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The Complexity of Suicide: Review of Recent Neuroscientific Evidence

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Abstract

Two important aspects of human behaviour that become maladaptive in those individuals who are at high risk for suicide include: (a) the ability to engage in self-referential thought; and (b) the ability to feel complex and abstract emotions. Research suggests that the aberrant connectivity between and within important neural structures plays a major role in the problematically altered perceptions often held by highly depressed individuals, which ultimately contributes a great deal to the expression of the symptoms characteristic of the disorder. The present work provides a general overview of findings gathered from recent neuroscientific literature, synthesizing a comprehensive view that emphasizes the importance of interconnected networks in the brain in major depressive disorder (MDD), made possible by recent advances in neuroimaging technology. Of particular importance appears to be the ventromedial prefrontal cortex (VMPFC), the dorsomedial prefrontal cortex (DMPFC), and the pre/subgenual anterior cingulate cortices (pgACC/sgACC), the amygdala, and the insula. It is suggested that, rather than being basic diagnoses that can be identified through confirming items on an inventory of symptoms, major depressive disorder may be viewed as a malfunction in an intricate system of networks in the brain.

Keywords

Suicide, Depression, Neuroimaging, Prefrontal Cortex, Anterior Cingulate Cortex, Amygdala, Insula, Networks

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In the last two decades, convergent research on suicidal behaviour has made use of core concepts from a variety of different theoretical models, including the diathesis-stress (Mann et al. 1999), social interactionist (Lam et al. 2010), cognitive (Dieserud et al. 2001), and molecular models (Mann 2003; Turecki 2014). However, there has been little done toward integrating these diverse models of behaviour to synthesize a comprehensive neuropsychological view, despite the recent advances in neuroimaging technologies that have been made. Many neuroimaging studies focus on neurotransmitter receptor action (i.e., dopamine, serotonin, N-methyl-D-aspartate) in suicidal behaviour (Reisch et al. 2010), but few have been done to try to understand the functional connectivity of neural circuits in profoundly depressed individuals who express an intention to end their lives. Given the devastating consequences of untreated or treatment-resistant cases of depression, it is imperative that research efforts continue toward developing more

effective treatment and prevention strategies. Up to 15% of patients with treatment-resistant depression die by suicide (Souery, Papakostas, and Trivedi 2006). The aim of the present work is to review recent evidence from neuroimaging studies, lesion studies, connection and network studies, in an investigation of the structural and functional components of the mechanisms involved in suicidal behaviour.

Complexity, Importance, and Uniqueness to Human Life

Some aspects of depression may be represented somewhat analogically through animal models (Malkesman et al. 2009), but even the most sophisticated of these models cannot adequately inform us on the debilitating human psychiatric illness of major depressive disorder (MDD) and its consequences (Anisman and Matheson 2005). At best, these animal models merely give us insight on a small number of depression-relevant behaviours implicated in the illness (Grippo, Cushing, and Carter 2010). Included among these may be learned helplessness (Chourbaji et al. 2005; Seligman 1972), chronic stress (Blanchard, McKittrick, and Blanchard 2001), dysfunctional social behaviours (Pryce et al. 2005), reward prediction (Slattery, Markou, and Cryan 2007), and pain-like behaviours (Blackburn-Munro 2004). However, diverse as they are, animal models are unable to truly provide us with a holistic view of suicidal behaviour.

Despite the fact that these depression-relevant behaviours can be modelled and investigated in animals, the phenomena of suicide and of MDD as an illness, with all associated psychiatric and somatic markers (Penninx et al. 2013), appear to be limited to humans (Preti 2011). In changing significant aspects of behaviour, motivation, cognition, and self-perception (American Psychiatric Association 2000), being affected by MDD unequivocally shrouds all of the characteristics that defines one as human. Based on evidence that has emerged from research in neuroscience, it has become clear that the mechanisms that allow for the perception of self and for engaging in complex and abstract thought may also contribute to what makes the problem of suicide a uniquely human problem (Preti 2011).

Overview of Recent Neuroscientific Research

A wealth of research has focused on investigating risk factors associated with suicidal behaviour (Joiner, Brown, and Wingate 2005; Nock et al. 2008; Pompili 2010). It is evident that there are a number of factors that contribute to the manifestation of suicidal behaviour in patients with MDD. With the aid of recent developments in brain imaging techniques, such as positron emission tomography (PET) and functional

magnetic resonance imaging (fMRI), it has become possible study connectional abnormalities in humans, insofar as correlating activational patterns between brain regions in healthy controls and in MDD patients who have attempted suicide can shed light on the dysfunctional connectivities of these circuits (Anand et al. 2005). In addition, lesion studies (Drevets 2000) can even further strengthen the conclusions drawn from imaging research. This review focuses on two important aspects of human behaviour that become maladaptive in those who engage in or have engaged in suicidal behaviour: (a) the ability to engage in self-referential thought; and (b) the ability to feel complex and abstract emotions. Research suggests that the aberrant connectivity between and within important neural structures plays a major role in the problematically altered perceptions often held by highly depressed individuals, which ultimately contributes a great deal to the expression of the symptoms characteristic of the disorder.

A. Self-Referential Thought and Emotion Regulation

Suicidal behaviour is most commonly implicated in cases in which patients have a history of mood disorders (including both unipolar and bipolar depression), although Shneidman (1993) maintains that the presence of a clinical disorder is not always necessary for suicidal behaviour. Suicidal behaviour is linked to highly negative appraisals of the self (Habenstein, Reisch, and Michel 2013; Meerwijk, Ford, and Weiss 2013), such that the self-concept, in this case pertaining to the process of viewing oneself in a self-referential or phenomenological manner (Northoff et al. 2006), is cognitively distorted. Self-conscious emotions, such as guilt, are considered by emotion researchers (Lewis 2008) to be much more complex, and tend to have greater intensities in individuals with suicidal thoughts or intentions. For instance, these individuals commonly experience feelings of being burdensome on others (Beck and Lester 1976; Ribeiro and Joiner 2009; Van Orden et al. 2006); it would thus be fruitful to examine the neural activity among the cortical networks involved in self-referential thought processes in those individuals who are prone to suicidal behaviour.

Although the regions that are typically activated during processing of emotional stimuli include subcortical structures such as the nucleus accumbens, the amygdala, and the insula (Lemogne et al. 2012), one influential meta-analysis (Northoff et al. 2006) of 27 PET and fMRI studies found that among the areas most prominently activated during self-referential thought are the structures of the anterior cortical midline structures (anterior CMS); namely, the ventromedial prefrontal cortex (VMPFC), the dorsomedial prefrontal cortex (DMPFC), and the pre/subgenual anterior cingulate cortices (pgACC,

sgACC). Structural imaging accounts provide evidence for a reduction in volumetric grey matter particularly in the sgACC across depressive episodes, in both unipolar and bipolar depression (Drevets 2007).

An early model of self-focus proposed by Carver and Scheier (as cited in Lemogne et al., 2012) defined it as the process of adjusting the discrepancy between one's currently perceived state of self and a salient standard to which one holds oneself; depressive moods or symptoms arise when individuals consistently fall short of this and are unable to negate this discrepancy. Given the aberrant functional connectivity between the VMPFC/DMPFC and the amygdala, which receives input pertaining to affective states, patients with MDD are subject to chronically experiencing negative or aversive emotion when engaging in self-referential thought (Lemogne et al. 2012). Evidence suggests that the VMPFC plays an important role in integrating visceromotor aspects of emotional processing by synthesizing environmental and sensory cues, received via the orbitofrontal cortex (OFC), with internal affective states, and in light of this, it is suggested that the VMPFC may even be implicated in the decision-making process (Gusnard et al. 2001). In MDD, abnormalities exist in the networks formed between the MPFC, OFC, and their connected limbic structures, which together form a 'visceromotor network' responsible for modulating emotional behaviour (see Drevets 2007). The medial region of the PFC has been found to have decreased levels of cerebral blood flow (CBF) and glucose metabolism in patients with MDD—and an increase in these levels has been found in patients who have successfully remitted (Klein et al. 2010; Drevets 2007). Neural activity in the limbic system organize outward expressions of behaviour to stressors and emotional stimuli, and so the disconnectivity among components of the anterior CMS with the core limbic structures thus may provide an explanation for why depressed patients, and patients with a history of suicidal behaviour especially, have emotional responses that are incongruent with the nature of stimuli. Based on the conclusions drawn from these imaging studies, it is clear that the integrative networks among the MPFC, the OFC, and the amygdala serve critical functions in both emotional inhibition and expression.

The use of lesion studies is valuable because unlike imaging methods, which provide insight into correlational patterns in brain activity, they can be used to attribute changes in behaviour to certain areas (Koenigs and Grafman 2009). Thus, they can often provide stronger evidence for causal processes involved with certain behavioural expressions. Lesions of the MPFC and OFC have been associated with socially inappropriate behaviour, impulsivity, and lack of concern for moral principles (Ciaramelli et al. 2007). On the other hand, overactivity across these neural networks in patients with MDD could

have implications in the fact that feelings of guilt and burdensomeness is a common characteristic of the disorder.

B. Complex and Abstract Emotions in Perception of Pain

While the amygdala receives affective input, the insula receives interoceptive input (Lemogne et al. 2012), which is implicated in the emotional perception of pain. Results of fMRI studies consistently suggest that two areas that have substantial involvement in pain perception are the anterior cingulate cortex (ACC) and the insula (Zhuo 2006)—areas that, as first described by Broca and then later Papez (as cited in Mayberg et al., 1997), also have critical roles in moderating emotional states. The pathways linking the dorsal and ventral areas of the ACC, which contribute to the normal coordination of autonomic and willed behaviour, motor activity, and mood, are disrupted in patients with MDD (Mayberg et al. 1997). Data from PET scans indicate that the nociceptive pathway also includes the prefrontal cortex (PFC) and the amygdala (Mee et al. 2006); it appears that the only area that is exclusive to pain perception is the somatosensory cortex—all other brain areas have been found to be common to the perception of pain, the regulation of emotion, and the appraisal of self. A surgical procedure known as subcaudate tractotomy disconnects white matter tracts that connect the VMPFC with the subcortical structures has been successful in reducing symptoms of both depression was well as anxiety (Koenigs et al. 2008), further suggesting that it is the excess of neural activity along these connections that contributes to the expression of depressive symptoms.

The term psychache is used in the literature to mean a chronic, seemingly endless and inescapable experience of unbearable amounts of intense psychological pain, likely a result of consistent negative and aversive self-appraisals (Mee et al. 2011; Meerwijk and Weiss 2011; Shneidman 1993). Two leading researchers of suicide, Shneidman (1993) and Joiner (2005), have suggested that the most prominent risk factor contributing to suicidal behaviour is the intensity of the psychological, social, or emotional pain experienced by an individual, regardless of whether or not a clinical diagnosis for a depressive disorder exists. Indeed, some of the measure that are used to assess this mental pain are illustrative of this, containing items such as "My pain makes my life seem dark," "I hurt because I feel empty," and "My soul aches" (Holden et al. 2001, 225). In a review of psychological pain, Mee and colleagues (2006) compiled a brief list of statements made by patients in description of their personal experiences, for example, "It is like being in a black hole and trying to claw my way up to get out of it but I keep slipping further and further down

that hole. The suffering is torture. It is the worst pain that I know" (Holden et al. 2001, 682).

Incredibly loaded with complex and abstract representations of emotion, these scale items and statements seem to reflect characteristics that are uniquely human. With its connectivity to core structures of the limbic system, the VMPFC plays a key role in making appropriate appraisals and making logical decisions (Ciaramelli et al. 2007) based on information received from emotional processing centres (such as the amygdala), erratic signals sent from these centres is likely to lead to faulty appraisals of the self, of the situation, or of others—congruent with this emotional information.

Lesion studies of the ACC has demonstrated that damage sustained to this area results in a significant increase in response to pain, as well as heightened emotional sensitivity to aversive pain-related memories (Johansen, Fields, and Manning 2001), which may provide an explanation for why depressed individuals experience intense psychological pain. When this pain becomes unbearable, patients are at a much greater risk for committing suicide.

Conclusions and Findings

Given the fact that many of the same structures involved in all of self-perception, perception of the environment, and emotion regulation share communicative networks, it brings together a perspective on the structural and functional mechanisms implicated in MDD and suicide to understand how the connections work together on the scale of the whole brain. As is suggested by Long and colleagues (2015), all of the characteristics that come together to become what is known as a depressive disorder are likely not the result of a dysfunction in any single connection or structural component, but rather, an exceedingly complex interplay of problems that involve several networks and nodes across the entire brain.

Without the use of the neuroimaging and surgical techniques that we have access to, treatments such as deep brain stimulation (DBS) or transcranial magnetic stimulation (TMS) would not be possible. Although methods such as DBS and TMS are usually used only in cases where the depression appears to be resistant to treatment (Schlaepfer et al. 2014), and still bear the chance of relapse, they are inarguably much more effective than last-resort treatment measures taken in past (i.e., induced lesioning in performing lobotomies, or removal of whole brain areas; see Corkin 2002), before advanced neuroimaging technology was available.

Clinical Implications

In the course of a year, suicide accounts for over one million deaths worldwide (Jollant et al. 2010). Understanding the nature of suicide is critical to develop more effective treatment strategies, and one way that this is made possible is through neuroimaging technologies.

The overall benefits of having these advanced neuroscientific techniques is that treatment methods can potentially become more available and accessible to patients who are in need of better paradigms that will assist them in overcoming treatment-resistant depression. Determining a timely, effective line of treatment is critical especially in those patients who are at risk for suicide. However, the problem with more intensive treatment methods is that they can be costly (Hallett 2000), thus making them largely inaccessible. Especially given the consequences of profound, untreated depression, understanding the disorder from both a functional and structural perspective, through the use of neuroimaging, lesion, and network techniques, is a critical step in treating it in the most effective manner possible. However, it is critical to ensure that a balance is achieved in developing these treatments. As is illustrated by studies using populations who had suffered lesions, a complete deactivation of a system of networks can produce the opposite effect, such as aggression a complete deactivation of a system of networks can produce an effect on the polar opposite of the behavioural spectrum, such as the aggression, apathy, callousness, and impulsivity often implicated in fronto-temporal dementia (Ciaramelli et al. 2007). Ultimately, the goal is to strike this balance in allowing patients to be in control of their emotions, but not so much that they hardly feel obligated to adhere to social or moral norms.

Future Directions

It is worth considering that depression as a psychiatric illness may be a complex system of disruptions in functional connectivity, rather than a dysfunction of a single network (Long et al. 2015). It is common for researchers to use a region of interest (ROI) strategy when investigating the neural bases of particular behaviours; however, using this strategy can significantly limit the findings because if researchers decide to examine a particular area a priori, affected structures and networks which are not directly in the locus of the ROI may be missed and a truly holistic view of the system would not be achieved.

One notable question that has been proposed but not yet examined in depth pertains to the differential function of the dorsomedial versus the ventromedial prefrontal cortex.

There have been preliminary studies conducted on these two areas (Koenigs and Grafman 2009; Koenigs et al. 2008) and even in the case that regions are cytoarchitectonically universal, the functions and processes that are carried out by individual neurons may follow a different pattern even in the same conventional brain area. The distinctive functional characteristics between the areas would be worth investigating in greater depth in order to develop solutions to better target these networks.

In closing, it is suggested that, rather than being basic diagnoses that can be identified through confirming items on an inventory of symptoms, major depressive disorder may be viewed as intricate plexa that all interact with one another. Moreover, the characteristics implicated in these complex networks of behaviour are not ones that can be entirely eliminated in the treatment of disorders in which they have gone awry; instead, these are characteristics that must be preserved insofar as they are part of what makes us human. In bringing together convergent evidence using a variety of different techniques, the goal of finally bringing treatments that are more effective to patients is something that current research efforts should aim to achieve.

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