A Meta-analytic framework for investigating differential bio-markers of functional and structural connectivity: Application to sex differences underlying suicide and depression.

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Introduction: Although men represent approximately 80% of people who die by suicide in the United States,women are much more likely than men are to make non-fatal suicide attempts [1]. This gender paradox can be explained by a recent theoretical conceptualization of suicidal behavior (SB), the interpersonal-psychological theory of suicide[2,3],which proposes a novel psychological construct known as the acquired capability for suicide (ACS). It is comprised of two facets: fearlessness about death and physical pain insensitivity. Men have higher ACS than women do, and the relationship between gender and ACS is mediated by emotion regulation and risk-seeking [4].This is proposed as an explanation for why men die by suicide more than women do, despite a lower risk of non-fatal suicidal behavior [5]. However, the neural substrates of ACS have not been investigated. Most of the studies of the neural bases of SB identify it as a co-morbid condition with depression, characterized by prefrontal hypo-activity. Differential hypo-activity due to lower serotonin in women has been suggested as the basis for their higher vulnerability to both depression and non-fatal suicidal behavior. However, hypo-activity of the prefrontal cortex is not exclusive to SB. Further, these findings do not explain why more men die by suicide than women. The goal of this study was to delineate the neural mechanisms that are differentially activated in individuals with SB as compared to depression, and simultaneously investigate underlying gender differences in ACS.

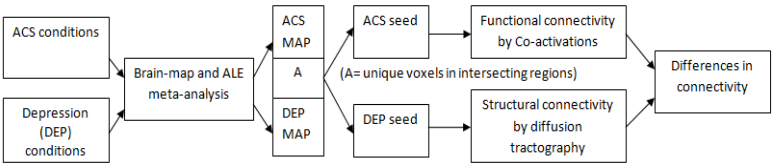

Fig.1 *Schematic illustrating proposed method*

Methods: In order to form a neural hypothesis underlying ACS, we performed a meta-analysis using the BrainMap database[6], and subsequently used activation likelihood estimation (ALE) statistical methods[7] to identify the regions activated in the following conditions: emotional regulation, pain insensitivity, risk-seeking, fearlessness, and gender differences.These conditions were chosen because they form the core psychological components of ACS and as such, the regions commonly activated(intersection) by all these conditions were hypothesized to be the ACS network. To generate a depression network, we ran ALE meta-analysis for the following conditions: depression and gender difference. The resultant co-activation maps for both ACS and depression networks demonstrated some of the same anatomical regions, but different voxels within them. For example, although the insula was shown to be a key node in both networks, spatially distinct voxels were identified between the two. The voxels that were uniquely activated in ACS and depression networks from the same anatomical region were taken as seed voxels for subsequent functional and structural analysis. Functionally, the co-activations for these seed voxels were examined using ALE in order to determine regions functionally connected to them. Structurally, white matter axonal tracts from these seed voxels were calculated using diffusion-weighted data from 49 healthy individuals in order to determine regions structurally connected to them.

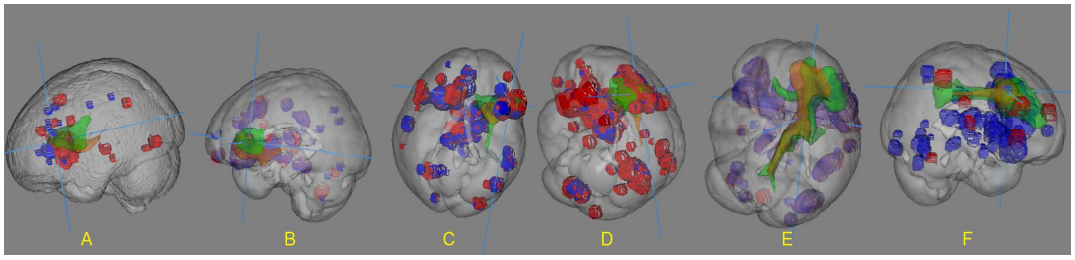

Fig.2 *Co-activations for DEP seed (red), ACS seed (blue). Axonal trajectories from DEP seed(green), ACS seed (orange). Maps for different seed regions: Insula (A), claustrum (B), inferior frontal (C), medial frontal (D), striatum (E), cingulate (F)*

Results: The regions that were commonly activated in both ACS and DEP networks were insula, claustrum, inferior frontal gyrus, medial frontal gyrus, striatum, and cingulate. However, voxels belonging to both networks in these regions were unique to either one of the conditions and did not intersect. Fig.2 shows the co-activations and axonal trajectories derived from the unique voxels from each network. The co-activations of ACS and DEP seeds from the same anatomical regions have both common and exclusive regions. This implies a difference in functional connectivity of the seed voxels. The tractography from the seeds led to different white matter tracts of the brain, demonstrating distinct variations in the structural connectivity likely involved in the two networks. For example, DEP and ACS seeds in the cingulate shared common white matter tracts within the cingulumbundle, however the DEP seed led to white matter within the cingulum bundle that extended anteriorly into the prefrontal cortex.

Discussion: Here we demonstrate that meta-analysis and meta-analytic connectivity modeling can be used to develop and test neural models of competing psychological constructs. First, we found that the ACS network, which by definition is upregulated in men, shares common neuroanatomical regions involved in gender differences. This may explain higher rate of suicide by death in men. Second, we found that despite sharing common neuroanatomical substrates, the DEP and ACS networks have slightly different foci within those anatomical clusters, which lead to distinct functional and structural connectivity differences. For example, tractography results from the cingulate DEP seed extend further into the prefrontal cortex than the ACS seed, suggesting that the region of the cingulate most commonly associated with ACS behaviors does not have access to the regulatory functions of the prefrontal cortex. In fact, in almost all cases, the DEP seeds demonstrated a more extensive functional and structural connectivity pattern than the ACS seeds. Our results have important implications for the construct validity of the ACS. Further, the identification of the ACS network provides a foundation for developing psychosocial and pharmacological treatments that may prevent fatal suicidal behavior.

References:[1]American Association of Suicidology, (2011).**[2]**Joiner,Why People Die by Suicide,*Harvard University Press,* (2005).**[3]**Van Orden et al, *Journal of Consulting and Clinical Psychology*,76,72-8, (2008).**[4]** Witte et al, *Journal of Research in Personality, 46,* 384-392.**[5]**Van Orden et al,*Psych Review*, 117,575-600,(2010).**[6]**Laird et al,*Neuroinformatics*,17,143–55, (2005).**[7]**Eickhoff et al. *HBM*, 30,2907-2926, (2009).