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The cognitive-emotional brain: Opportunities and challenges for understanding neuropsychiatric disorders

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Abstract

Many of the most common neuropsychiatric disorders are marked by prominent disturbances of cognition and emotion. Characterizing the complex neural circuitry underlying the interaction and integration of cognition and emotion is critically important, not just for clarifying the nature of the mind, but also for discovering the root causes of debilitating mental disorders, including anxiety, schizophrenia, and chronic pain.

Until the 20th century, the study of cognition and emotion was largely a philosophical matter. But recent years have witnessed the emergence of powerful new tools for interrogating the brain and new areas of multidisciplinary research focused on identifying the neurobiological mechanisms underlying cognition, emotion, and their role in mental health and disease. In *The Cognitive-Emotional Brain*, Luiz Pessoa provides an authoritative perspective on this recent work and its implications for our understanding of the basic building blocks of the mind. Here, we highlight four of the book's most important implications for understanding neuropsychiatric disorders, including anxiety, schizophrenia, substance abuse, chronic pain, and autism. These disorders cause enormous suffering for millions of patients and their families, outstripping the global burden of cancer or cardiovascular disease (Collins et al., 2011; Goldberg & McGee, 2011; Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012; Whiteford et al., *in press*). Importantly, these disorders involve prominent alterations in both cognition and emotion (Millan et al., 2012), pointing to the need for a deeper understanding of the cognitive-emotional brain.

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First, *The Cognitive-Emotional Brain* reminds us that mental faculties emerge from the coordinated interactions of large-scale brain networks. Put simply, fear, reward, attention, and other psychological processes cannot be mapped to isolated brain regions because no one region is both necessary and sufficient. Conversely, similar symptoms can emerge from damage to different regions in the same functional network (Karnath & Smith, 2014). Pain, which is among the most prevalent clinical disorders (Research, 2011), nicely illustrates this point. Pain is a multidimensional experience, involving systematic changes in both cognition and emotion: painful stimuli elicit anxiety, capture attention, and motivate action. Neurobiologically, pain is associated with a complex pattern of regional activation, often termed the 'pain matrix' (Iannetti, Salomons, Moayedi, Mouraux, & Davis, 2013). Stimulation of individual components of the pain matrix does not consistently elicit pain, suggesting that pain and its disorders are emergent properties of regional interactions. This is not a new or contentious idea; pioneers like Mesulam, Goldman-Rakic, and LeDoux highlighted the importance of distributed neural circuits more than two decades ago and there is widespread agreement amongst basic and translational researchers (Bullmore & Sporns, 2012; Goldman-Rakic, 1988; LeDoux, 1995, 2012; Mesulam, 1998; Uhlhaas & Singer, 2012). *The Cognitive-Emotional Brain* is a bracing call for accelerating the transition from localization strategies (i.e., mapping brain structures to function; sometimes termed 'neo-phrenology') to a network-centered approach. From a clinical neuroscience perspective, this suggests that understanding neuropsychiatric disorders will require embracing the kinds of analytic tools (e.g., functional connectivity fingerprinting, graph theoretic and machine learning approaches) that are necessary for elucidating how psychological constructs and mental disorders are realized in brain circuits.

Pessoa's second key conclusion is that the identity of brain functional networks, including the circuitry that underlies clinically-relevant phenotypes, cannot be inferred from neuroanatomy alone. Pessoa makes it clear that the networks identified by functional magnetic resonance imaging (fMRI) and other neurophysiological techniques do not necessarily recapitulate the pattern of direct connections revealed by invasive anatomical tracing techniques. Indeed, there is ample evidence of robust functional connectivity between brain regions that lack direct structural connections (Adachi et al., 2012; Birn et al., 2014; Honey et al., 2009; Vincent et al., 2007) and increasing evidence that regulatory signals can propagate across complex, indirect pathways (Ekstrom, Roelfsema, Arsenault, Bonmassar, & Vanduffel, 2008). From a clinical perspective, this indicates that fMRI-derived measures of functional connectivity are particularly useful because they can be used to assay dysfunctional networks that encompass polysynaptically connected nodes (Birn et al., 2014), just as viral tracers can be used to delineate polysynaptic anatomical pathways in the nervous system (Dum, Levinthal, & Strick, 2009). More broadly, *The Cognitive-Emotional Brain* implies that many of the signs and symptoms of mental disorders—anhedonia, hypervigilance for threat, working memory impairments, drug seeking, and so on—will reflect complex brain circuits (Seminowicz et al., 2004; Shackman et al., 2013).

The third key conclusion is that emotion and cognition are not different in kind, but are instead deeply interwoven in the fabric of the brain. Subjectively, we often experience cognition and emotion as fundamentally different. Emotion is saturated 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 have led many scholars to treat emotion and cognition as categorically distinct, even oppositional, mental forces, that presumably reflect the operation of segregated brain circuits (de Sousa, 2014; Schmitter, 2014). A similar dichotomy pervades psychiatric nosology. But careful scrutiny reveals contrary evidence; cognition can arouse the face and body; conversely, emotion can profoundly alter attention, working memory, and cognitive control (Grupe & Nitschke, 2013; Shackman et al., 2011). *The Cognitive-Emotional Brain* provides a useful survey of recent brain imaging research demonstrating the integration of emotional and cognitive processes in the brain (Shackman et al., 2011). Largely on the basis of brain imaging data, Pessoa joins with other theorists in rejecting claims that emotion and cognition are categorically different (Barrett & Satpute, 2013; Damasio, 2005; Duncan & Barrett, 2007; Lindquist & Barrett, 2012). Elucidating the contribution of the cognitive-emotional brain to psychopathology mandates the joint efforts of cognitive, affective, computational, and clinical neuroscientists. This kind of multi-disciplinary research would refine our understanding of the mechanisms that give rise to 'mixed' cognitive-emotional symptoms, such as hypervigilance or aberrant reinforcement learning (Cavanagh & Shackman, *in press*), and provide novel targets for intervention.

Pessoa's fourth and most original conclusion is a powerful synthesis of the first three. Pessoa argues that widely held beliefs about the constituents of 'the emotional brain' and 'the cognitive brain' are fundamentally flawed. Regions such as the amygdala are not 'emotional;' regions such as the dorsolateral prefrontal cortex (dlPFC) are not 'cognitive' (Birn et al., 2014; Buhle et al., *in press*; Fox et al., 2005; Shackman, McMenamin, Maxwell, Greischar, & Davidson, 2009). Both regions play a central role in the regulation of adaptive behavior. This should not be surprising—the human brain did not evolve to optimize performance on artificial laboratory probes of 'pure' cognition or emotion. Pessoa also makes it clear that brain regions can be dynamically assume different roles. Just as an individual can perform psychologically-distinct roles in different social networks (e.g., executive, mother, sister, daughter), brain regions are poised to perform a range of functions (a property termed functional 'superimposition') in different neural 'contexts' corresponding to their level of participation in particular functional networks. To paraphrase Pearson and colleagues (Pearson, Watson, & Platt, 2014), key brain regions, such as the orbitofrontal cortex, are functionally heterogeneous, with individual neurons dynamically multiplexed into different functional roles. As such, they will "evade a single, modular, functional role assignment," (p. 954). Our brain reflects evolutionary pressures that demanded distributed neural systems capable of using information about pleasure and pain, derived from stimuli saturated with hedonic and motivational significance, to adaptively regulate attention, learning, somatic mobilization, and action in the service of maximizing reproductive fitness. From this perspective, it is easy to imagine how dysfunction of circumscribed territories of the brain can have a deep impact on distal regions and circuits, as recent work by our group and others demonstrates (Fox & Kalin, *in press*; Fox et al., 2010; Gratton, Nomura, Perez, & D'Esposito, 2012). This may help to explain the co-occurrence of cognitive and emotional symptoms as well as frequent comorbidities among psychiatric and neurological disorders. Clarifying the nature of the cognitive-emotional brain is likely to have substantial benefits

for our understanding of disorders marked by symptoms that blend elements of cognition and emotion (e.g., hypervigilance to potential threat or over-generalization of threat, in the case of the anxiety disorders (Grupe & Nitschke, 2013)).

While many challenges remain, *The Cognitive-Emotional Brain* provides a roadmap to the most fruitful avenues for future research. One of the most important unresolved questions concerns the functional significance of regions activated by both cognitive and emotional challenges. For example, Pessoa highlights a recent meta-analysis from our group demonstrating that the elicitation of negative affect, pain, or cognitive control are associated with activation in an overlapping region of the MCC (Shackman et al., 2011). A key unresolved question is whether the MCC and other regions implicated in both cognitive and emotional processes, such as the anterior insula, perform a single general function (e.g., adaptive control (Cavanagh & Shackman, *in press*; Shackman et al., 2011) or salience detection (Iannetti et al., 2013) or multiple specific functions.

On a broader note, much of the evidence surveyed by Pessoa comes from the human brain imaging literature. Accordingly, his conclusions are ultimately tempered by questions about the origins and significance of the fMRI signal and the measures of functional connectivity that underlie network-centered approaches to understanding the cognitive-emotional brain (Akam & Kullmann, 2014; Cabral, Kringelbach, & Deco, 2014; Logothetis, 2008). An important challenge for future studies will be to combine mechanistic techniques in animal models (e.g., optogenetics) with the same whole-brain imaging strategies routinely applied in humans (Birn et al., 2014; Borsook, Becerra, & Hargreaves, 2006; Casey et al., 2013; Narayanan, Cavanagh, Frank, & Laubach, 2013; Oler et al., 2012). Combining noninvasive mechanistic techniques (e.g., transcranial magnetic stimulation or transcranial direct current stimulation) or pharmacological manipulations with fMRI provides another opportunity for understanding how circumscribed perturbations can produce distributed dysfunction (Chen et al., 2013; Guller et al., 2012; Paulus, Feinstein, Castillo, Simmons, & Stein, 2005; Reinhart & Woodman, 2014).

For many disorders marked by cognitive and emotional disturbances, extant treatments are inconsistently effective or associated with significant adverse effects (e.g., Bystritsky, 2006). *The Cognitive-Emotional Brain* provides an insightful survey of state of the science and a useful stimulus for the next generation of basic and clinical research, reminding us that we have a remarkable opportunity to use new tools for understanding brain function to discover the origins of neuropsychiatric disease.

References

Adachi Y, Osada T, Sporns O, Watanabe T, Matsui T, Miyamoto K, & Miyashita Y (2012). Functional connectivity between anatomically unconnected areas is shaped by collective network-level effects in the macaque cortex. Cerebral Cortex, 22(7), 1586–1592. doi: 10.1093/cercor/bhr234 [PubMed: 21893683]

Akam T, & Kullmann DM (2014). Oscillatory multiplexing of population codes for selective communication in the mammalian brain. Nature Reviews. Neuroscience, 15, 111–122. doi: 10.1038/nrn3668 [PubMed: 24434912]

Barrett LF, & Satpute AB (2013). Large-scale brain networks in affective and social neuroscience: towards an integrative functional architecture of the brain. Current Opinion in Neurobiology, 23(3), 361–372. doi: 10.1016/j.conb.2012.12.012 [PubMed: 23352202]

Birn RM, Shackman AJ, Oler JA, Williams LE, McFarlin DR, Rogers GM,…Kalin NH (2014). Evolutionarily-conserved dysfunction of prefrontal-amygdalar connectivity in early-life anxiety. Molecular Psychiatry, 19, 915–922. [PubMed: 24863147]

Borsook D, Becerra L, & Hargreaves R (2006). A role for fMRI in optimizing CNS drug development. Nature Reviews. Drug Discovery, 5(5), 411–424. doi: 10.1038/nrd2027 [PubMed: 16604100]

Buhle JT, Silvers JA, Wager TD, Lopez R, Onyemekwu C, Kober H,… Ochsner KN (in press). Cognitive reappraisal of emotion: A meta-analysis of human neuroimaging studies. Cerebral Cortex. doi: bht154[pii]10.1093/cercor/bht154

Bullmore E, & Sporns O (2012). The economy of brain network organization. Nature Reviews. Neuroscience, 13(5), 336–349. doi: 10.1038/nrn3214 [PubMed: 22498897]

Bystritsky A (2006). Treatment-resistant anxiety disorders. Molecular Psychiatry, 11, 805–814. doi: 4001852[pii]10.1038/sj.mp.4001852 [PubMed: 16847460]

Cabral J, Kringelbach ML, & Deco G (2014). Exploring the network dynamics underlying brain activity during rest. Progress in Neurobiology, 114C, 102–131. doi: 10.1016/j.pneurobio.2013.12.005

Casey BJ, Craddock N, Cuthbert BN, Hyman SE, Lee FS, & Ressler KJ (2013). DSM-5 and RDoC: progress in psychiatry research? Nature Reviews. Neuroscience, 14(11), 810–814. doi: 10.1038/nrn3621 [PubMed: 24135697]

Cavanagh JF, & Shackman AJ (in press). Frontal midline theta reflects anxiety and cognitive control: Meta-analytic evidence Journal of Physiology, Paris

Chen AC, Oathes DJ, Chang C, Bradley T, Zhou ZW, Williams LM,… Etkin A (2013). Causal interactions between fronto-parietal central executive and default-mode networks in humans. Proceedings of the National Academy of Sciences of the United States of America, 110(49), 19944–19949. doi: 10.1073/pnas.1311772110 [PubMed: 24248372]

Collins PY, Patel V, Joestl SS, March D, Insel TR, Daar AS,… Stein DJ (2011). Grand challenges in global mental health. Nature, 475, 27–30. doi: 475027a[pii]10.1038/475027a [PubMed: 21734685]

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

de Sousa R (2014). Emotion. In Zalta EN (Ed.), Stanford encyclopedia of philosophy.

Dum RP, Levinthal DJ, & Strick PL (2009). The spinothalamic system targets motor and sensory areas in the cerebral cortex of monkeys. Journal of Neuroscience, 29, 14223–14235. doi: 29/45/14223[pii]10.1523/JNEUROSCI.3398-09.2009 [PubMed: 19906970]

Duncan S, & Barrett LF (2007). Affect as a form of cognition: A neurobiological analysis. Cognition & Emotion, 21, 1184–1211. [PubMed: 18509504]

Ekstrom LB, Roelfsema PR, Arsenault JT, Bonmassar G, & Vanduffel W (2008). Bottom-up dependent gating of frontal signals in early visual cortex. Science, 321, 414–417. [PubMed: 18635806]

Fox AS, & Kalin NH (in press). A translational neuroscience approach to understanding the development of social anxiety disorder and its pathophysiology. American Journal of Psychiatry.

Fox AS, Oakes TR, Shelton SE, Converse AK, Davidson RJ, & Kalin NH (2005). Calling for help is independently modulated by brain systems underlying goal-directed behavior and threat perception. Proceedings of the National Academy of Sciences USA, 102, 4176–4179. doi: 0409470102 [pii]10.1073/pnas.0409470102 [doi]

Fox AS, Shelton SE, Oakes TR, Converse AK, Davidson RJ, & Kalin NH (2010). Orbitofrontal cortex lesions alter anxiety-related activity in the primate bed nucleus of stria terminalis. Journal of Neuroscience, 30, 7023–7027. [PubMed: 20484644]

Goldberg DS, & McGee SJ (2011). Pain as a global public health priority. BMC Public Health, 11, 770. doi: 10.1186/1471-2458-11-770 [PubMed: 21978149]

Goldman-Rakic PS (1988). Topography of cognition: parallel distributed networks in primate association cortex. Annual Review of Neuroscience, 11, 137–156. doi: 10.1146/annurev.ne.11.030188.001033 [doi]

Gratton C, Nomura EM, Perez F, & D'Esposito M (2012). Focal brain lesions to critical locations cause widespread disruption of the modular organization of the brain. Journal of Cognitive Neuroscience, 24(6), 1275–1285. doi: 10.1162/jocn_a_00222 [PubMed: 22401285]

Grupe DW, & Nitschke JB (2013). Uncertainty and anticipation in anxiety: an integrated neurobiological and psychological perspective. Nature Reviews. Neuroscience, 14, 488–501. doi: nrn3524 [pii] 10.1038/nrn3524 [PubMed: 23783199]

Guller Y, Ferrarelli F, Shackman AJ, Sarasso S, Peterson MJ, Langheim FJ,… Postle BR (2012). Probing thalamic integrity in schizophrenia using concurrent transcranial magnetic stimulation and functional magnetic resonance imaging. Archives of General Psychiatry, 69(7), 662–671. doi: 10.1001/archgenpsychiatry.2012.23 [PubMed: 22393203]

Honey CJ, Sporns O, Cammoun L, Gigandet X, Thiran JP, Meuli R, & Hagmann P (2009). Predicting human resting-state functional connectivity from structural connectivity. Proceedings of the National Academy of Sciences of the United States of America, 106(6), 2035–2040. doi: 10.1073/pnas.0811168106 [PubMed: 19188601]

Iannetti GD, Salomons TV, Moayedi M, Mouraux A, & Davis KD (2013). Beyond metaphor: Contrasting mechanisms of social and physical pain. Trends in Cognitive Sciences, 17, 371–378. [PubMed: 23796880]

Karnath H-O, & Smith DV (2014). The next step in modern brain lesion analysis: multivariate pattern analysis. Brain, 137, 2405–2406. [PubMed: 25125587]

Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, & Wittchen HU (2012). Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. Int J Methods Psychiatr Res, 21, 169–184. doi: 10.1002/mpr.1359 [PubMed: 22865617]

LeDoux JE (1995). Emotion: clues from the brain. Annual Review of Psychology, 46, 209–235. doi: 10.1146/annurev.ps.46.020195.001233 [doi]

LeDoux JE (2012). Rethinking the emotional brain. Neuron, 73(4), 653–676. doi: 10.1016/j.neuron.2012.02.004 [PubMed: 22365542]

Lindquist KA, & Barrett LF (2012). A functional architecture of the human brain: Insights from emotion. Trends in Cognitive Sciences, 16, 533–540. [PubMed: 23036719]

Logothetis NK (2008). What we can do and what we cannot do with fMRI. Nature, 453, 869–878. doi: nature06976 [pii] 10.1038/nature06976 [PubMed: 18548064]

Mesulam MM (1998). From sensation to cognition. Brain, 121 (Pt 6), 1013–1052. [PubMed: 9648540]

Millan MJ, Agid Y, Brune M, Bullmore ET, Carter CS, Clayton NS,… Young LJ (2012). Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. Nature Reviews. Drug Discovery, 11(2), 141–168. doi: 10.1038/nrd3628 [PubMed: 22293568]

Narayanan NS, Cavanagh JF, Frank MJ, & Laubach M (2013). Common medial frontal mechanisms of adaptive control in humans and rodents. Nature Neuroscience, 16(12), 1888–1895. doi: 10.1038/nn.3549 [PubMed: 24141310]

Oler JA, Birn RM, Patriat R, Fox AS, Shelton SE, Burghy CA,… Kalin NH (2012). Evidence for coordinated functional activity within the extended amygdala of non-human and human primates. Neuroimage, 61, 1059–1066. doi: S1053–8119(12)00326–6 [pii] 10.1016/j.neuroimage.2012.03.045 [PubMed: 22465841]

Paulus MP, Feinstein JS, Castillo G, Simmons AN, & Stein MB (2005). Dose-dependent decrease of activation in bilateral amygdala and insula by lorazepam during emotion processing. Archives of General Psychiatry, 62(3), 282–288. doi: 62/3/282 [pii] 10.1001/archpsyc.62.3.282 [PubMed: 15753241]

Pearson JM, Watson KK, & Platt ML (2014). Decision making: the neuroethological turn. Neuron, 82(5), 950–965. doi: 10.1016/j.neuron.2014.04.037 [PubMed: 24908481]

Reinhart RM, & Woodman GF (2014). Causal control of medial-frontal cortex governs electrophysiological and behavioral indices of performance monitoring and learning. Journal of Neuroscience, 34(12), 4214–4227. doi: 10.1523/JNEUROSCI.5421-13.2014 [PubMed: 24647942]

Research I o. M. U. C. o. A. P. (2011). Relieving pain in America: A blueprint for transforming prevention, care, education, and research.

Schmitter AM (2014). 17th and 18th century theories of emotions. In Zalta EN (Ed.), Stanford encyclopedia of philosophy.

Seminowicz DA, Mayberg HS, McIntosh AR, Goldapple K, Kennedy S, Segal Z, & Rafi-Tari S (2004). Limbic-frontal circuitry in major depression: a path modeling metanalysis. Neuroimage, 22, 409–418. doi: 10.1016/j.neuroimage.2004.01.015S1053811904000497 [pii] [PubMed: 15110034]

Shackman AJ, Fox AS, Oler JA, Shelton SE, Davidson RJ, & Kalin NH (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. doi: 1214364110 [pii] 10.1073/pnas.1214364110 [PubMed: 23538303]

Shackman AJ, McMenamin BW, Maxwell JS, Greischar LL, & Davidson RJ (2009). Right dorsolateral prefrontal cortical activity and behavioral inhibition. Psychological Science, 20, 1500–1506. [PubMed: 19906125]

Shackman AJ, Salomons TV, Slagter HA, Fox AS, Winter JJ, & Davidson RJ (2011). The integration of negative affect, pain and cognitive control in the cingulate cortex. Nature Reviews. Neuroscience, 12, 154–167. doi: nrn2994 [pii] 10.1038/nrn2994 [PubMed: 21331082]

Uhlhaas PJ, & Singer W (2012). Neuronal dynamics and neuropsychiatric disorders: toward a translational paradigm for dysfunctional large-scale networks. Neuron, 75(6), 963–980. doi: 10.1016/j.neuron.2012.09.004 [PubMed: 22998866]

Vincent JL, Patel GH, Fox MD, Snyder AZ, Baker JT, Van Essen DC,… Raichle ME (2007). Intrinsic functional architecture in the anaesthetized monkey brain. Nature, 447, 83–86. doi: nature05758 [pii] 10.1038/nature05758 [PubMed: 17476267]

Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE,… Vos T (in press). Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010 Lancet. doi: 10.1016/S0140-6736(13)61611-6