Understanding the suicidal brain

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It has been suggested that the key to preventing suicide is not in the study of the brain, but in the direct study of the human emotions (Shneidman, 1996). However, recent advances in neuroscience are providing support for a theory of human emotions that implicates increasingly well-defined brain regions (Stuss *et al*, 2001). The frontal lobes appear to be essential, with the right frontal lobe having a central role in the neural network for social cognition, including inferences about feelings of others. The ventral medial frontal regions are also important, possibly through their connections with the amygdala and other limbic structures which give them a key role in the neural network for behavioural modulation based upon emotion and drives (Phillips, 2003). It has been difficult to dissociate social cognitive processes from the behavioural expression of these processes, but insights are rapidly increasing based upon recent neuropsychological and neuroimaging studies.

Brain regions shown to be involved in suicidal behaviour constitute what may be called the 'suicidal brain'. Moreover, the current state of knowledge of neuropsychological and cognitive psychological aspects of suicidal behaviour allows for a description of the roles of these areas in the development of suicidal ideation and behaviour, and more particularly for a dissociation of the social cognitive processes and the behavioural expression of these processes. It is now clear that these brain structures contribute to the trait-like characteristics that constitute the vulnerability to suicidal behaviour.

SUICIDE RISK: FROM BODY TO BRAIN

One can show that there is an association between brain dysfunction and suicidal behaviour by comparing the risk of suicide behaviour in various groups of physical disorders. The risk of suicide increases the nearer the disorder or dysfunction is to the brain. When compared with the general population, suicide risk is doubled in people with disorders such as diabetes and cancer, approximately five times greater in people with peripheral neurological disorders (e.g. 2–7 times greater in multiple sclerosis and 4–9 times greater in spinal cord lesions) and more than five times greater in people with central neurological disorders such as stroke and epilepsy (particularly treatment-resistant epilepsy: 25 times) (Stenager & Stenager, 2000).

The prevalence of mental disorders, being strongly associated with an increased risk of suicidal behaviour, also increases as the primary location of the disorder or dysfunction moves closer to the brain. However, this probably does not explain sufficiently the association between brain dysfunction and the occurrence of suicidal behaviour. Indeed, certain personality traits that are also involved in the development of suicidal behaviour (e.g. emotional lability, impulsivity and aggressivity) are found in ascending order of frequency in the general population, those who are physically ill (e.g. hostility in coronary disease) and those with brain disorders (e.g. personality changes in epilepsy or brain injury).

COGNITION AND THE SUICIDAL BRAIN

Knowledge about the state of mind of suicidal individuals remains limited. Although thoughts and attitudes around the time of a suicidal act may predict future suicidal behaviour (Beck *et al*, 1999), relatively little is known about the most basic aspects of cognitive processing in suicidal individuals. However, impaired cognitive functioning in psychiatric disorders for which suicide risk is elevated is now well documented (Mann *et al*, 1999), and insight into the cognitive characteristics of

suicidal individuals is increasing (Williams & Pollock, 2001). It has thus become clear that three characteristics differentiate people with depression who are suicidal from people with depression who are not. These characteristics include:

(a) a sensitivity to particular life events reflecting signals of defeat, based on attentional biases ('perceptual pop-out') leading to involuntary hypersensitivity to stimuli signalling 'loser' status;

(b) the sense of being trapped, which is related to an insufficient capacity to solve problems, commonly of an interpersonal or social nature;

(c) the absence of rescue factors, mediated by deficient prospective cognitive processes and leading to feelings of hopelessness.

Although the involvement of these cognitive characteristics in the development of suicidal behaviour has been shown consistently, little is known about their neural basis.

With regard to sensitivity to life events, early studies focused on the hypothesis that a generalised cognitive rigidity mediates the relationship between stressful life events and suicidal behaviour. However, more recent findings are consistent with the possibility that among people with depression those who attempt suicide differ from those who do not on some but not all neuropsychological tests (King *et al*, 2000). Using a modified Stroop task, Becker *et al* (1999) found that the level of suicidal ideation in people with depression correlated particularly with biases in selective attention. Another study could not demonstrate any difference in attention measures between suicide attempters and non-attempters in a group of people with depression (Keilp *et al*, 2001). Although clearly much more research is needed, these findings suggest a role of attentional bias in the development of suicidal ideation – but not suicidal behaviour – in people with depression.

Williams & Pollock (2001) have convincingly argued with regard to the second characteristic that the sense of being trapped is associated with trait-dependent deficiencies in problem-solving skills, which in turn appear to depend upon deficits in autobiographical memory. Several studies have shown an association between attempted suicide and overgeneral autobiographical memory (Evans *et al*, 1992; Sidley *et al*, 1997). These studies indicate that overgeneral autobiographical recall

(probably mediated by the frontal lobes) affects suicidal behaviour by its effect on the ability to recall specific memories among people who attempt suicide, which correlates positively with the effectiveness of the solutions suggested for solving hypothetical social problems.

With regard to the third cognitive characteristic, the relatively new research approach addressing prospective cognition may well be useful. One study (Audenaert et al, 2002) but not another (McLeod et al, 1993) found differences between those who had attempted suicide and a non-depressed control group using a neutral fluency task. By using a modified fluency test it was recently demonstrated that participants who had attempted suicide were less fluent in coming up with positive events that might happen in the future. Moreover, hopelessness – which is a core psychopathological characteristic in association with suicidal behaviour – was found to correlate significantly with the lack of generating future positive events and not with an excessive anticipation of negative things in the future (Williams & Pollock, 2001). Using a split-dose activation paradigm with the Verbal Fluency Test we recently showed a blunted increase in prefrontal blood flow in the brains of people who had attempted suicide when compared with a healthy control group (Audenaert et al, 2002).

It thus appears that these three core cognitive psychological characteristics are associated with biases in neuropsychological functioning in terms of attention, memory and fluency, respectively.

Neural substrate of suicidal cognitive processes

Recent neurobiological findings converge to a substantial level with this cognitive and neuropsychological approach, leading to insights into the dissociation of social cognitive processes from behavioural expression involved in suicidal behaviour (Deakin, 1996; Van Heeringen, 2001). The social cognitive component is thought to be modulated by the frontal and temporal cortices in conjunction with the hippocampus, and mediated by the serotonin $(5-HT)_{1A}$ and noradrenalin neurotransmission systems. Sensitivity to social stimuli (measured by means of the personality dimension reward dependence, supposedly mediated by the noradrenergic system) strongly correlates with the activation of the stress system in those who

attempt suicide by violent means (Van Heeringen et al, 2000). A second component addresses executive functions, which may be modulated by the prefrontal cortex in conjunction with the amygdala and mediated by $5-HT_{2A}$ and dopamine, and comprise, among others, the abilities needed to achieve and maintain a problem-solving set – the second of the cognitive processes involved in suicidal behaviour described above.

Suicidal behaviour occurs at the crossroads of the past (recent with regard to precipitating stressors, and more distant with regard to its effect on our resilience against these stressors) and the future (or at least the way it is perceived on the basis of previous experiences). The frontal lobes are responsible for the integration of sensations, perceptions, consciousness and memory into organised and planned behaviours (Fuster, 1997), and the prefrontal cortex thus also mediates prospective cognitive processes. In vivo functional neuroimaging recently demonstrated that suicidal behaviour is associated with a decreased binding potential of prefrontal $5-HT_{2A}$ receptors, which in turn correlates significantly with increased levels of hopelessness and of behavioural inhibition (Van Heeringen et al, 2003). In a similar way it appears that dysfunctional attitudes, i.e. negatively biased views of oneself, the world and the future, are associated with cortical $5-HT_2$ binding (Meyer et al, 2003). It thus appears that the third cognitive process involved in suicidal behaviour, as described above, is associated with a decreased serotonergic functioning in the prefrontal cortex, which may become manifest as increased levels of hopelessness and behavioural inhibition following exposure to adverse circumstances. Based on these findings it can be hypothesised that increased behavioural inhibition (i.e. anxiety-based avoidance) is the primary mechanism involved, which might lead to suicidal behaviour only in the presence of a (dopamine-driven?) force, which is strong enough to break through this inhibition and which might manifest itself as hostility or aggression. This may explain the association between serotonergic dysfunction and impulsivity or dysregulation of aggression, as found in post-mortem studies of those who have died by suicide (Mann et al, 1999). Although this has been recently questioned, particularly with regard to the $5-HT_{2A}$ system (De Deurwaerdère & Spampinato, 1999), serotonin acts in an antagonistic way to dopamine,

so that a depletion of serotonin might indeed disinhibit aggressive behaviour.

There is thus increasing evidence that the suicidal brain comprises different (connected) cortical and subcortical brain structures, which constitute the social cognitive and behavioural expressive components of the predisposition for suicidal behaviour. Insight into the neuropsychological basis and neurobiological modulation of these components is increasing. Evidence can be found for a role of social cognitive processes (a sensitivity to particular social circumstances) and the behavioural expression of these processes (due to a dysregulation of anxiety and/or aggression). The dissection of the predisposition for suicidal behaviour in the components as described above is supported by studies of the neurobiological modulation of neuropsychological functions. For instance, attention level is related to noradrenalin release (Kodama et al, 2002), and drugs that influence $5-HT_{1A}$ function (such as buspirone) selectively affect performance on neuropsychological tests of memory and learning without affecting executive functions; the reverse appears to be the case for drugs that influence the $5-HT_2$ system (Deakin, 1996). Animal studies have shown that a balance between (hippocampal) $5-HT_{1A}$ and (cortical) $5-HT_2$ functioning is essential for an adequate response to social stress (McKittrick et al, 1995). Further research is needed to study the relevance of such findings to the understanding of the suicidal brain. Moreover, the effects of state-dependent conditions (such as those associated with the increased stress response or with excessive alcohol intake) on serotonergic neural activity requires further study, because of their potential influence on the course of the suicidal process (Van Heeringen, 2001).

Although the proposed model of the predisposition to suicidal behaviour most probably is to be regarded as simplistic, the complexity of the cortico-subcortical circuits involved in the different components of the predisposition to suicidal behaviour, their neuropsychological expression and their neurobiological modulation may well reflect the complexity of predicting and treating suicidal ideation and behaviour.

DECLARATION OF INTEREST

None.

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