

(dHPC). Extensive work on hippocampal theta oscillations has demonstrated how theta is generated via the interplay of precisely timed inputs. It has led to the notion of inhibition as a theta pacemaker, and clarified the role theta has in organizing cell activity and other oscillations. During behavior, hippocampal theta has been implicated in creating windows for Hebbian plasticity, as well as organizing neural coding for memory formation and spatial navigation. This review focuses on theta oscillations in fear and anxiety, a topic of recently increased interest.

Initial efforts at characterizing the role of theta in fear began with an examination of theta oscillations in the amygdala and related structures. For example, pyramidal cells of the basolateral amygdala (BLA) show a prominent theta oscillation and have a combination of ionic conductances that allow cells to intrinsically resonate at the theta frequency (Pape and Driesang, 1998). Furthermore, the amygdala shows increased theta activity and synchrony with the hippocampus during presentation of fear-conditioned stimuli (Seidenbecher *et al*, 2003). Similarly, hippocampal recordings have shown that in the ventral (vHPC) but not dorsal hippocampus, theta increases with innate anxiety (Adhikari *et al*, 2011), indicating that theta modulates anxiety in the vHPC separately from spatial navigation in the dHPC.

Recent studies focusing on theta in circuit-level communication during fear and safety suggest that it may open temporary windows of communication between areas. Simultaneous recordings show increased theta-range synchrony between the BLA and hippocampus during presentations of fear-conditioned stimuli and in sleep after fear conditioning, possibly aiding memory consolidation (Seidenbecher *et al*, 2003; Popa *et al*, 2010). Similarly, recordings in the vHPC and prefrontal cortex (mPFC) demonstrate increased theta-frequency synchrony between the two regions during anxiety. Moreover, mPFC neurons become more phase-locked to vHPC theta input with elevated anxiety (Adhikari *et al*, 2011),

indicating that vHPC sends information about anxiety to the mPFC.

Interestingly, as fear subsides during extinction of conditioned fear, BLA–mPFC theta synchrony increases (Lesting *et al*, 2011), indicating that prefrontal inputs to the amygdala use theta as a mechanism for communicating safety. Indeed, neural firing in the BLA becomes entrained to incoming mPFC theta only when animals are presented with conditioned stimuli that are recognized as safe or when animals are in the relative safety of the periphery in the otherwise aversive open field (EL and JAG, unpublished observations). Thus, mPFC–BLA synchrony increases and cellular networks in the BLA are entrained to theta input from the mPFC when animals actively recognize safety, likely driving local inhibitory networks that decrease fear.

Recent evidence shows that interneurons in the BLA can be organized by hippocampal theta (Bienvenu *et al*, 2012), opening the possibility that the same could be true for prefrontal inputs. Therefore, entrainment of BLA cell assemblies by mPFC theta input could organize local inhibitory circuits of the BLA to provide an effective mechanism for the mPFC to signal safety.

ACKNOWLEDGEMENTS

Dr Likhtik's research was supported by F32 MH088103 from the NIH, and Charles H Revson Foundation. Dr Gordon's research has been funded by the NIH (R01 MH081968 and P50 MH096891), the Hope for Depression Research Foundation and the International Mental Health Research Organization.

Ekaterina Likhtik¹ and Joshua A Gordon¹

¹Division of Integrative Neuroscience, Department of Psychiatry, Columbia University, New York, NY, USA
E-mail: jg343@columbia.edu

FUNDING AND DISCLOSURE

The authors declare no conflict of interest.

Adhikari A, Topiwala MA, Gordon JA (2011). Single units in the medial prefrontal cortex with

anxiety-related firing patterns are preferentially influenced by ventral hippocampal activity. *Neuron* **71**: 898–910.

Bienvenu TC, Busti D, Magill PJ, Ferraguti F, Capogna M (2012). Cell-type-specific recruitment of amygdala interneurons to hippocampal theta rhythm and noxious stimuli *in vivo*. *Neuron* **74**: 1059–1074.

Lesting J, Narayanan RT, Kluge C, Sangha S, Seidenbecher T, Pape HC (2011). Patterns of coupled theta activity in amygdala-hippocampal-prefrontal circuits during fear extinction. *PLoS ONE* **6**: e21714.

Pape HC, Driesang RB (1998). Ionic mechanisms of intrinsic oscillations in neurons of the basolateral amygdaloid complex. *J Neurophysiol* **79**: 217–226.

Popa D, Duvarci S, Popescu AT, Léna C, Paré D. (2010). Coherent amygdalocortical theta promotes fear memory consolidation during paradoxical sleep. *Proc Natl Acad Sci USA* **107**: 6516–6519.

Seidenbecher T, Laxmi TR, Stork O, Pape HC (2003). Amygdalar and hippocampal theta rhythm synchronization during fear memory retrieval. *Science* **301**: 846–850.

Neuropsychopharmacology Reviews (2014) **39**, 235–236; doi:10.1038/npp.2013.228

Toward Identification of Neural Markers of Suicide Risk in Adolescents

Suicide remains a leading cause of adolescent morbidity and mortality. Despite identification of risk factors and protective factors for suicidal behavior, we have limited understanding of the mechanisms underlying risk for suicide attempt. Adolescence is a time of high risk for suicidal behavior, as well as a time that intervention and treatment may have the greatest impact because of structural brain changes and significant psychosocial development during this period. Functional magnetic resonance imaging (fMRI) studies have promise to yield markers of risk for suicidal behavior in adolescents because they can help identify neurobiological underpinnings of pathophysiological mechanisms that are not observable at the behavioral level, and can also provide targets for future neurobiological interventions. Markers of risk for suicidal behavior are beginning to be elucidated, but as yet have not been applied to the clinical management of adolescents at risk for suicide.

Neuroimaging studies indicate neural circuitry abnormalities in adult suicide attempters. One study in adult suicide attempters reported lower glucose uptake in the prefrontal cortex and dorsal anterior cingulate gyrus in high vs low lethality suicide attempters (Oquendo *et al*, 2003). With regard to emotion processing, vulnerability to suicidal behavior has been associated with differences in response to negative emotion. Specifically, adult male suicide attempters showed greater activity in the right lateral orbitofrontal cortex and decreased activity in the right superior frontal gyrus to intense angry vs neutral faces relative to healthy and depressed non-attempter controls. In addition, cognitive inflexibility (inability to change strategy) is well documented in studies of adult patients with a history of suicide attempt (Jollant *et al*, 2005). However, few studies have explored the neural circuitry underlying adolescent suicidal behavior. This is an important oversight because suicide is one of the leading causes of death in adolescence, and the developing brain may provide a window into risk for suicidal behavior and allow for earlier intervention to prevent suicide.

Our functional neuroimaging studies indicate differences in emotion processing in adolescents with history of depression and suicide attempt relative to healthy control adolescents. Here, we have shown differences in the attention and salience networks (Pan *et al*, 2013). Our findings differ from those in adult males with depression, in whom the functional connectivity of the striatal-anterior cortical midline structures circuit is implicated in suicidal ideation (Marchand *et al*, 2012). Specifically, we have shown increased attentional control network activity and decreased functional connectivity between the dorsal anterior cingulate gyrus, implicated in attentional control of emotion, and the insula, a neural region associated with interoceptive processing of emotion, when viewing angry faces in adolescents with a history of depression and suicide attempt compared with

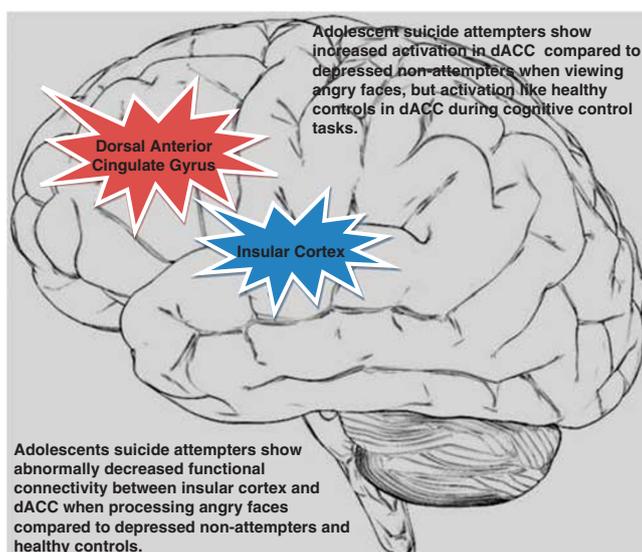


Figure 1. Summary of described functional neuroimaging abnormalities in adolescents with a history of suicide attempt.

healthy controls and depressed adolescent non-attempters (Figure 1). In contrast, adolescents with a history of depression and suicide attempt showed no abnormalities in levels of performance accuracy or dorsal anterior cingulate activity and attentional control network activity on tasks of cognitive control and learning in the context of risk (Pan *et al*, 2011; 2013). Together, these findings suggest that abnormal functioning of the salience and attention networks in the setting of emotion processing, with normal function in these networks in the absence of emotional stimuli, may represent markers of past suicide attempt. These networks are thus promising foci for future neuroimaging studies aiming to identify markers of risk for future suicide attempt in adolescent populations.

ACKNOWLEDGEMENTS

This research was supported by the American Foundation for Suicide Prevention, the Klingenstein Third Generation Foundation Fellowship for Adolescent Depression, NIMH/National Institute of Child Health (NICHD) 1K23MH082884-01 to LAP, and NIMH MH076971 (to MLP).

Lisa A Pan¹ and Mary L Phillips^{1,2}

¹Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA;

²Department of Psychological Medicine, School of Medicine, Cardiff University, Cardiff, UK
E-mail: thomasla@upmc.edu

FUNDING AND DISCLOSURE

The authors declare no conflict of interest.

Jollant F, Bellivier F, Leboyer M, Astruc B, Torres S, Verdier R *et al* (2005). Impaired decision making in suicide attempters. *Am J Psychiatry* **162**: 304–310.

Marchand WR, Lee JN, Johnson S, Thatcher J, Gale P, Wood N *et al* (2012). Striatal and cortical midline circuits in major depression: implications for suicide and asymptom expression. *Prog Neuropsychopharmacol Biol Psychiatry* **36**: 290–299.

Oquendo MA, Placidi G, Malone KM, Campbell C, Keilp J, Brodsky B *et al* (2003). Positron emission tomography of regional brain metabolic responses to a serotonergic challenge and lethality of suicide attempts in major depression. *Arch Gen Psychiatry* **60**: 14–22.

Pan L, Segreti A, Almeida J, Jollant F, Lawrence N, Brent D *et al* (2013). Preserved hippocampal function during learning in the context of risk in adolescent suicide attempt. *Psych Res* **211**: 112–118.

Pan LA, Batezati-Alves SC, Almeida JR, Segreti A, Akkal D, Hassel S *et al* (2011). Dissociable patterns of neural activity during response inhibition in depressed adolescents with and without suicidal behavior. *J Am Acad Child Adolesc Psychiatry* **50**: 602–611.

Pan LA, Hassel S, Segreti AM, Nau SA, Brent DA, Phillips ML (2013). Differential patterns of activity and functional connectivity in emotion processing neural circuitry to angry and happy faces in adolescents with and without suicide attempt. *Psychol Med* **9**: 1–14.

Neuropsychopharmacology Reviews (2014) **39**, 236–237; doi:10.1038/npp.2013.233