enhanced activation in sensory cortex (Lim et al., 2009). Manipulations that increase amygdala reactivity also enhance behavioral measures of threat vigilance (Herry et al., 2007). Conversely, disorders (e.g., autism) and manipulations that reduce the amount of attention allocated to aversive or potentially threat-relevant information lead to decreased amygdala engagement (Dalton et al., 2005; Pessoa, McKenna, Gutierrez, & Ungerleider, 2002; Urry, 2010; van Reekum et al., 2007). Likewise, patients with amygdala damage and monkeys with selective amygdala lesions fail to show enhanced activation to emotional cues in sensory cortex, indicating that the amygdala mechanistically contributes to the attention-grabbing properties of emotional stimuli (Hadj-Bouziane et al., 2012; Rotshtein et al., 2010; Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004).

The amygdala is not a passive recipient of emotional information in the environment. In addition to boosting sustained attention and vigilance, the amygdala plays a key role in redirecting gaze (i.e., overt attention) to the most emotionally salient features of facial expressions (Shackman, Kaplan, et al., 2016). Using a combination of eye tracking and brain imaging, we have demonstrated that humans are biased to reflexively attend the eye region of the face, that this bias is most pronounced for fearful faces, and that individuals showing greater amygdala activation are more likely to shift their gaze to the eyes (Gamer & Buchel, 2009; Scheller, Buchel, & Gamer, 2012). This bias appears to be exaggerated among individuals with a more anxious, neurotic disposition (Perlman et al., 2009). Importantly, individuals with damage to amygdala do not show reflexive saccades to the eyes (Gamer, Schmitz, Tittgemeyer, & Schilbach, 2013). This observation is consistent with evidence that patient SM, who is characterized by near-complete, bilateral destruction of the amygdala, fixates the mouth rather than the eyes in both real-world social interactions and well-controlled laboratory assessments (Adolphs et al., 2005; Spezio, Huang, Castelli, & Adolphs, 2007). Collectively, these observations indicate that the amygdala is crucial for the rapid detection and reorienting of attention to emotionally and motivationally significant cues.

Emotional Cues Hijack Working Memory Capacity

Selective attention is tightly linked with working memory (Ikkai & Curtis, 2011). Working memory is the 'blackboard of the mind' (Goldman-Rakic, 1996), a limited-capacity workspace where information is actively maintained, recalled, and manipulated (D'Esposito & Postle, 2015). The transient representation of task-sets, goals, and other kinds of information in working memory plays a crucial role in sustaining goal-directed attention, biasing behavior in the face of distraction, and regulating emotion (Miller & Cohen, 2001). In short, information transiently held in working memory is a key determinant of our momentary thoughts, feelings, and behavior.

Recent work by our group indicates that emotionally salient information enjoys privileged access to working memory. Using a combination of electrophysiological and behavioral assays, we showed that threat-related distracters infiltrate working memory and that this effect is exaggerated among individuals with a more anxious disposition (Stout, Shackman, Johnson, & Larson, 2014; Stout, Shackman, & Larson, 2013). In other words, anxious individuals allocate excess storage capacity to threat, even when it is completely irrelevant to the task at hand and no longer present in the external world. This may help to explain anxious individuals' tendency to experience heightened distress and intrusive thoughts in the absence of clear and immediate danger (Barlow, Sauer-Zavala, Carl, Bullis, & Ellard, 2013; Grupe & Nitschke, 2013; Shackman, Tromp, et al., 2016). Once lodged in working memory, threat-related information is poised to bias the stream of information processing (i.e., attention, memory retrieval, and action) long after it is no longer present in the real world, promoting worry and other maladaptive cognitions (Thiruchselvam, Hajcak, & Gross, 2012). Consistent with this hypothesis, recent work suggests that interventions aimed at strengthening working memory can cause lasting reductions in anxiety (Sari, Koster, Pourtois, & Derakshan, *in press*).

Emotional States Strengthen Some Cognitive Processes While Weakening Others

Classically, cognition and emotion have been viewed as oppositional forces (Shackman, Fox, & Seminowicz, 2015). From this perspective, moods and other emotional states simply short-circuit cognition. But with the ascent of evolutionary theory in the 19th century, many scientists adopted the view that emotions are functional and enhance fitness (Darwin, 1872/2009; Schwabe & Wolf, 2013; Todd & Anderson, 2013). In short, emotions are more adaptive than not and "there is typically more cooperation than strife" between emotion and cognition (Levenson, 1994). Consistent with this more nuanced perspective, there is growing evidence that experimentally elicited states of stress and anxiety facilitate some kinds of information processing, while degrading others. For example, anxiety enhances sustained attention and vigilance, potentiating early sensory cortical responses to innocuous environmental stimuli and increasing the likelihood that emotionally-salient information will be detected (Shackman, Maxwell, McMenamin, Greischar, & Davidson, 2011). Other work indicates that stress and anxiety disrupt working memory (Arnsten, 2009; Arnsten & Goldman-Rakic, 1998; Moran, 2016; Robinson, Vytal, Cornwell, & Grillon, 2013; Shackman et al., 2006).

Recent work suggests that some of these consequences may reflect stress-induced sensitization of the amygdala. Brief exposure to acute stressors (e.g., threat-of-shock, aversive film clips) potentiates defensive reactions elicited by threat-related facial expressions (Grillon & Charney, 2011), promotes sustained increases in spontaneous amygdala activity (Cousijn et al., 2010), and amplifies amygdala reactivity to threat-related faces (Pichon, Miendlarzewska, Eryilmaz, & Vuilleumier, 2015; van Marle, Hermans, Qin, & Fernandez, 2009). Acute stressors produce even longer-lasting changes (minutes to hours) in the functional connectivity of the amygdala (Vaisvaser et al., 2013; van Marle, Hermans, Qin, & Fernandez, 2010). Stress-induced sensitization appears to be elevated in individuals with a more anxious, neurotic disposition (Everaerd, Klumpers, van Wingen, Tendolkar, & Fernandez, 2015).

COGNITION REGULATES EMOTION

In the first edition of *The Nature of Emotion*, Ekman and Davidson wondered whether we can control our emotions. Two decades later, there is ample affirmative evidence. In fact, humans frequently regulate their emotions and we do so using a variety of increasingly well understood cognitive strategies (Gross, 2015a, 2015b; Sheppes, Suri, & Gross, 2015). Work to understand the neurobiological underpinnings of this core human capacity indicates that circuits involved in attention and working memory play a crucial role in the regulation of emotion and other, closely related aspects of motivated behavior, such as temptation and craving (Etkin, Buchel, & Gross, 2015; Hare, Malmaud, & Rangel, 2011; Kelley, Wagner, & Heatherton, 2015).

Perhaps the most basic strategy for reducing distress is attentional avoidance; that is, simply shift attention look away from the source of distress (Gross, 2015a). Covert or overt attentional redeployment is a potent, relatively effortless means of regulating the engagement of subcortical structures, such as the amygdala, that play a key role in orchestrating emotional states (Dalton et al., 2005; Okon-Singer, Lichtenstein-Vidne, & Cohen, 2013; Okon-Singer, Tzelgov, & Henik, 2007; Pessoa et al., 2002; Urry, 2010; van Reekum et al., 2007).

Other strategies for regulating emotional states, such as cognitive reframing and reappraisal (e.g., Heller et al., 2009), require the effortful maintenance of an explicit regulatory goal or model and depend on a working memory circuit encompassing the lateral prefrontal (PFC) and posterior parietal cortices (PPC) (Buhle et al., 2014; Rolls, 2013). Consistent with this perspective, individual differences in working memory capacity are predictive of reappraisal success (Etkin et al., 2015) and experimentally elicited stress, which is known to degrade working memory, disrupts the regulation of aversive emotional states (Raio, Orederu, Palazzolo, Shurick, & Phelps, 2013). Moreover, recent work using transcranial direct-current stimulation demonstrates that the lateral PFC is crucial for emotion regulation (Feeser, Prehn, Kazzer, Mungee, & Bajbouj, 2014), consistent with work focused on the neurobiology of impulsivity and self-control (Wagner & Heatherton, 2014).

EMOTION AND COGNITION ARE FUNCTIONALLY AND ANATOMICALLY INTEGRATED

Humans tend to experience cognition and emotion as fundamentally different. Emotion is infused with feelings of pleasure or pain and manifests in readily discerned changes in the body, whereas cognition often appears devoid of substantial hedonic, motivational, or somatic features. These apparent differences in phenomenological experience and peripheral physiology led many classical scholars to treat emotion and cognition as distinct mental faculties (Okon-Singer, Hendler, Pessoa, & Shackman, 2015).

But contemporary theorists have increasingly rejected the claim that emotion and cognition are categorically different (Barrett & Satpute, 2013; Damasio, 2005; Lindquist & Barrett, 2012; Pessoa, 2013). This perspective reflects four lines of evidence. First, imaging research demonstrates that key emotional and cognitive processes are co-localized in the brain (Shackman, Salomons, et al., 2011). Second, electrophysiological research shows that prototypical cognitive control signals (e.g. No-Go N2, error-related negativity) systematically co-vary with emotional traits and states (Cavanagh & Shackman, 2015). Third, canonical territories of 'the cognitive brain' (e.g., lateral PFC) play a central role in regulating emotion and motivated behavior (Buhle et al., 2014). Fourth, canonical territories of 'the emotional' brain (e.g., amygdala) regulate cognition via their influence over the brainstem neurotransmitter systems (Arnsten, 2009; Davis & Whalen, 2001). In this way, the amygdala can transiently assume control over attention, working memory, and behavior in situations that favor immediate responses over slower, more deliberate forms of reasoning. Of course, this can be maladaptive and there is abundant evidence that stress promotes impulsive, risky behaviors (Kelley et al., 2015; Wagner & Heatherton, 2014) and disrupts volitional forms of emotion regulation (Raio et al., 2013).

CONCLUSIONS

The last decade has witnessed an explosion of interest in the interplay of emotion and cognition and greater attention to key methodological and inferential pitfalls (Shackman et al., 2015; Shackman et al., 2006). The work we have highlighted illustrates the tremendous advances that have already been made. This body of research demonstrates that emotional cues, states, traits, and disorders can profoundly influence key elements of cognition, including selective attention, working memory, and cognitive control. In turn, circuits involved in attention and working memory contribute to the regulation of emotion. The distinction between 'the emotional brain' and 'the cognitive brain' is blurry and context-dependent. Indeed, there is compelling evidence that territories (e.g., dlPFC, MCC) and processes (e.g., attention, working memory, cognitive control) conventionally associated with cognition play a central role in emotional states, traits, and disorders. Furthermore, putatively emotional and cognitive regions dynamically influence one another via a complex web of recurrent, often indirect anatomical connections in ways that jointly contribute to adaptive behavior. These observations show that emotion and cognition are deeply interwoven in the fabric of the brain, suggesting that widely held beliefs about the key constituents of 'the emotional brain' or 'the cognitive brain' are fundamentally flawed.

Despite this progress, our understanding of the interplay of emotion and cognition remains far from complete and a number of important challenges remain. Indeed, we are reminded of Ekman and Davidson's comment in the first edition of *The Nature of Emotion*: "There are many promising findings, many more leads, [and] a variety of theoretical stances" (Ekman & Davidson, 1994). As described in detail elsewhere, addressing these challenges will require a greater emphasis on: (a) assessing the real-world relevance of laboratory assays, including measures of brain activity; (b) characterizing the distributed circuits underlying emotion-cognition interactions, and (c) integrating mechanistic and non-mechanistic research strategies (Okon-Singer et al., 2015; Shackman et al., 2015).

Developing a deeper understanding of the interplay of emotion and cognition is a matter of theoretical as well as practical importance. Many of the most common, costly, and challenging to treat neuropsychiatric disorders—anxiety, depression, schizophrenia, substance abuse, chronic pain, autism, and so on—involve prominent disturbances of both cognition and emotion, suggesting that they can be conceptualized as disorders of the emotional-cognitive brain. These disorders impose a larger burden on public health and the global economy than either cancer or cardiovascular disease (Collins et al., 2011; DiLuca & Olesen, 2014; Whiteford et al., 2013), underscoring the need to accelerate efforts to understand the mechanisms underlying the interplay and integration of emotion and cognition.

REFERENCES

Adolphs, R., Gosselin, F., Buchanan, T. W., Tranel, D., Schyns, P., & Damasio, A. R. (2005). A mechanism for impaired fear recognition after amygdala damage. *Nature, 433*, 68-72.

Arend, I., Henik, A., & Okon-Singer, H. (2015). Dissociating emotion and attention functions in the pulvinar nucleus of the thalamus. *Neuropsychology, 29*, 191-196.

Armstrong, T., & Olatunji, B. O. (2012). Eye tracking of attention in the affective disorders: a meta-analytic review and synthesis. *Clinical Psychology Review, 32*, 704-723.

Arnsten, A. F. (2009). Stress signalling pathways that impair prefrontal cortex structure and function. *Nature Reviews. Neuroscience, 10*, 410-422.

Arnsten, A. F., & Goldman-Rakic, P. S. (1998). Noise stress impairs prefrontal cortical cognitive function in monkeys: evidence for a hyperdopaminergic mechanism. *Archives of General Psychiatry, 55*, 362-368.

Aue, T., & Okon-Singer, H. (2015). Expectancy biases in fear and anxiety and their link to biases in attention. *Clinical Psychology Review, 42*, 83-95.

Bar-Haim, Y., Lamy, D., Pergamin, L., Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2007). Threat-related attentional bias in anxious and nonanxious individuals: a meta-analytic study. *Psychological Bulletin, 133*, 1-24.

Barlow, D. H., Sauer-Zavala, S., Carl, J. R., Bullis, J. R., & Ellard, K. K. (2013). The nature, diagnosis, and treatment of neuroticism: Back to the future. *Clinical Psychological Science, 2*.

Barrett, L. F., & Satpute, A. B. (2013). Large-scale brain networks in affective and social neuroscience: towards an integrative functional architecture of the brain. *Current Opinion in Neurobiology, 23*, 361–372.

Buhle, J. T., Silvers, J. A., Wager, T. D., Lopez, R., Onyemekwu, C., Kober, H., . . . Ochsner, K. N. (2014). Cognitive reappraisal of emotion: A meta-analysis of human neuroimaging studies. *Cerebral Cortex, 24*, 2981-2990.

Carretie, L. (2014). Exogenous (automatic) attention to emotional stimuli: a review. *Cogn Affect Behav Neurosci, 14*, 1228-1258.

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.

Chase, H. W., Eickhoff, S. B., Laird, A. R., & Hogarth, L. (2011). The neural basis of drug stimulus processing and craving: an activation likelihood estimation meta-analysis. *Biological Psychiatry, 70*, 785-793.

Chun, M. M., Golomb, J. D., & Turk-Browne, N. B. (2011). A taxonomy of external and internal attention. *Annual Review of Psychology, 62*, 73-101.

Cisler, J. M., & Koster, E. H. W. (2010). Mechanisms of attentional biases towards threat in anxiety disorders: An integrative review. *Clinical Psychology Review, 30*, 203-216.

Collins, P. Y., Patel, V., Joestl, S. S., March, D., Insel, T. R., Daar, A. S., . . . Stein, D. J. (2011). Grand challenges in global mental health. *Nature, 475*, 27-30.

Costafreda, S. G., Brammer, M. J., David, A. S., & Fu, C. H. (2008). Predictors of amygdala activation during the processing of emotional stimuli: a meta-analysis of 385 PET and fMRI studies. *Brain Research Reviews, 58*, 57-70.

Cousijn, H., Rijpkema, M., Qin, S., van Marle, H. J., Franke, B., Hermans, E. J., . . . Fernandez, G. (2010). Acute stress modulates genotype effects on amygdala processing in humans. *Proceedings of the National Academy of Sciences of the United States of America, 107*, 9867-9872.

D'Esposito, M., & Postle, B. R. (2015). The cognitive neuroscience of working memory. *Annual Review of Psychology, 66*, 115-142.

Dalton, K. M., Nacewicz, B. M., Johnstone, T., Schaefer, H. S., Gernsbacher, M. A., Goldsmith, H. H., . . . Davidson, R. J. (2005). Gaze fixation and the neural circuitry of face processing in autism. *Nature Neuroscience, 8*, 519-526.

Damasio, A. (2005). *Descartes' error: Emotion, reason, and the human brain*. NY: Penguin.

Darwin, C. (1872/2009). *The expression of the emotions in man and animals* (4th ed.). NY: Oxford University Press.

Davis, M., & Whalen, P. J. (2001). The amygdala: vigilance and emotion. *Molecular Psychiatry, 6*, 13-34.

Dennis, T. A., & O'Toole, L. (2014). Mental health on the go: Effects of a gamified attention bias modification mobile application in trait anxious adults. *Clin Psychol Sci, 2*, 576-590.

Desimone, R., & Duncan, J. (1995). Neural mechanisms of selective visual attention. *Annual Review of Neuroscience, 18*, 193-222.

Di Simplicio, M., Doallo, S., Costoloni, G., Rohenkohl, G., Nobre, A. C., & Harmer, C. J. (2014). 'Can you look me in the face?' Short-term SSRI administration reverts avoidant ocular face exploration in subjects at risk for psychopathology. *Neuropsychopharmacology, 39*(13), 3059-3066.

DiLuca, M., & Olesen, J. (2014). The cost of brain diseases: a burden or a challenge? *Neuron, 82*, 1205-1208.

Dudeney, J., Sharpe, L., & Hunt, C. (2015). Attentional bias towards threatening stimuli in children with anxiety: A meta-analysis. *Clinical Psychology Review, 40*, 66-75.

Ekman, P., & Davidson, R. J. (Eds.). (1994). *The nature of emotion. Fundamental questions*. NY: Oxford University Press.

Etkin, A., Buchel, C., & Gross, J. J. (2015). The neural bases of emotion regulation. *Nature Reviews. Neuroscience*(11), 693-700.

Everaerd, D., Klumpers, F., van Wingen, G., Tendolkar, I., & Fernandez, G. (2015). Association between neuroticism and amygdala responsivity emerges under stressful conditions. *Neuroimage, 112*, 218-224.

Feeser, M., Prehn, K., Kazzer, P., Mungee, A., & Bajbouj, M. (2014). Transcranial direct current stimulation enhances cognitive control during emotion regulation. *Brain Stimul, 7*, 105-112.

Fox, A. S., & Kalin, N. H. (2014). A translational neuroscience approach to understanding the development of social anxiety disorder and its pathophysiology. *American Journal of Psychiatry, 171*, 1162-1173.

Freese, J. L., & Amaral, D. G. (2009). Neuroanatomy of the primate amygdala. In P. J. Whalen & E. A. Phelps (Eds.), *The human amygdala* (pp. 3-42). NY: Guilford.

Fried, I., MacDonald, K. A., & Wilson, C. L. (1997). Single neuron activity in human hippocampus and amygdala during recognition of faces and objects. *Neuron, 18*, 753-765.

Fusar-Poli, P., Placentino, A., Carletti, F., Landi, P., Allen, P., Surguladze, S., . . . Politi, P. (2009). Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. *Journal of Psychiatry and Neuroscience, 34*, 418-432.

Gamer, M., & Buchel, C. (2009). Amygdala activation predicts gaze toward fearful eyes. *Journal of Neuroscience, 29*, 9123-9126.

Gamer, M., Schmitz, A. K., Tittgemeyer, M., & Schilbach, L. (2013). The human amygdala drives reflexive orienting towards facial features. *Current Biology, 23*, R917-918.

Goldman-Rakic, P. S. (1996). Regional and cellular fractionation of working memory. *Proceedings of the National Academy of Sciences of the United States of America, 93*, 13473-13480.

Gothard, K. M., Battaglia, F. P., Erickson, C. A., Spitler, K. M., & Amaral, D. G. (2007). Neural responses to facial expression and face identity in the monkey amygdala. *Journal of Neurophysiology, 97*, 1671-1683.

Grillon, C., & Charney, D. R. (2011). In the face of fear: anxiety sensitizes defensive responses to fearful faces. *Psychophysiology, 48*, 1745-1752.

Gross, J. J. (2015a). Emotion regulation: Current status and future prospects. *Psychological Inquiry, 26*, 1-26.

Gross, J. J. (2015b). The extended process model of emotion regulation: Elaborations, applications, and future directions. *Psychological Inquiry, 26*, 130-137.

Grupe, D. W., & Nitschke, J. B. (2013). Uncertainty and anticipation in anxiety: an integrated neurobiological and psychological perspective. *Nature Reviews. Neuroscience, 14*, 488-501.

Hadj-Bouziane, F., Liu, N., Bell, A. H., Gothard, K. M., Luh, W. M., Tootell, R. B., . . . Ungerleider, L. G. (2012). Amygdala lesions disrupt modulation of functional MRI activity evoked by facial expression in the monkey inferior temporal cortex. *Proceedings of the National Academy of Sciences of the United States of America, 109*, E3640-3648.

Hare, T. A., Malmaud, J., & Rangel, A. (2011). Focusing attention on the health aspects of foods changes value signals in vmPFC and improves dietary choice. *Journal of Neuroscience, 31*, 11077-11087.

Heeren, A., Mogoase, C., Philippot, P., & McNally, R. J. (2015). Attention bias modification for social anxiety: A systematic review and meta-analysis. *Clinical Psychology Review, 40*, 76-90.

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.

Herry, C., Bach, D. R., Esposito, F., Di Salle, F., Perrig, W. J., Scheffler, K., . . . Seifritz, E. (2007). Processing of temporal unpredictability in human and animal amygdala. *Journal of Neuroscience, 27*, 5958-5966.

Hoffman, K. L., Gothard, K. M., Schmid, M. C., & Logothetis, N. K. (2007). Facial-expression and gaze-selective responses in the monkey amygdala. *Current Biology, 17*, 766-772.

Ikkai, A., & Curtis, C. E. (2011). Common neural mechanisms supporting spatial working memory, attention and motor intention. *Neuropsychologia, 49*, 1428-1434.

Kelley, W. M., Wagner, D. D., & Heatherton, T. F. (2015). In search of a human self-regulation system. *Annual Review of Neuroscience, 38*, 389-411.

Kirby, L. A., & Robinson, J. L. (*in press*). Affective mapping: An activation likelihood estimation (ALE) meta-analysis. *Brain and Cognition*.

Kouider, S., Eger, E., Dolan, R. J., & Henson, R. N. (2009). Activity in face-responsive brain regions is modulated by invisible, attended faces: evidence from masked priming. *Cerebral Cortex, 19*, 13–23.

Kuhn, S., & Gallinat, J. (2011). Common biology of craving across legal and illegal drugs - a quantitative meta-analysis of cue-reactivity brain response. *European Journal of Neuroscience, 33*, 1318-1326.

Levenson, R. W. (1994). Human emotion: A functional view. In P. Ekman & R. J. Davidson (Eds.), *The nature of emotion. Fundamental questions* (pp. 123-126). NY: Oxford University Press.

Lim, S. L., Padmala, S., & Pessoa, L. (2009). Segregating the significant from the mundane on a moment-to-moment basis via direct and indirect amygdala contributions. *Proceedings of the National Academy of Sciences of the United States of America, 106*, 16841-16846.

Lindquist, K. A., & Barrett, L. F. (2012). A functional architecture of the human brain: emerging insights from the science of emotion. *Trends in the Cognitive Sciences, 16*, 533–540.

Lindquist, K. A., Wager, T. D., Kober, H., Bliss-Moreau, E., & Barrett, L. F. (2012). The brain basis of emotion: A meta-analytic review. *Behavioral and Brain Sciences, 35*, 121-143.

Linetzky, M., Pergamin-Hight, L., Pine, D. S., & Bar-Haim, Y. (2015). Quantitative evaluation of the clinical efficacy of attention bias modification treatment for anxiety disorders. *Depression and Anxiety, 32*, 383-391.

MacLeod, C., & Clarke, P. J. F. (2015). The attentional bias modification approach to anxiety intervention. *Clinical Psychological Science, 3*, 58-78.

MacLeod, C., & Mathews, A. (2012). Cognitive bias modification approaches to anxiety. *Annu Rev Clin Psychol, 8*, 189-217.

Markovic, J., Anderson, A. K., & Todd, R. M. (2014). Tuning to the significant: neural and genetic processes underlying affective enhancement of visual perception and memory. *Behavioural Brain Research, 259*, 229-241.

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience, 24*, 167-202.

Mogg, K., & Bradley, B. P. (2016). Anxiety and attention to threat: Cognitive mechanisms and treatment with attention bias modification. *Behaviour Research and Therapy, 87*, 76-108.

Moran, T. P. (2016). Anxiety and working memory capacity: A meta-analysis and narrative review. *Psychological Bulletin, 142*, 831-864.

Okon-Singer, H., Alyagon, U., Kofman, O., Tzelgov, J., & Henik, A. (2011). Fear-related pictures deteriorate the performance of university students with high fear of snakes or spiders. *Stress, 14*, 185-193.

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., Lichtenstein-Vidne, L., & Cohen, N. J. (2013). Dynamic modulation of emotional processing. *Biological Psychology, 92*, 480-491.

Okon-Singer, H., Tzelgov, J., & Henik, A. (2007). Distinguishing between automaticity and attention in the processing of emotionally significant stimuli. *Emotion, 7*, 147-157.

Onnis, R., Dadds, M. R., & Bryant, R. A. (2011). Is there a mutual relationship between opposite attentional biases underlying anxiety? *Emotion, 11*, 582-594.

Perlman, S. B., Morris, J. P., Vander Wyk, B. C., Green, S. R., Doyle, J. L., & Pelphrey, K. A. (2009). Individual differences in personality predict how people look at faces. *PLoS ONE, 4*, e5952.

Pessoa, L. (2013). *The cognitive-emotional brain: From interactions to integration*. Cambridge, MA: MIT Press.

Pessoa, L., & Adolphs, R. (2010). Emotion processing and the amygdala: from a 'low road' to 'many roads' of evaluating biological significance. *Nature Reviews. Neuroscience, 11*, 773-783.

Pessoa, L., McKenna, M., Gutierrez, E., & Ungerleider, L. G. (2002). Neural processing of emotional faces requires attention. *Proceedings of the National Academy of Sciences of the United States of America, 99*, 11458-11463.

Pichon, S., Miendlarzewska, E. A., Eryilmaz, H., & Vuilleumier, P. (2015). Cumulative activation during positive and negative events and state anxiety predicts subsequent inertia of amygdala reactivity. *Soc Cogn Affect Neurosci, 10*, 180-190.

Pool, E., Brosch, T., Delplanque, S., & Sander, D. (2016). Attentional bias for positive emotional stimuli: A meta-analytic investigation. *Psychological Bulletin, 142*, 79-106.

Pourtois, G., Schettino, A., & Vuilleumier, P. (2013). Brain mechanisms for emotional influences on perception and attention: what is magic and what is not. *Biological Psychology, 92*, 492-512.

Raio, C. M., Orederu, T. A., Palazzolo, L., Shurick, A. A., & Phelps, E. A. (2013). Cognitive emotion regulation fails the stress test. *Proceedings of the National Academy of Sciences of the United States of America, 110*, 15139-15144.

Robinson, O. J., Vytal, K., Cornwell, B. R., & Grillon, C. (2013). The impact of anxiety upon cognition: perspectives from human threat of shock studies. *Front Hum Neurosci, 7*, 203.

Rolls, E. T. (2013). A biased activation theory of the cognitive and attentional modulation of emotion. *Front Hum Neurosci, 7*, 74.

Rotshtein, P., Richardson, M. P., Winston, J. S., Kiebel, S. J., Vuilleumier, P., Eimer, M., . . . Dolan, R. J. (2010). Amygdala damage affects event-related potentials for fearful faces at specific time windows. *Human Brain Mapping, 31*, 1089-1105.

Rudaizky, D., Basanovic, J., & MacLeod, C. (2014). Biased attentional engagement with, and disengagement from, negative information: independent cognitive pathways to anxiety vulnerability? *Cogn Emot, 28*, 245-259.

Sabatinelli, D., Fortune, E. E., Li, Q., Siddiqui, A., Krafft, C., Oliver, W. T., . . . Jeffries, J. (2011). Emotional perception: Meta-analyses of face and natural scene processing. *Neuroimage, 54*, 2524-2533.

Sari, B. A., Koster, E. H., Pourtois, G., & Derakshan, N. (*in press*). Training working memory to improve attentional control in anxiety: A proof-of-principle study using behavioral and electrophysiological measures. *Biological Psychology*.

Scheller, E., Buchel, C., & Gamer, M. (2012). Diagnostic features of emotional expressions are processed preferentially. *PLoS ONE, 7*, e41792.

Schwabe, L., & Wolf, O. T. (2013). Stress and multiple memory systems: from 'thinking' to 'doing'. *Trends Cogn Sci, 17*, 60-68.

Sergerie, K., Chochol, C., & Armony, J. L. (2008). The role of the amygdala in emotional processing: a quantitative meta-analysis of functional neuroimaging studies. *Neuroscience and Biobehavioral Reviews, 32*, 811-830.

Sescousse, G., Caldu, X., Segura, B., & Dreher, J. C. (2013). Processing of primary and secondary rewards: a quantitative meta-analysis and review of human functional neuroimaging studies. *Neuroscience and Biobehavioral Reviews, 37*, 681-696.

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., 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., 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.

Sheppes, G., Suri, G., & Gross, J. J. (2015). Emotion regulation and psychopathology. *Annual Review of Clinical Psychology, 11*, 379-405.

Spezio, M. L., Huang, P. Y., Castelli, F., & Adolphs, R. (2007). Amygdala damage impairs eye contact during conversations with real people. *Journal of Neuroscience, 27*, 3994-3997.

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.

Tang, D. W., Fellows, L. K., Small, D. M., & Dagher, A. (2012). Food and drug cues activate similar brain regions: a meta-analysis of functional MRI studies. *Physiology and Behavior, 106*, 317-324.

Thiruchselvam, R., Hajcak, G., & Gross, J. J. (2012). Looking inward: shifting attention within working memory representations alters emotional responses. *Psychol Sci, 23*, 1461-1466.

Todd, R. M., & Anderson, A. K. (2013). Salience, state, and expression: the influence of specific aspects of emotion on attention and perception. In K. N. Ochsner & S. M. Kosslyn (Eds.), *Oxford Handbook of Cognitive Neuroscience* (Vol. 2, pp. 11-30). NY: Oxford University Press.

Urry, H. L. (2010). Seeing, thinking, and feeling: emotion-regulating effects of gaze-directed cognitive reappraisal. *Emotion, 10*(1), 125-135.

Vaisvaser, S., Lin, T., Admon, R., Podlipsky, I., Greenman, Y., Stern, N., . . . Hendler, T. (2013). Neural traces of stress: cortisol related sustained enhancement of amygdala-hippocampal functional connectivity. *Front Hum Neurosci, 7*, 313.

Van Bockstaele, B., Verschuere, B., Tibboel, H., De Houwer, J., Crombez, G., & Koster, E. H. (2014). A review of current evidence for the causal impact of attentional bias on fear and anxiety. *Psychological Bulletin, 140*, 682-721.

van Marle, H. J., Hermans, E. J., Qin, S., & Fernandez, G. (2009). From specificity to sensitivity: how acute stress affects amygdala processing of biologically salient stimuli. *Biological Psychiatry, 66*, 649-655.

van Marle, H. J., Hermans, E. J., Qin, S., & Fernandez, G. (2010). Enhanced resting-state connectivity of amygdala in the immediate aftermath of acute psychological stress. *Neuroimage, 53*, 348-354.

van Reekum, C. M., Johnstone, T., Urry, H. L., Thurow, M. E., Schaefer, H. S., Alexander, A. L., & Davidson, R. J. (2007). Gaze fixations predict brain activation during the voluntary regulation of picture-induced negative affect. *Neuroimage, 36*, 1041-1055.

Vuilleumier, P., Armony, J. L., Clarke, K., Husain, M., Driver, J., & Dolan, R. J. (2002). Neural response to emotional faces with and without awareness: event-related fMRI in a parietal patient with visual extinction and spatial neglect. *Neuropsychologia, 40*, 2156-2166.

Vuilleumier, P., Richardson, M. P., Armony, J. L., Driver, J., & Dolan, R. J. (2004). Distant influences of amygdala lesion on visual cortical activation during emotional face processing. *Nature Neuroscience, 7*, 1271-1278.

Wagner, D. D., & Heatherton, T. F. (2014). Self-regulation and its failures. In M. S. Gazzaniga & G. R. Mangun (Eds.), *The cognitive neurosciences* (5th ed., pp. 709-717). Cambridge, MA: MIT Press.

Wang, S., Tudusciuc, O., Mamelak, A. N., Ross, I. B., Adolphs, R., & Rutishauser, U. (2014). Neurons in the human amygdala selective for perceived emotion. *Proceedings of the National Academy of Sciences of the United States of America, 111*, E3110-3119.

Weierich, M. R., Treat, T. A., & Hollingworth, A. (2008). Theories and measurement of visual attentional processing in anxiety. *Cognition and Emotion, 22*, 985-1018.

Whiteford, H. A., Degenhardt, L., Rehm, J., Baxter, A. J., Ferrari, A. J., Erskine, H. E., . . . Vos, T. (2013). Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet, 382*, 1575-1586.

Zvielli, A., Bernstein, A., & Koster, E. H. (2014). Dynamics of attentional bias to threat in anxious adults: bias towards and/or away? *PLoS ONE, 9*, e104025.