Neural Circuitry of Suicidality

May 20, 2015 | CME [1]
By Lisa Pan, MD [2]

Structural neuroimaging, functional neuroimaging, and psychometabolomics in the identification of markers for suicidal behavior are discussed in this CME.

Premiere Date: May 20, 2015
Expiration Date: May 20, 2016

This activity offers CE credits for:
1. Physicians (CME)
2. Other

ACTIVITY GOAL
To understand the contributions of structural neuroimaging, functional neuroimaging, and psychometabolomics in the identification of markers for suicidal behavior

LEARNING OBJECTIVES
At the end of this CE activity, participants should be able to:
1. Understand how structural neuroimaging, functional neuroimaging, and psychometabolomics are used to identify markers of suicidality
2. Describe the evidence for using structural neuroimaging, functional neuroimaging, and psychometabolomics

TARGET AUDIENCE
This continuing medical education activity is intended for psychiatrists, psychologists, primary care physicians, physician assistants, nurse practitioners, and other health care professionals who seek to improve their care for patients with mental health disorders.

CREDIT INFORMATION
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More than 36,000 people in the US die by suicide annually. In the next 12 minutes, another person will have completed suicide. Despite identification of risk factors and protective factors for suicidal behavior, we have limited understanding of the mechanisms underlying risk for suicide attempt. The first suicide in recorded history was 4000 years ago, yet today we often remain unable to identify those at risk in time. This is true despite progress in identifying risk factors for suicide attempt and prevention strategies, and it indicates the need for utilization of our newest tools to understand the pathophysiology underlying suicidal behavior.

Structural and functional neuroimaging studies show promise as markers of suicidal behavior. They elucidate neurobiological underpinnings of pathophysiologic mechanisms that are not observable at the behavioral level and can also provide targets for future neurobiological interventions. Studies in psychometabolomics and neurochemistry hint at possible targets for treatment. Markers of risk for suicidal behavior are beginning to be elucidated but as yet have not been applied to the clinical management of persons at risk for suicide.2-6

Structural neuroimaging studies

Structural neuroimaging studies in adults who have attempted suicide suggest abnormally decreased gray matter volume in the cortical regions. One study showed significantly decreased gray matter volume in a frontostriatal-limbic network in adults who attempted suicide; diminished rostral anterior cingulate volume was also seen.7 Women who attempted suicide were found to have decreased gray matter volume in the bilateral orbitofrontal cortex and greater right amygdala volumes.8 A postmortem study of suicide victims found diminished right parahippocampal cortex volume.9

There are few structural neuroimaging studies of adolescents who attempt suicide. One recent study showed that adolescents with depression and a history of suicide attempt had smaller right superior temporal gyrus volumes than healthy controls.10 This is similar to the finding of reduced gray matter volume associated with empathy and theory of mind deficits in patients with schizophrenia.11 The right superior temporal gyrus is involved in attention to emotion, spatial perception and exploration, and face processing. 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 adolescents in an inpatient psychiatric hospital with a history of depression with or without a history of suicide attempt revealed that those with a history of attempt had a higher number of white matter hyperintensities and more parietal concentration of white matter hyperintensities.12,13 However, it was not determined whether these white matter hyperintensities preceded or followed a suicide attempt.

Functional neuroimaging studies

Functional neuroimaging studies of adult suicide attempters indicate neural circuitry abnormalities. One such study reported lower glucose uptake in the prefrontal cortex and dorsal anterior cingulate gyrus in high-lethality suicide attempters than in low-lethality suicide attempters.14 With regard to emotion processing, vulnerability to suicidal behavior has been associated with differences in response to negative emotion. Specifically, men with a history of suicide attempt had greater activity in the right lateral orbitofrontal cortex and decreased activity in the right superior frontal gyrus in response to 100% intensity angry versus neutral faces.5 Risky decision making and abnormalities of cognitive control are well documented in studies of adult patients with a history of suicide attempt (especially high lethality).15,16

Few functional neuroimaging studies explore the neural circuitry underlying adolescent suicidal behavior. A better understanding is still needed of the differences in the neural circuitry of adolescents and adults who have a history of suicide attempt, because suicide is one of the leading causes of death in adolescence. Neuroimaging studies of the developing brain may provide a window into risk of suicidal behavior and allow for earlier intervention. Our preliminary functional neuroimaging studies indicate differences in emotion processing and cognitive control of emotion neural circuitry in adolescents who have a history of depression and suicide attempt.5 The Figure shows differences in the salience network of the brain. Specifically, increased attentional control network activity and decreased functional connectivity between the dorsal anterior cingulate gray matter and the prefrontal cortex were seen in adolescents with a history of suicide attempt compared to healthy controls.17,18

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 gyrus and the insular cortex (a neural region associated with interoceptive processing of emotion) are seen in adolescents with a history of depression and suicide attempt when viewing angry faces. These brain regions are implicated in attentional and emotional control, including attentional control 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 dorsal anterior cingulate gyrus activation in tasks of cognitive control or learning in the context of risk.4,6

**Psychometabolomics**

Over 3 decades ago, Asberg and colleagues17 found low levels of 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid (CSF) samples obtained from adults with a history of suicide attempt. This work contributed to the development of SSRIs. Recent findings indicate that folate metabolism has a role in depression, and studies are exploring supplementation with 5-methyltetrahydrofolate to reduce depressive symptoms.18 A variety of known inborn errors of metabolism present with concomitant neuropsychiatric symptoms, including suicidal behavior.19 Single gene defects that contribute to inborn errors of metabolism are almost certainly underestimated. Established neurological disorders of neurotransmitter metabolism may in fact present in milder forms, with depression and suicidal behavior in the absence of other physical symptoms.

Relevant examples include dihydrofolate reductase defect in the folate metabolism pathway, and guanosine triphosphate (GTP) cyclohydrolase and associated tetrahydrobiopterin (BH4) deficiencies in the serotonin, dopamine, and nitrous oxide pathways.20-23 Disorders of metabolism in suicidal behavior, particularly aberration of flux through metabolic pathways rather than complete deficiencies, may be far more common than we think. A study of 34 adults with severe MDD revealed that 21% had previously unrecognized reduced folate levels (less than 150 ng/mL), which correlated with lower CSF 5-HIAA levels.24 Niederwieser and colleagues25 screened 673 children with elevated phenylalanine levels for biopterin synthesis defects. They found that 7.5% of the children had a neurometabolic disorder: 1 had GTP cyclohydrolase I deficiency; 36 had dihydrobiopterin synthetase deficiency; and 14 had dihydropteridine reductase deficiency.

The potential relationship between suicidal behavior, particularly in the setting of a treatment-refractory psychiatric disorder, and a CNS-specific metabolic disorder should not be underestimated. The profound effect of such a disorder on a patient’s life and our ability to intervene is illustrated in a published case report of a young man with deficient CSF BH4 and 5-HIAA levels.23 The patient was a 19-year-old with treatment-refractory suicidal ideation, multiple suicide attempts, and severe depression. BH4 is a cofactor for 3 enzymes: conversion of phenylalanine-4-hydroxylase (to phenylalanine), tyrosine-3-hydroxylase (to catecholamines), and tryptophan-5-hydroxylase (to serotonin).

Nearly 200 different mutant alleles have been identified that can result in deficient CSF BH4 levels. Treatment options should include sapropterin and the deficient monoaamine. In this patient, treatment with sapropterin (off-label use) was started. After 2.5 months, the patient reported stable improvement and diminished suicidal ideation, but mood remained low. He received 5-hydroxytryptophan (5-HP) supplementation with carbidopa to block peripheral effects of serotonin and increase conversion in the CNS. 5-HP was started at 50 mg/d and titrated to 200 mg/d. The patient reported improved mood and continued relief of suicidal ideation. After 8 months of treatment with sapropterin, CSF neopterin and biopterin levels were in the normal range. Following a trial off all medications, CSF metabolites returned to their original abnormal levels. Treatment was reinitiated and continued, and the patient remains in remission after 48 months of therapy, now with sapropterin alone.

**Conclusion**

Interventions that we know are effective in reducing the risk of completed suicide include screening and engaging individuals; targeted psychotherapy; pharmacotherapy; monitoring patients with past suicide attempts; limiting access to lethal means, especially firearms; education; and outreach. However, this is not enough. Suicidal behavior must be recognized as the distinct, deadly disease that it is, with a goal to understand the underlying pathophysiology and neural circuitry.

**CME POST-TEST**

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Figure. Bilateral dorsal anterior cingulate gyrus and insula are ident...

Disclosures:
Dr Pan is Assistant Professor of Psychiatry at the University of Pittsburgh and Attending Physician at Services for Teens at Risk in Pittsburgh.

References:


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