CNS Spectrums (2015), **20**, 355–358. © Cambridge University Press 2015
doi:10.1017/S1092852915000048

REVIEW ARTICLE

Magnetic resonance imaging markers of suicide attempt and suicide risk in adolescents

*Petra C. Martin, Thomas J. Zimmer, and Lisa A. Pan**

University of Pittsburgh School of Medicine, Department of Psychiatry

More than 36,000 people in the United States die from suicide annually, and suicide is the third leading cause of death in adolescence. 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 and structural neuroimaging studies in adults who have attempted suicide suggest distinct gray matter volume abnormalities in cortical regions, as well as prefrontal cortical and dorsal anterior cingulate gyrus neural circuitry differences compared with affective and healthy adult controls. Recent functional neuroimaging studies in adolescents with a history of suicide attempt suggest differences in the attention and salience networks compared with adolescents with depression and no history of suicide attempt and healthy controls when viewing angry faces. In contrast, no abnormalities are seen in these areas in the absence of emotional stimuli. These networks may represent promising targets for future neuroimaging studies to identify markers of risk for future suicide attempt in adolescents.

Received 25 August 2014; Accepted 1 December 2014; First published online 24 April 2015

Key words: Adolescent, depression, neuroimaging, salience network, suicide.

The Scope of the Problem: Adolescent Suicide Attempt

More than 36,000 people in the United States die from suicide annually, and suicide is the third leading cause of death in adolescence, with 4% of adolescents aged 10–18 attempting suicide.[1] Suicide attempt thus remains a leading cause of adolescent morbidity and mortality.[1,2] A suicide attempt is defined as self-injurious behavior, associated with at least some intent to die as a result of the act.[3] Despite identification of risk factors and protective factors for suicidal behavior,[4] we have limited understanding of the mechanisms underlying risk for a suicide attempt. The prevailing framework guiding this exploration is the stress-diathesis model, wherein certain individuals possess traits that render them vulnerable to suicidal behavior in reaction to stressors which would not induce suicidal behavior in the general population.[5] In particular, differences in cognitive rigidity, decision making, impulse control, and poor emotional regulation have been implicated. 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.[6] Functional magnetic resonance imaging (fMRI) studies show promise to yield markers of risk for suicidal behavior in adolescents because they can help identify neurobiological underpinnings of pathophysiologic 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.

* Address for correspondence: Lisa Pan, University of Pittsburgh SOM/WPIC, 3811 O'Hara Street, 100 N. Bellefield Ave., Room 320, Pittsburgh, PA 15213, USA. (Email: thomasla@upmc.edu)

Structural Neuroimaging Studies of Suicide Attempt

Structural neuroimaging studies in adults who have attempted suicide suggest abnormally decreased gray matter volume in cortical regions. One study reported significantly decreased gray matter volume in the fronto-striatal-limbic network in adults who attempted suicide versus healthy controls, and diminished rostral anterior cingulate volume compared with nonsuicidal individuals with major depressive disorder (MDD).[7] Adult females who attempted suicide showed decreased gray matter volume in the bilateral orbitofrontal cortex and greater right amygdala volumes than non-attempters.[8] Furthermore, a postmortem study of suicide victims found diminished right parahippocampal cortex volume

relative to healthy controls.[9] A meta-analysis of 12 studies in adults with a history of suicide attempt revealed that a history of suicidal behavior is interrelated with structural and functional deficits in brain areas that contribute to decision making, defined as "reduced motivational control over the intentional behavioral reaction to salient negative stimuli."[10] While studies in nonsuicidal adolescents with MDD report abnormally decreased volumes of the prefrontal cortex, whole brain,[11] hippocampus,[12] and amygdala[13], there are few structural neuroimaging studies of adolescent attempters.

We recently showed that adolescents (ages 14–17) with depression and history of suicide attempt had smaller right superior temporal gyrus volumes than healthy controls.[14] The right superior temporal gyrus is involved in attention to emotion, spatial perception and exploration, and face processing. Given our previous findings of salience neural network abnormalities in adolescent attempters during processing of socially relevant stimuli, angry faces,[15,16] the finding of abnormally decreased right superior temporal gyrus volume may be a structural neural marker of social-emotional information evaluation abnormalities in adolescent attempters.

Structural studies in adolescent suicide attempters have also revealed relationships between white matter intensities and suicidal behavior. A study of 102 adolescent and child (14.6 ± 3.4 years) inpatients with a history of depression with or without a history of suicide attempt revealed that adolescents with a history of an attempt had a greater total number of white matter hyper-intensities[17] and more parietal concentration of white matter hyper-intensities.[18] However, it was impossible to determine if these white matter intensities preceded or followed the attempt.

Functional Neuroimaging Studies of Suicide Attempt

Functional neuroimaging studies of adult suicide attempters indicate neural circuitry abnormalities. One study in adult suicide attempters[19] reported lower glucose uptake in the prefrontal cortex and dorsal anterior cingulate gyrus (dACG) in high versus low lethality suicide attempters. Lethality was scored using the Beck Medical Lethality Scale based on the degree of medical damage caused by the attempter's most lethal attempt; high-lethality attempters required hospitalization for treatment of sequelae related to the suicide attempt.[20] With regard to emotion processing, vulnerability to suicidal behavior has been associated with differences in response to negative emotion. Specifically, adult males with a history of suicide attempt showed greater activity in the right lateral orbitofrontal cortex and decreased activity in the right superior frontal gyrus to 100% intensity angry versus 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 (especially high lethality).[21,22]

There are few functional neuroimaging studies exploring 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 preliminary functional neuroimaging studies indicate differences in emotion processing and cognitive control of emotion neural circuitry in adolescents (ages 14–17) with a history of depression and suicide attempt relative to healthy control adolescents.[23] Here, we have shown differences particularly in the salience network[24] (Figure 1).

Specifically, we have shown increased attentional control network activity and decreased functional connectivity between the dACG and the insular cortex when viewing angry faces, but not happy faces, in adolescents with a history of depression and suicide attempt compared with healthy controls and adolescents with a history of depression but no history of suicide attempt (Figure 2). The dACG is implicated in attentional and emotional control, including attentional control of emotion. The insular cortex is a neural region associated with interoceptive processing of emotion. This may indicate inefficient recruitment of attentional control neural circuitry when regulating attention to mild intensity angry faces. In contrast, adolescents with a history of depression and suicide attempt showed no abnormalities in levels of performance accuracy or dACG activation in tasks of attentional control compared with healthy controls. These findings may indicate greater attention to negative emotional stimuli in adolescents with a history of suicide attempt and depression than healthy controls, despite normal recruitment of attentional control circuitry during non-emotional attentional control tasks. In summary, we have found that while adolescents with a history of attempt showed normal cognitive performance, they showed the greatest abnormalities when processing angry emotion. Taken together, these data indicate rapid and fixed responses to cognitive problems and impaired emotion processing in adolescents with a history of suicide attempt.

Additionally, there are limited neuroimaging studies exploring circuitry in adolescents engaging in nonsuicidal self-injury (NSSI). NSSI includes self-injurious behaviors, such as self-cutting, burning, or biting, that cause direct and deliberate harm to oneself without lethal intent. Prior NSSI is one of the strongest predictors of future suicide attempts.[25] One pilot study examined emotional processing in female adolescents (ages 14–18) with a history of NSSI using fMRI.[26] The subjects were shown pictures with self-injurious reference. Adolescents with NSSI rated the

https://doi.org/10.1017/S1092852915000048 Published online by Cambridge University Press

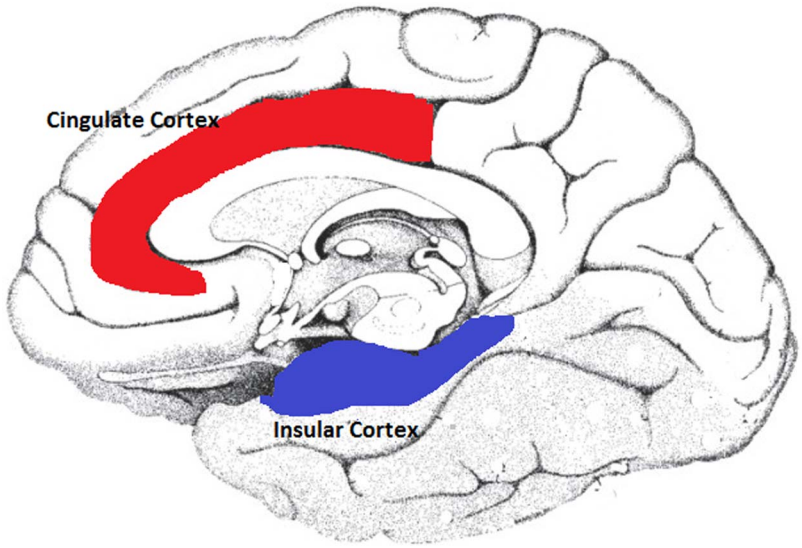

FIGURE 1. The salience network. Bilateral dACG and insulae are identified nodes in the salience network, which are implicated in sensory processing, modulation of attention to emotion, and fluid reasoning capacity (the ability to solve problems logically in novel situations).[24]

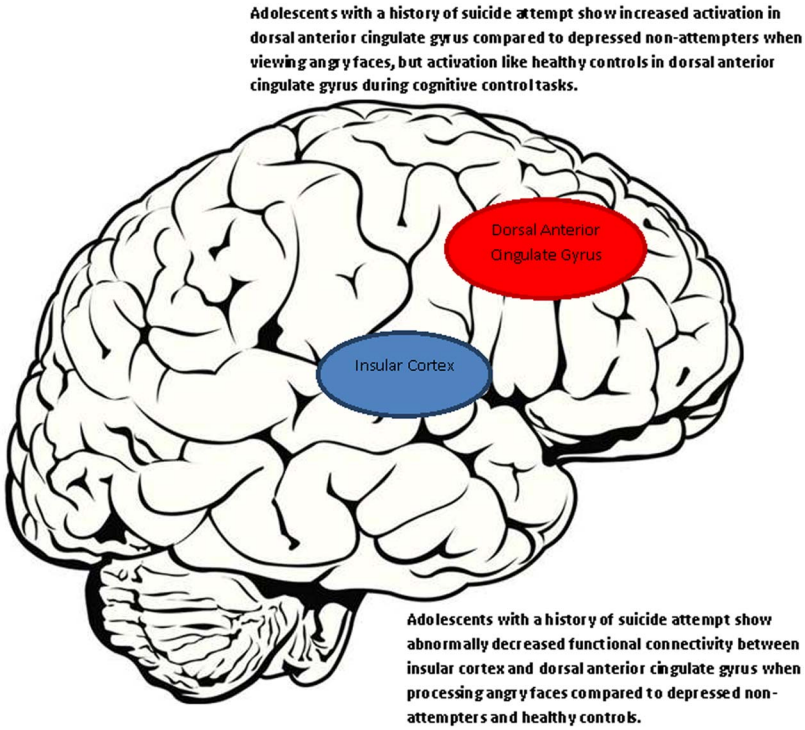

FIGURE 2. Summary of described functional neuroimaging abnormalities in adolescents with a history of suicide attempt.

pictures significantly more arousing than healthy controls without a history of NSSI. On imaging, adolescents with NSSI showed increased activity in the amygdala and in the ACG, along with increased activity in inferior and middle orbitofrontal cortex bilaterally when shown such images.

Future Directions

The structural and functional neuroimaging studies reviewed in this article indicate abnormalities in neural circuitry underlying emotional processing and emotion regulation in adolescent suicidal behavior. Functional

https://doi.org/10.1017/S1092852915000048 Published online by Cambridge University Press

neuroimaging to identify biomarkers of risk and elucidate neural circuitry underlying psychopathology is a relatively young field. There is a paucity of studies in functional neuroimaging in adolescent suicidal behavior. The work that has been done indicates differences in adolescents with a history of suicide attempt compared with adult suicide attempters. The application of these techniques to adolescents has focused primarily on diagnostic categories. The identification of potential markers of risk in adolescents who have attempted suicide is a first step toward understanding both which adolescents will progress to suicide attempt and the pathophysiology underlying suicidal behavior. Future studies building on these findings may aid in the clinical identification of those at risk for suicide, create a platform for longitudinal study of suicidal behavior, and allow for future intervention development.

Disclosures

Petra Martin and Thomas Zimmer have nothing to disclose. Lisa Pan has the following disclosures: NIMH/NICHD, K23 MH0828844, Grant; Klingenstein Third Generation Foundation Award, Grant; American Foundation for Suicide Prevention Young Investigator Award, Grant.

REFERENCES:

1. Centers for Disease Control and Prevention. Web-Based Injury Statistics Query and Reporting System (WISQARS). [online]. 2011. Available at http://www.cdc.gov/injury/wisqars/index.html.
2. Lubell KM, Kegler SR, Crosby AE, Karch D. Suicide trends among youths and young adults aged 10–24 years, United States, 1990–2004. *MMWR Morb Mortal Wkly Rep*. 2007; **56**(35): 905–908.
3. Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry*. 2007; **164**(7): 1035–1043.
4. Bridge JA, Goldstein TR, Brent DA. Adolescent suicide and suicidal behavior. *J Child Psychol Psychiatry*. 2006; **47**(3–4): 372–394.
5. Van Heeringen K. Stress–Diathesis Model of Suicidal Behavior. In Y. Dwivedi ed. *The Neurobiological Basis of Suicide*. Boca Raton, FL: CRC Press; 2012.
6. Maalouf FT, Brent DA. Child and adolescent depression intervention overview: what works for whom and how well? *Child Adolesc Psychiatr Clin N Am*. 2012; **21**(2): 299–312.
7. Wagner G, Koch K, Schachtzabel C, Schultz CC, Sauer H, Schlösser RG. Structural brain alterations in patients with major depressive disorder and high risk for suicide: evidence for a distinct neurobiological entity? *Neuroimage*. 2011; **54**(2): 1607–1614.
8. Monkul ES, Hatch MA, Nicoletti S, *et al*. Fronto-limbic brain structures in suicidal and non-suicidal female patients with major depressive disorder. *Mol Psychiatry*. 2006; **12**(4): 360–366.
9. Altshuler LL, Casanova MF, Goldberg TE, Kleinman JE. The hippocampus and parahippocampus in schizophrenic, suicide, and control brains. *Arch Gen Psychiatry*. 1990; **47**(11): 1029–1034.
10. Van Heeringen K, Bijttebier S, Desmyter S, Vervaet M, Baeken C. Is there a neuroanatomical basis of the vulnerability to suicidal behavior? A coordinate-based meta-analysis of structural and functional MRI studies. *Front Hum Neurosci*. 2014; **22**(8): 824.
11. Steingard RJ, Renshaw PF, Hennen J, *et al*. Smaller frontal lobe white matter volumes in depressed adolescents. *Biol Psychiatry*. 2002; **52**(5): 413–417.
12. MacMaster FP, Kusumakar V. Hippocampal volume in early onset depression. *BMC Med*. 2004; **2**(1): 2–8.
13. Rosso IM, Cintron CM, Steingard RJ, Renshaw PF, Young AD, Yurgelun-Todd DA. Amygdala and hippocampus volumes in pediatric major depression. *Biol Psychiatry*. 2005; **57**(1): 21–26.
14. Pan L, Ramos L, Segreti A, Phillips M, Brent D. Abnormally diminished right superior temporal gyrus volume in adolescents with a history of suicide attempt. *Br J Psychiatry*. 2015; **206**(4): 339–340.
15. Pan LA, Batezati-Alves SC, Almeida JR, *et al*. Dissociable patterns of neural activity during response inhibition in depressed adolescents with and without suicidal behavior. *J Am Acad Child Adolesc Psychiatry*. 2011; **50**(6): 602–611.
16. Pan L, Phillips ML. Toward identification of neural markers of suicide risk in adolescents. *Neuropsychopharmacology*. 2014; **39**(1): 236–237.
17. Ehrlich S, Noam GG, Lyoo IK, Kwon BJ, Clark MA, Renshaw PF. White matter hyperintensities and their associations with suicidality in psychiatrically hospitalized children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 2004; **43**(6): 770–776.
18. Ehrlich S, Noam GG, Lyoo IK, Kwon BJ, Clark MA, Renshaw PF. Subanalysis of the location of white matter hyperintensities and their association with suicidality in children and youth. *Ann N Y Acad Sci*. 2003; **1008**: 265–268.
19. Oquendo MA, Placidi G, Malone KM, *et al*. Positron emission tomography of regional brain metabolic responses to a serotonergic challenge and lethality of suicide attempts in major depression. *Arch Gen Psychiatry*. 2003; **60**(1): 14–22.
20. Beck AT, Beck R, Kovacs M. Classification of suicidal behaviors, I: quantifying intent and medical lethality. *Am J Psychiatry*. 1975; **132**(3): 285–287.
21. Jollant F, Bellivier F, Leboyer M, *et al*. Impaired decision making in suicide attempters. *Am J Psychiatry*. 2005; **162**(2): 304–310.
22. Keilp JG, Sackeim HA, Brodsky BS, Oquendo MA, Malone KM, Mann JJ. Neuropsychological dysfunction in depressed suicide attempters. *Am J Psychiatry*. 2001; **158**(5): 735–741.
23. Pan LA, Hassel S, Segreti AM, Nau SA, Brent DA, Phillips ML. 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*. 2013; **43**(10): 2129–2142.
24. Ham T, Leff A, de Boissezon X, Joffe A, Sharp DJ. Cognitive control and the salience network: an investigation of error processing and effective connectivity. *J Neurosc*. 2013; **33**(16): 7091–7098.
25. Hamza CA, Stewart SL, Willoughby T. Examining the link between nonsuicidal self-injury and suicidal behavior: a review of the literature and an integrated model. *Clin Psychol Rev*. 2012; **32**(6): 482–495.
26. Plener PL, Bubalo N, Fladung AK, Ludolph AG, Lulé D. Prone to excitement: adolescent females with non-suicidal self-injury (NSSI) show altered cortical pattern to emotional and NSS-related material. *Psychiatry Res*. 2012; **203**(2–3): 146–152.