

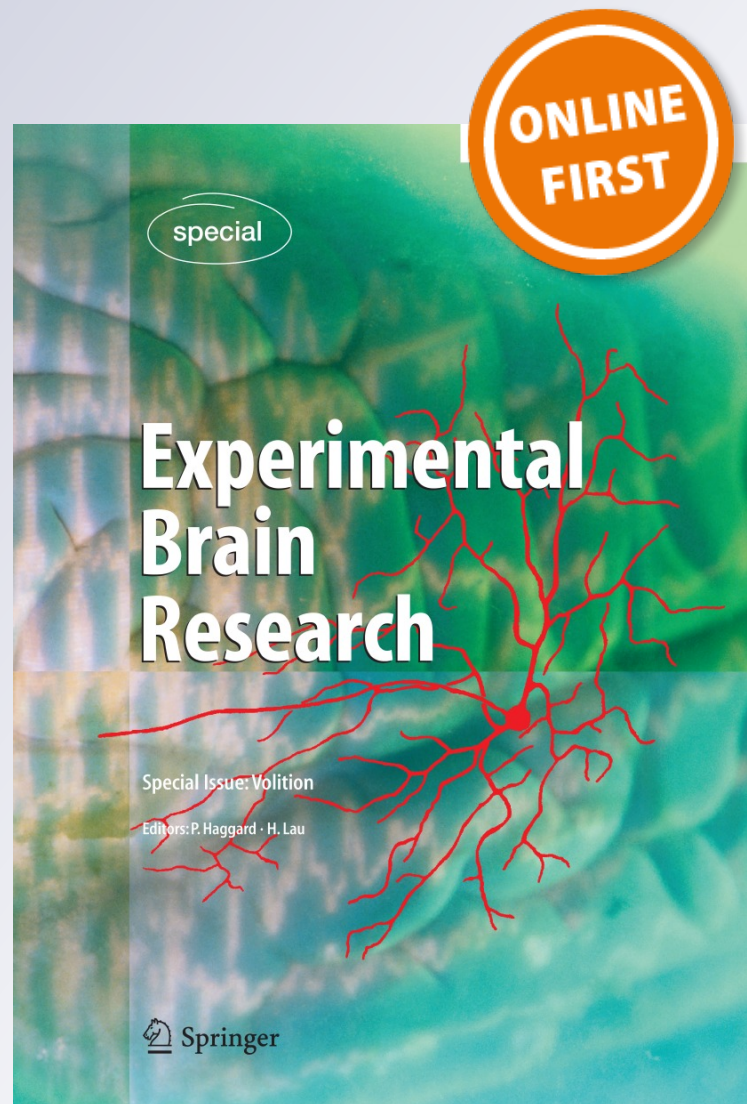
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Serotonergic modulation of suicidal behaviour: integrating preclinical data with clinical practice and psychotherapy

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Abstract Many studies have provided important information regarding the anatomy, development and functional organization of the 5-HT system and the alterations in this system that are present within the brain of the suicidal patient. There is also a growing interest in genetic factors associated with suicide, since these may lead to the emergence of personality traits that prove to be long-term predictors of suicidal behaviour. This review will focus on presenting the scientific literature on the role of the serotonergic system in suicidal behaviour as well as dysfunctional attitudes and personality traits associated with the suicidal patient. The association of the serotonin transporter gene, the 5-HT₂ receptors and its metabolite 5-hydroxyindoleacetic acid with suicidal behaviour and animal models that may capture the complexity of suicidal behaviour will be discussed. Finally, the relationship between neurobiological models and psychotherapeutic interventions for suicide prevention will be considered with a focus on Schema Therapy (an approach that has shown particular promise in the treatment of suicidal individuals

with personality disorders), aiming to invite the reader to integrate some aspects of the neurobiology of human suicidal behaviour into a model of suicide that can be used in a clinical encounter.

Keywords Suicide · Serotonin · 5-HT₂ receptors · 5-HTTLPR · Serotonin transporter · Schema therapy · Borderline personality disorder

Introduction

Suicide is receiving increasing attention worldwide, with many countries developing national strategies for prevention. Suicide accounts for almost 2 % of deaths worldwide, and attempted suicide is more frequent than completed suicide, with a prevalence of 3.5 % (Suominen et al. 2004). The definition of suicidal behaviours encompasses a broad constellation of heterogeneous entities differing not only in manifestation, but also in their background (Courtet et al. 2004).

Forms of suicidality include suicidal ideations, impulsive suicide attempts with low lethality, highly lethal failed suicide attempts and completed suicide (Bondy et al. 2000) and involve the intention to die and the lethality of method (Bondy et al. 2000). The nature of the suicidal act may range from impulsive to carefully premeditated and from aggressive/punitive or violent to non-violent or passive.

Suicide can either be attempted or completed, although an overlap has been noted given that about two-thirds of suicide victims have made one or more prior suicide attempt(s), and non-violent suicide attempters frequently change their suicide method from non-violent to violent (Rihmer 2007). Attempted suicide is a self-damaging act aimed at ending one's life resulting in failed suicide

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and suicide gesture. Failed suicide, provoked by a strong intent to die, involves careful planning and a highly lethal method, whereas suicide gesture (usually provoked by an interpersonal conflict) involves less preparation and less lethal methods with low intent to die (Mann 1998).

The great diversity of suicidal behaviours reflects their association with a range of disorders. These include major depressive disorder (MDD), substance-related disorders and personality disorders, including borderline personality disorder (BPD). Comorbidity among these disorders and between these disorders and suicide behaviour is common (Bondy et al. 2000; Dumais et al. 2005a, b). Suicide and attempted suicide are complex behaviours. A large number of proximal and distal risk factors have been identified (Hawton and van Heeringen 2009) which can be categorized into explanatory models aiming to understand suicidal individuals and facilitate suicide risk assessment. The most widely accepted risk factors for suicidal behaviour involve psychiatric–psychological and socioeconomic factors, while the biological, neurochemical and genetic contributions to suicidality have not yet been as fully elucidated.

On a neurobiological level, dysfunction of the serotonergic system has been shown to be implicated in a number of psychiatric afflictions including MDD, BPD and suicide (Oquendo and Mann 2000; Bortolato et al. 2013; Di Giovanni et al. 2008). Many studies have provided important information regarding the anatomy, development and functional organization of the 5-HT system and the alterations in this system that are present within the brain of the suicidal patient (Pandey 2013). On a psychotherapeutic level, early models have identified key determinants operating during the development of disorders or behavioural problems. Several have focused on, among other factors, the cognitive and emotional characteristics of depression and personality disorders. This conceptual approach and the empirical research motivated by such models have led to significant insights into these disorders (Ingram and Luxton 2005; Nadort et al. 2009).

Our aim is to review the scientific literature on the contribution of the serotonergic system to suicidal behaviour as well as to dysfunctional attitudes and personality traits associated with the suicidal patient. Although we will discuss data from studies investigating both suicide completers and attempters interchangeably, we acknowledge that these two phenotypes are likely to only partly share underlying aetiological and neurobiological mechanisms (Turecki et al. 2012). The association of the 5-hydroxyindoleacetic acid (5-HIAA), the 5-HT_{2A/2C} receptors and the serotonin transporter promoter region (5-HTTLPR) polymorphism and suicidal behaviour along with animal models will be discussed. Finally, the relationship between neurobiological models and psychotherapeutic interventions for suicide prevention will be discussed with a focus on Schema

Therapy (an approach that has shown particular promise in the treatment of suicidal individuals with personality disorders), aiming to invite the reader to integrate some aspects of neurobiology of human suicidal behaviour into a model of suicide that can be used in a clinical encounter.

Serotonergic function in suicide

Cerebral spinal fluid 5-hydroxyindoleacetic acid in suicidal behaviour

Given the inaccessibility of the human brain, initial studies of the biology of suicidal behaviour and development of biomarkers focused on peripheral tissues such as cerebrospinal fluid (CSF), urine, platelets and serum. Initial evidence for the involvement of 5-HT in suicide stemmed from findings of low CSF 5-hydroxyindoleacetic acid (5-HIAA) levels in depressed suicide attempters and in the brain stems of completed suicides (Asberg 1997; Asberg et al. 1976; Banki et al. 1984; Carlsson et al. 1980; Mann and Malone 1997; Placidi et al. 2001; Roy et al. 1986; Träskman et al. 1981). Although the link between low CSF 5-HIAA and suicidality has been debated (Roggenbach et al. 2002), significantly lower levels of CSF 5-HIAA have also been reported in a meta-analysis of CSF metabolite studies in subjects who made prior suicide attempts and those who subsequently committed suicide (Lester 1995). Further investigation on the relationship between CSF 5-HIAA and prefrontal (PFC) 5-HT has shown a positive correlation between the two in autopsied subjects (Stanley et al. 1985). In addition, more recent studies have shown that suicide attempters exhibit a blunted release of prolactin in response to administration of fenfluramine, a measure of 5-HT activity (Dulchin et al. 2001; Duval et al. 2001; Malone et al. 1996; Mann 1995; Pandey 1997; Weiss and Coccaro 1997).

5-HT receptor in suicidal behaviour

With regard to 5-HT receptor dysfunction in suicide and aggression, the most studied have been the 5-HT₁, 5-HT₂ subtypes (Bortolato et al. 2013; Panariello et al. 2011). We will focus on 5-HT₂ receptors that have been implicated in a wide variety of conditions including obesity, anxiety, depression, obsessive compulsive disorder, schizophrenia, migraine and erectile dysfunction (Di Giovanni et al. 2008, 2011).

5-HT_{2A} receptor in suicidal behaviour

In vivo neuroimaging techniques provide a great opportunity to further elucidate the link between adverse

environmental conditions, biomarkers and the symptoms or traits implicated in suicidal behaviour. Early evidence suggests that increased 5-HT_{2A} receptor binding in the prefrontal cortex, specifically Brodmann area 9, constitutes the most consistent post-mortem biological abnormality of suicide (Arango et al. 1990, 1992; Mann et al. 1986; Stockmeier et al. 1997; Turecki et al. 1999; Pandey et al. 2002; Stockmeier 2003). Although these abnormalities were reported as alterations in 5-HT₂ receptor binding, it seems as if these studies investigated 5-HT_{2A} receptors as ligand binding to 5-HT_{2C} receptors (Hoyer et al. 1986). In addition, the mRNA of 5-HT_{2B} receptors has low expression levels in cortex (Schmuck et al. 1994). Given that these findings were reported in studies in which diagnosis of the suicide victim was unrestricted together with the consistency noted between those studies with depressed and medication-free suicide victims (Hrdina et al. 1993; Yates et al. 1990), questions are raised concerning the extent to which this finding is associated with a specific diagnosis, a symptom cluster associated with suicide or represented a biomarker of suicidal ideation. Although the aforementioned finding was noted in studies of victims who committed suicide by violent means (Arango et al. 1990; Arora and Meltzer 1989; Mann 1996; Hrdina et al. 1993), it was unclear how this abnormality could be linked with symptomatology or personality traits. A recent autopsy study has proposed that suicide victims dying by violent means exhibited greater planning of suicide or a predisposition towards aggressive behaviour (Dumais et al. 2005a, b). Since it is much easier to recruit subjects with specific diagnoses in vivo, most neuroimaging studies of 5-HT_{2A} receptors focused upon three diagnostic areas in relation to 5-HT_{2A} receptors: MDD, BPD and antisocial personality disorder (APD).

MDD and prefrontal 5-HT_{2A} binding in suicidal behaviour

Neuroimaging studies of 5-HT_{2A} receptors in depressed and healthy samples seem to be inconsistent with the post-mortem findings as many of these between-group comparisons reported a regional decrease in 5-HT_{2A} binding, which could probably be attributed to selective serotonin reuptake inhibitor (SSRI) treatment (Dhaenen et al. 1992; Biver et al. 1997; Attar-Levy et al. 1999; Mintun et al. 2004; van Heeringen et al. 2003; Audenaert et al. 2001). Since these initial studies sampled people with recent antidepressant treatment, the initial impression was that regional 5-HT_{2A} binding tended to be reduced in MDD. However, further studies on depressed subjects not being in antidepressant treatment failed to reveal any differences compared to healthy controls (Meyer et al. 1999; Meltzer et al. 1999). Specifically, Meyer et al. (1999) sampled medication-free (>6 months) subjects with no comorbid psychiatric afflictions, in the

midst of a major depressive episode (MDE) from early onset MDD and by applying [¹⁸F]setoperone, a very good radioligand for imaging 5-HT_{2A} receptors, no difference in prefrontal cortex 5-HT_{2A} binding was found as compared to healthy controls.

The inconsistency between studies of suicide victims and neuroimaging studies of MDEs could be attributed to the presence of a subgroup of subjects with MDEs who have the biological abnormality reported in suicide victims (e.g. low extracellular serotonin). 5-HT_{2A} receptor density has an inverse relationship with extracellular serotonin levels, i.e. the density of 5-HT_{2A} receptors in the cortex increases after chronic serotonin depletion and decreases after chronically raising extracellular serotonin (O'Regan et al. 1987; Todd et al. 1995). The symptom used to identify this subgroup was the elevated pessimism (dysfunctional attitudes) observed during MDEs. There is a modest level of dysfunctional attitudes in health, which increases to a variable extent during depressive episodes (Simons et al. 1986; Fava et al. 1994). Greater pessimism during MDEs is an important symptom that contributes to the generation of sad mood and is targeted by cognitive therapy as well as SSRI treatment (Simons et al. 1986; Fava et al. 1994). Increasing extracellular serotonin after administration of intravenous d-fenfluramine is associated with a strong shift in dysfunctional attitudes towards optimism in healthy individuals (Meyer et al. 2003). This argues that among the many roles of serotonin, one of them is to modulate dysfunctional attitudes in humans. Both the anterior cingulate cortex and dorsolateral and medial PFC participate in functions related to optimism and pessimism (Sharot et al. 2007; Mitterschiffthaler et al. 2008; Elliott et al. 2002).

A strong correlation has been observed between the severity of dysfunctional attitudes (pessimism) and elevation in cortex 5-HT_{2A} binding potential, reflecting specific binding relative to free and non-specific binding (BP_{ND}). Moreover, cortex 5-HT_{2A} BP_{ND} was significantly elevated in subjects with MDE and severe pessimism (Meyer et al. 2003). There was a strong, significant correlation between severity of pessimism and prefrontal cortex 5-HT_{2A} BP_{ND}. In a separate study of a large sample of healthy subjects, two personality facets related to pessimism (vulnerability and anxiety) were also positively correlated with prefrontal cortex, temporal cortex and left insula 5-HT_{2A} BP_{ND} (Frokjaer et al. 2008).

The investigations correlating severity of dysfunctional attitudes with greater 5-HT_{2A} BP_{ND} (Meyer et al. 2003) are highly consistent with post-mortem investigations reporting greater 5-HT_{2A} receptor density in the prefrontal cortex of suicide victims. Fifty per cent of suicide victims suffer from MDD (Robins et al. 1959). The dysfunctional attitudes scale (DAS) is highly correlated with hopelessness measured with the Beck Hopelessness Scale (Cannon

et al. 1999; Norman et al. 1988). Given that hopelessness is a risk factor for suicide (Beck et al. 1985, 1989), it is plausible that investigations of suicide victims reporting increased 5-HT_{2A} BP_{ND} sampled depressed subjects with a greater severity of pessimism.

Personality disorders (BPD/APD) and prefrontal 5-HT_{2A} binding in suicidal behaviour

BPD and APD constitute two other psychiatric conditions on which the studies of suicide victims have focused (Barraclough et al. 1974; Robins et al. 1959; Brodsky et al. 1997). 5-HT_{2A} binding in medication-free BPD patients showed no difference in the prefrontal cortex (Meyer et al. 2003); however, an increase in 5-HT_{2A} binding in the hippocampus was found (Soloff et al. 2007). 5-HT_{2A} binding in aggressive individuals revealed no group difference in any region, but an age interaction such that 5-HT_{2A} binding tended to increase considerably more with age in individuals with aggression (Meyer et al. 2008). This age-related effect might represent an index of differential change in pyramidal cell loss, since most 5-HT_{2A} receptors are found in apical dendrites of pyramidal cell neurons and the pattern of loss of pyramidal cells matches the loss in 5-HT_{2A} receptors with age (Jacobs et al. 1997; Jakab and Goldman-Rakic 1998; Santana et al. 2004). Greater 5-HT_{2A} receptor binding has also been reported recently in the orbitofrontal cortex of impulsively aggressive personality disordered individuals (Rosell et al. 2010). However, this finding should be treated with caution as participants were not subjected to urine screening for substance abuse, a condition commonly comorbid with aggression. Such substances may bias 5-HT_{2A} receptor binding (Bubar and Cunningham 2008). Consequently, among the investigations of 5-HT_{2A} binding, there is support for increased binding in older individuals with aggression throughout the cortex and in the orbitofrontal cortex in people with aggression.

The evidence of greater 5-HT_{2A} density in the PFC of suicide victims in post-mortem studies should be reinterpreted through the prism of diagnostic and symptom-specific findings from neuroimaging studies of 5-HT_{2A} binding. MDD with high levels of pessimism is associated with greater prefrontal cortex 5-HT_{2A} binding. Half of the suicide victims have MDD and hopelessness (highly correlated with pessimism), which is associated with heightened risk of suicide (Beck et al. 1985, 1989; Cannon et al. 1999). The diagnosis of BPD does not contribute to the finding of greater prefrontal cortex 5-HT_{2A} density in suicide victims since no change in prefrontal 5-HT_{2A} BP_{ND} was found (Meyer et al. 2003; Soloff et al. 2007). In those with aggressive behaviour, a subgroup of subjects older than age 34 show a similar neurobiological finding and would be expected to also contribute to the original findings of

greater prefrontal 5-HT_{2A} density in suicide victims (Meyer et al. 2008; Rosell et al. 2010).

5-HT_{2A} receptors in aggression and suicide

Impulsive and aggressive traits are postulated to be part of the diathesis for suicidal behaviour (Mann et al. 1999). High levels of aggressive behaviour have been associated with suicidal behaviour, especially lethal suicide attempts. Impulsive behaviour has been shown to be highly related to non-fatal suicide attempts (Oquendo et al. 2004). As mentioned earlier, low levels of 5-HT have been implicated in impulsive violence and aggression in studies including low CSF 5-HIAA in individuals with a lifetime history of aggressive behaviour with personality and other psychiatric disorders (Brown and Goodwin 1986; Stanley et al. 2000). Low levels of 5-HT have also been associated with a blunted prolactin response to serotonin-releasing agent fenfluramine in personality disorder patients (Coccaro et al. 1989, 1995). Increased levels of 5-HT_{2A} receptor binding correlated with aggressive behaviour in personality and other psychiatric disorder patients (McBride et al. 1994; Coccaro et al. 1989). A role for serotonergic function in aggressive and to a lesser extent, impulsive behaviour, is well documented (Ryding et al. 2006; Congdon et al. 2008), consistent with observations that low SERT binding associated with suicide appears to be concentrated in the ventromedial PFC and anterior cingulate regions, which play a role in mediating inhibition and restraint (Arango et al. 1995; Mann et al. 2000). However, using post-mortem brain tissue, platelets, and DNA from suicide completers and attempters has not provided unequivocal evidence for a pre-eminent role for the SERT in the pathophysiology of suicide (Purselle and Nemeroff 2003).

5-HT_{2C} receptors in aggression and suicide

Despite the intense research on 5-HT_{2C} receptors showing its pivotal involvement in different neuropsychiatric disorders, only recently has the first selective agonist lorcaserin (Beliviq, Arena Pharmaceutical) advanced into the clinic, it was approved in 2013 by FDA for the treatment of obesity (Berlie and Hurren 2013). This paradoxical situation is due to the lack of selective pharmacological tools capable of overcoming the high degree of homology among 5-HT₂ receptors and, above all, the complexity of 5-HT_{2C} signalling. Indeed, the 5-HT_{2C} receptor is the only known G protein-coupled receptor (GPCR) subject to a form of post-transcriptional modification known as RNA editing (Di Giovanni et al. 2006). This is a process in which specific adenosine residues are converted to inosine resulting in functional recoding of the mRNA that can generate up to 24 different protein isoforms with distinct

functional properties. Post-mortem, animal and pharmacological studies have suggested that 5-HT_{2C} receptor and their altered RNA editing is involved in the pathophysiology of mental disorders including aggression and suicide, although results remain inconsistent (Panariello et al. 2011; Bortolato et al. 2013; Di Giovanni et al. 2006, 2011). For instance, an increased density of prefrontal cortex 5-HT_{2C}R mRNA (Pandey et al. 2006) and differences in pre-mRNA editing of these receptors between control subjects and suicidal victims have been found (Gurevich et al. 2002; Dracheva et al. 2008). Consistently, full edited 5-HT_{2C}R receptor mice displayed enhanced anxiety-like behaviour in response to the preferential 5-HT_{2C} agonist, m-chlorophenylpiperazine (mCPP; Di Giovanni et al. 2000), in the social interaction test and increase in freezing behaviours in reaction to an innately aversive ultrasonic stimulus (Martin et al. 2013). These authors suggested that enhanced 5-HT_{2C} receptor editing through interference from alternative splicing would lead to a deficit of truncated receptors that normally exert a dominant negative effect on the addressing of the full-length 5-HT_{2C} receptor protein to the membrane (Martin et al. 2013). Moreover, it is known that the pharmacological stimulation of 5-HT_{2C} receptors reduces aggressive responses and enhances the display of submissive behaviour (Rosenzweig-Lipson et al. 2007; Dekeyne et al. 2012; Harvey et al. 2012). These effects, however, may result from a general enhancement in social anxiety caused by drugs acting at 5-HT_{2C} receptors capable of inducing panic attack in humans (Charney et al. 1987). Indeed, increased neuroendocrine and anxiety responses to mCPP were observed in some individuals with MDD (Ghaziuddin et al. 2000). In addition, an increased in response to mCPP in cerebral blood flow of left frontal of individuals carrying the 5-HT_{2C}-Cys-23-Ser polymorphism in the 5-HT_{2C} coding region was observed (Kuhn et al. 2004). In contrast, most studies failed to identify significant associations among polymorphisms of this receptor and suicidal attempts (Zhang et al. 2008; Turecki et al. 2003; Serretti et al. 2007, 2009; Arias et al. 2001), completed suicide (Stefulj et al. 2004), the severity of suicidal behaviours (De Luca et al. 2008; Di Giovanni et al. 2011; Panariello et al. 2011) or suicide risk and deliberate self-harm (Pooley et al. 2003). On the other hand, the latest available study detected a significant association between completed suicide and the variants of 5-HT_{2C}-Cys-23-Ser polymorphism but not the mutation G-995A (promoter region) in the 5-HT_{2C} of Slovenian suicide victims (Videtic et al. 2009).

Since 5-HT_{2C} receptors are preferentially expressed on GABAergic interneurons (Serrats et al. 2005; Boothman et al. 2006; Liu et al. 2007; Di Giovanni et al. 2001), their hyperactivity and/or increase density/editing lead to an increase in the GABAergic function in areas such as the frontal cortex, other limbic structures and the raphe nuclei

determining a decrease in 5-HT turnover seen in aggression and suicide (Bortolato et al. 2013; Oquendo and Mann 2000).

Serotonin transporter imaging and post-mortem studies of suicide victims

In addition to the post-mortem studies of serotonin transporter (5-HTT) binding in depression (with or without concurrent suicide), decreased 5-HTT binding has been reported in the ventral prefrontal cortex associated with suicide, independent of diagnosis (Mann et al. 2000; Arango et al. 1995). Comparison between suicide victims with a history of depression and suicide victims without a history of depression yielded significantly lower 5-HTT binding in ventral prefrontal cortex in the suicide victims (Mann et al. 2000). Additionally, both groups of suicide victims had lower ventral prefrontal cortex 5-HTT binding as compared to non-suicide controls.

Further neuroimaging investigations have identified the conditions associated with decreased global 5-HTT binding describing a region-specific pattern that matches a predominant lower level of ventral prefrontal cortex binding (Meyer et al. 2001, 2004). Global reductions in 5-HTT binding may be observed following antidepressant treatment (Meyer et al. 2001, 2004; Suhara et al. 2003), in fall/winter season relative to spring/summer (Praschak-Rieder et al. 2005), as well as following ecstasy abuse, where a reduction in 5-HTT binding seems to be selectively affecting cortical regions including the striatum and mid-brain (McCann et al. 2005; Selvaraj et al. 2009). A similar region-specific effect has been recently reported in studies with patients suffering from obsessive-compulsive disorder (OCD) where the lowest 5-HTT binding was noted in ventral prefrontal cortex (Matsumoto et al. 2010; Reimold et al. 2007). Given that substance abuse and anxiety disorders are correlated with higher risk for suicide, it could be argued that ecstasy abuse and OCD could contribute to the diminished ventral prefrontal cortex 5-HTT binding in suicide completers (Mann et al. 2000).

Further experimentation supports the hypothesis that 5-HTT binding in impulsivity, as well as other maladaptive behaviours related to risk for suicide, is associated with 5-HTT binding reduction. Studies on early maternal separation in peer-reared rhesus monkeys (an animal model which will be discussed in another section of this review), who later exhibited aggressive and impulsive behaviour, have reported loss of 5-HTT binding restricted in areas including the midbrain, thalamus, caudate, putamen and anterior cingulate cortex, but not the prefrontal cortex (Ichise et al. 2006). Neuroticism, a personality trait which may involve impulsivity, has been positively correlated with thalamic 5-HTT binding (Takano et al. 2007) and

negatively associated with openness to values, the latter of which has shown a negative correlation with 5-HTT binding in subcortical regions (Kalbitzer et al. 2009). Aggression has also been linked with low levels of 5-HTT binding in the anterior cingulate cortex (Frankle et al. 2005) but with greater 5-HTT binding in brain stem of people with BPD (Koch et al. 2007). The degree to which these binding changes take place in the prefrontal cortex cannot be assessed due to the radiotracing methods utilized in these studies. Neuroimaging studies of 5-HTT binding in impulsivity and related conditions have not provided evidence confirming the ventral prefrontal cortex pattern of 5-HTT binding loss reported by post-mortem studies targeting this specific region (Mann et al. 2000; Arango et al. 1995).

Serotonin transporter in personality traits linked with suicide

Genetic studies focusing on 5-HT-related genes in search of genetic markers of suicide suggest that the 5-HT transporter length polymorphic region (5-HTTLPR) polymorphism of the serotonin transporter gene is strongly related to suicide (Costanza et al. 2013; Gonda et al. 2011). The short (s) allele of the 5-HTTLPR is associated with reduced serotonin transporter (5-HTT) protein availability and function (Canli and Lesch, 2007) compared with the long (L) form. The presence of at least one s allele has been proposed as a predictor of suicidal behaviour (Bondy et al. 2006). Considering the different suicidal phenotypes, including a review of related meta-analyses, the s allele seems to be associated with impulsive and aggressive suicidal behaviours and completed suicide (Bondy et al. 2000) and violent (Bayle et al. 2003; Bellivier et al. 2000; Courtet et al. 2001) as well as repeated suicide attempts (Courtet et al. 2004). A recent meta-analysis suggests that 5HTTLPR and the RS1800532 (tryptophan hydroxylase variant) polymorphisms are significantly associated with suicide attempts, but not associated with completed suicides (Clayden et al. 2012).

The presence of the s allele of the 5HTTLPR has been associated with the development of BPD (Ni et al. 2006). A recent study has shown that among a broad range of psychiatric disorders, patients with BPD are at particularly high risk for suicide completion (Qin 2011) making up 9–33 % of the total number (Pompili et al. 2005). Two meta-analyses (Samual and Widiger 2008; Saulsman and Page 2004) have found consistent high positive correlations between various measures of BPD and neuroticism as defined and measure by the NEO PI-r (Costa and McCrae 1995). In fact, BPD has the strongest and most consistent correlation with neuroticism among the personality disorders with BPD having significant correlations with all six of its facets. Thus, neuroticism can be seen as a core

trait underlying BPD (Samual and Widiger 2008; Saulsman and Page 2004). Neuroticism is among the traits that consistently have been associated with suicide ideation, attempts and complete suicide (Brezo et al. 2006). Lesch et al. (1996) found a significant correlation between the s allele and neuroticism. This investigation inspired many subsequent attempts at replication. The results have been inconsistent with studies supporting (Gonda et al. 2009) and not supporting (Willis-Owen et al. 2005) this finding. The majority of these studies were underpowered, with sample sizes being small relative to what is needed to draw conclusions based on the small effect size that can be attributed to a single gene. Two studies that were adequately powered (Willis-Owen et al. 2005; Terracciano et al. 2009) did not find a correlation, however, several meta-analyses did (Schinka et al. 2004; Sen et al. 2004; Munafo et al. 2005). The latter two investigations clarified that finding a correlation was dependent upon the method of meta-analysis being used. Genetic variations other than those associated with 5-HTTLPR have been explored but to date, after a decade of effort, no others have been found to correlate with neuroticism, underscoring the importance of the link between the two (Canli 2008). Primates who carry the homologue of the s allele express phenotypic features of neuroticism (e.g. increased anxiety and reduced social interaction; Hariri 2006).

Another line of investigation has looked at the possibility that the s allele is not itself correlated with negative affect but interacts with adversity, leading to neuroticism or such states as depression or anxiety in the face of negative life events. These studies were also initially leading to inconsistent findings. A recent large-scale, highly powered study (Middeldorp et al. 2010) and two meta-analyses (Munafo et al. 2009; Risch et al. 2009) concluded that the s allele did not moderate the interaction between negative life events and neuroticism. However, Uher and McGuffin (2009) have shown that the method of assessment of environmental adversity led to these negative results. When self-report measures were used, no moderating effect was found, but when detailed interview-based measures were used, the s allele was indeed found to have a moderating effect. This moderating effect has been clearly demonstrated in non-human primates (rhesus macaques). Infant primates who were deprived of adequate maternal care (i.e. peer raised) and who carried the s allele manifested heightened anxiety and depression, reduced engagement in play, greater aggression and increased alcohol consumption relative to L allele carriers (Champoux et al. 2002; Meaney 2001; Nelson et al. 2009). Mother rearing eliminated the differences between the two groups. Studies that have demonstrated this interaction in humans have found that children who carried the s allele who were exposed to emotional and or physical abuse showed increased levels

of anxiety, depression and cortisol secretion (Caspi et al. 2003; Stein et al. 2008; Taylor et al. 2006). Human infants who carry the s allele and who experience poor childrearing conditions are more likely to develop a negative emotional temperament (Auerbach et al. 2001). Individuals diagnosed with BPD or APD almost always suffer from severe childhood adversity. The interaction between these adverse experiences and the s allele is demonstrated by the finding that the relative risk of developing BPD or APD has been shown to increase by a factor of 2 for each short allele the individual carries (Gunderson and Lyons-Ruth 2008).

It is important to note that the impact of the s allele goes beyond an influence on anxiety and depression. It has been associated with bipolar and unipolar affective disorder, OCD, eating disorders, attention-deficit/hyperactivity disorder, neurodegenerative disorders and of particular importance in relation to the current discussion, suicide (Murphy and Lesch 2008). The s allele has been found to be associated with general impulsivity in the context of a broad range of emotionally evocative situations when the individual has been exposed to adverse environments in childhood. The combination of greater impulsivity and heightened levels of emotional pain associated with the s allele \times childhood adversity interaction strengthens the link with suicidality. This combination is reflected in the significant and consistent negative correlation found between the Conscientiousness scale of the NEO PI-r and BPD and the strong positive correlations between neuroticism and BPD (Samual and Widiger 2008; Saulsman and Page 2004). Negative scores on the Conscientious scale reflect difficulties with restraint and impulse control.

The vast majority of this research has been conducted within the diathesis-stress framework and, as a result, has not examined these interactions from the vantage point of what is called the differential susceptibility or “plasticity hypothesis” (Belsky and Pluess 2009). The diathesis-stress model focuses solely on the negative impact stress can have when impinging on an area of vulnerability. The plasticity hypothesis suggests that some individual differences can lead to bad outcomes in the face of adversity or very good outcomes in the context of enriched environments. Metaphorically what was viewed as a source of fragility and as operating like glass in the face of a stone is now seen as something more like clay that can form a deep impression for the better or worse. Looking at the impact of both positive and negative life events on the link between the s allele and neuroticism would allow for an examination of the full scope of its potentially moderating effect. On the positive side, carriers of two short alleles have been found to have more pulvinar neurons (Young et al. 2007). Pulvinar neurons are involved in the processing of visual signals sent to the limbic system via a subcortical route. More neurons mean a stronger connection and may be associated

with a greater capacity to detect the emotional context of an environment. Short allele carriers express greater sympathetic reactivity when observing another person receiving a shock (Crisan et al. 2009), suggesting a possible link to a greater capacity for empathy. In another study, it was found that seeing a favourite person led to significantly higher amygdala activity in short allele carriers suggesting a higher reward value of positive interpersonal experience (Matsunaga et al. 2010). Homberg and Lesch (2011) have reviewed the many cognitive and emotional advantages that correspond to the greater sensitivity and emotional responsiveness that has been correlated with the s allele. They hypothesize that these advantages may counterbalance or completely offset the disadvantages and may also be a contributor to some of the inconsistent findings referred to above.

Working from the same premise, Pluess et al. (2010) studied the interaction between negative and positive life events in relation to neuroticism in individuals homozygous for s alleles and L alleles. Consistent with the plasticity hypothesis, they found that those with s alleles who experienced more negative life events had higher neuroticism scores and those experiencing more positive life events had lower neuroticism scores. Those with L alleles had consistent scores on neuroticism regardless of the number of positive or negative life events. Thus, neuroticism may be a more stable trait for those with the L allele and less so for those with an s allele. It also may be that those with s alleles are more likely to be negatively impacted by a toxic childhood, develop maladaptive schemas and exhibit a behavioural and affectional pattern that will be associated with higher neuroticism scores. As noted above, we know that s allele carriers are more likely to develop BPD when exposed to toxic environments. This greater degree of responsiveness to the environment is reflected in the finding that human and primate s allele carriers have been found to be more responsive at rest in many cortical sites (Canli 2008).

Another study supporting the plasticity hypothesis was conducted by Antypa and van der Does (2010). They asked 250 university students about experiences of emotional abuse in childhood. Emotional abuse is a frequently reported occurrence among patients suffering from BPD. Cognitive reactivity to sad mood was assessed using the Leiden Index of Depression Sensitivity Scale. This measures habitual negative cognitive patterns and yields scores that remain high even when symptoms are low and thus overlaps significantly with the notion of an early maladaptive schema described in the last section of this review (4. *Bridging neurobiological models with clinical psychotherapy*). The results confirmed the plasticity hypothesis. Short allele carriers whose scores were very low on a measure of childhood emotional abuse had extremely low scores

on the measure of cognitive vulnerability to depression and extremely high scores when they reported high scores on measures of abuse. Long allele carriers had moderate scores no matter what level of abuse they reported. Put another way, the short allele carriers were able to benefit far more from a good childhood than the long allele carriers. It is important to note that while these recent findings are intriguing, replication with a well-powered study is needed to confirm or refute these observations. It is estimated that a sample size over 1,000 will be needed to have 80 % power at a significance level of $p = 0.50$ (Munafo et al. 2009).

On a neural level, a meta-analysis found a consistent correlation between the s allele and greater amygdala reactivity to many forms of negative stimuli relative to neutral cues. This included faces expressing fear and anger, and negative scenes and words (Canli and Lesch 2007; Hariri 2006). The strength of this correlation was about six times greater than that found on self-report measures. Thus, it appears that when variables closer to the genetic level (endophenotypes) are studied, the links are stronger than those found on the phenotypic level (e.g. those assessed by the NEO PR-r). Human s allele carriers have also been found to have increased anterior cingulate activity, especially in response to social threat (Jahn et al. 2010; Way and Taylor 2010). This reactivity was associated with greatly increased cortisol secretion.

The L allele and the associated efficient serotonergic functioning may lead to greater self-reliance with more affective regulation occurring within one's own synapses. The s-allele, associated with less efficient serotonergic functioning, may lead to an adaptive strategy that draws more on deep and enriched ongoing attachments to regulate affect. We could view this as emphasizing regulation across a "social synapse". This is a genetic variation that goes deep into our past as a species and, interestingly, humans and rhesus macaques are the only two species which have it. Humans and rhesus macaques are known as the "weed" species since both proliferate wherever they are placed in the world. It seems that both adaptive strategies (self-reliance and strong attachments) are important to the collective whole in both of these species and that the latter flourishes in supportive and nurturing interpersonal environments and leads to considerable emotional suffering including despair and suicidal behaviour in toxic interpersonal contexts.

Animal models of suicide

Animal models are formidable tools to investigate the aetiology of an illness, its course, potential treatment (Collado and Serrano 2010; Lanzas et al. 2010) and the neurobiology of associated behaviour (McKinney 2001). No convincing animal models of suicide have been developed

to date, although many researchers have tried to identify suicide in non-human species in the natural setting (Preti 2007). A range of suicidal behaviour in animals has been claimed. For example, animals in captivity or separated from their master have been reported to starve to death voluntarily (Preti and Miotto 2005; Ramsden and Wilson 2010) or exhibit self-destructive behaviours (Crawley et al. 1985); uncontrolled anxiety provoking situations including isolation, separation and confinement have been reported to result in self-endangering behaviours in primates (Kraemer and Clarke 1990; Tiefenbacher et al. 2005); monkeys in reared isolation showed higher risk of self-endangered behaviour in adulthood (Crawley et al. 1985). This latter finding parallels the impact of childhood abuse or neglect on the risk of suicide in humans (Evans et al. 2005; Brodsky and Stanley 2008). However, the degree to which such self-endangering behaviours in animals resemble self-harming behaviour in humans is debatable.

While modelling suicidal behaviour in animals fails to reproduce the role of will and intention in suicide mechanics, current animal models are making an effort to forge a tighter link by studying each step along the chain of behaviours leading to suicide in humans (for review on animal models of suicide, see Preti 2011). Among the several distinct animal models of suicide, learned helplessness and maternal deprivation seem to be particularly promising.

As discussed earlier, hopelessness and pessimism are major cognitive factors for suicide, and hopelessness per se has emerged as a predictor of suicide attempt and completion in clinical samples (Beck et al. 1985). The learned helplessness paradigm (Seligman 1972) is considered as an analog of human hopelessness (Krishnan and Nestler. 2008). These studies have involved series of inescapable electrified foot shocks as aversive stimuli, after which a subgroup of animals stops any attempt to escape. Following retesting after some delay, some animals try to escape again, while others indefinitely exhibit despairlike behaviour, failing to escape. Although this model offers good face validity, as many symptoms in humans (weight loss, sleep disturbances, distorted perception of pleasure, etc.) can be modelled in animals once learned helplessness has established, its ecological validity (i.e. correspondence with a real situation in humans) is poor as the model utilizes painful stimuli to produce helplessness. Interestingly, all antidepressants are effective in reversing the helplessness within 3–5 days of administration, compared to a 2–3 week delay in humans.

Turning to the maternal deprivation model, it has been found that early adverse life events (i.e. childhood abuse or neglect) and disrupted parenting are associated with an increased risk for psychopathology and suicidal behaviour in adolescence and adulthood (Agerbo et al. 2002; Lu et al. 2008; Afifi et al. 2009). Maternal deprivation (Lovic et al.

2001; Gonzalez et al. 2001) in rodents has been used as a model of human disrupted parenting. Studies have shown that maternal separation leads to an increase in the typical markers of stress (Walker et al. 1991) and to reduced activity of the main inhibitory neurotransmitters in the brain (Newport et al. 2002). Moreover, female offspring separated from their mothers showed aberrant maternal care in adulthood (Lovic et al. 2001; Gonzalez et al. 2001). Maternally deprived monkeys exhibited depressive-like symptoms during development, including low CSF noradrenaline concentrations (Kraemer et al. 1991), increased self-administration of alcohol (Fahlke et al. 2002) and self-endangering behaviour (Kraemer and Clarke 1990; Tiefenbacher et al. 2005). All of these findings lend support to the face and predictive validity of this model regarding the main correlates of major depression [i.e. comorbidity with alcohol abuse (Grant and Harford 1995) and increased risk of self-harming behaviour (Angst et al. 2005; Tondo et al. 2008)].

Given the difficulties in animal modelling, an intermediate phenotype in the animal must be specifically tested for validity and reliability (Geyer and Markou 1995; Boulougouris et al. 2009). Isolating and studying relevant endophenotypes will also be important. This will involve a focus on intermediate and behavioural markers proximal to genes (Gottesman and Gould 2003). A number of investigators have begun this process focusing on rhesus macaques. This population is of particular importance in animal modelling since they share over 98 % of their genetic material with humans, and as mentioned above, rhesus macaques are linked with humans in terms of a number of key genetic polymorphisms. Since rhesus macaques' early development involves a strong, exclusive, unique and enduring bond between mother and infant that has a high degree of overlap with Bowlby's (1969) characterization of human mother–infant attachment, this work has direct relevance to the maternal deprivation model.

Peer-only (PO) rearing (maternally deprived) has been found to lead to monkeys that, at a phenotypic level, are highly anxious, aggressive and impulsive and on a neuroendocrine (HPA) level exhibit more extreme responses to social separation (Suomi 1997; Dettmer et al. 2012). They have lower levels of CSF 5-HIAA concentrations than mother-reared monkeys from early infancy to later adulthood (Shannon et al. 2005; Higley and Suomi 2011) and have significantly different peripheral measures of neurotrophic factors NGF and BDNF (Cirulli et al. 2009) and as adolescents and young adults consume significantly more alcohol than their mother-reared counterparts during a “happy hour” situation (Higley et al. 1991; Fahlke et al. 2002). Neuroimaging studies have also shown the PO-reared monkeys to differ significantly in brain function and structure (Doudet et al. 1995; Ichise et al. 2006; Spinelli et al. 2009). Finally, major differences have been found in

genome-wide expression in leucocytes between PO-reared and mother-reared monkeys (Cole et al. 2012). Deprivation of adequate maternal care clearly has profound negative consequences for rhesus monkeys at phenotypic levels as well as neuroendocrine output, neurotransmitter metabolism, brain structure and function and even genome-wide expression. These consequences are linked to risk factors associated with suicide (e.g. high emotional reactivity, aggression, impulsivity and increased alcohol consumption).

Studies of this population examining the interaction between maternal deprivation and genetic polymorphisms have led to several dramatic discoveries that contribute to animal models of suicidal behaviour and have a bearing on prevention and treatment. These discoveries, in line with the plasticity hypothesis described above, have demonstrated that when monkeys born with so-called risk alleles [such as the short allele of the 5-HTT or the less functionally efficient MAOA allele, in addition to polymorphisms in the corticotrophin releasing factor (CRH) 2A gene, the neuropeptide Y (NPY) gene and the mu opioid receptor gene] are deprived of adequate maternal care, they develop the range of negative consequences outlined above but when monkeys with these less efficient variants have normal mothering not only do they develop normally but in some ways (e.g. consuming *less* alcohol during happy hours) function better than their L allele counterparts. Thus, these alleles seem to be a risk factor in depriving or harsh environments and a protective factor in benevolent environments (Suomi 2011). The potential benefits of these less efficient variants are most likely underappreciated at present due to the fact that these studies, except for one that will be discussed later, have not been assessing the impact exceptionally good mothering over and above normal mothering has on these polymorphisms. The plasticity hypothesis would predict that these alleles have evolved in a way that capitalizes on this difference.

While endophenotypes, such as those discussed above, have been proposed as physiological and behavioural markers and important gene \times environment interactions identified that relate to susceptibility to a psychiatric disorder (Hitzemann 2000; Nestler and Hyman 2010), endophenotypes for each link in the suicidal behaviour chain have yet to be identified. Clarification of clinical and psychotherapeutic models of suicidal behaviour is a prerequisite for the implementation of valid and reliable animal models.

Bridging neurobiological models with clinical psychotherapy

Different aspects of suicidality that have been associated with serotonergic modulation have been the target of several

Table 1 Domains and early maladaptive schemas (EMS) of schema therapy [taken and adapted from Lockwood and Perris (2012)]

<i>Disconnection and rejection</i>	Typically arises from parenting that is detached, cold, rejecting, withholding, explosive, unpredictable or abusive	Mistrust/abuse Defectiveness/shame Emotional deprivation Social isolation/alienation Emotional inhibition Abandonment/instability; primary
<i>Impaired autonomy and performance</i>	Typically arises from parenting that is under or overprotective, enmeshed and does not help to build competent functioning outside of the family	Vulnerability to harm and illness Dependence/incompetence Enmeshment/undeveloped self Abandonment/instability; secondary Subjugation Failure
<i>Extreme conscientiousness</i>	Typically arises from parenting that is based on conditional approval, is controlling, emphasizes status and appearance, or emphasizes rigid rules and expectations about performance and/or ethical behaviour	Self-sacrifice Unrelenting standards
<i>Impaired limits</i>	Typically arises from parenting that is permissive, overindulgent, fails to provide structure and direction and/or imparts a sense of superiority	Entitlement Insufficient self-control

psychotherapeutic approaches. Hopelessness can be conceptualized as a relatively stable schema incorporating negative expectations concerning the future. Several techniques have been developed as a part of cognitive behavioural therapy (CBT) in order to challenge and modify negative core beliefs. Problem-solving techniques constitute part of CBT as well. Both cognitive therapy (Rush et al. 1982) and problem-solving training (Salkovskis et al. 1990) have been found to reduce hopelessness. Dialectical behavioural therapy (DBT) is a form of CBT developed by Linehan for the treatment of patients with BPD and suicidal behaviour. According to Linehan et al. (1993), BPD is primarily a dysfunction of the emotion regulation system which results from biological irregularities combined with certain dysfunctional environments, as well as from their interaction and transaction over time. Patients with BPD experience enduring aversive states with impulsive, suicidal behaviours appearing to be behavioural solutions to intolerably painful emotions (Linehan et al. 1993). The effectiveness of DBT in reducing suicidal behaviour has been demonstrated by Linehan et al. (1991) who found that a group of BPD patients who received DBT (1) had fewer incidences of parasuicide and less medically severe parasuicides, (2) were more likely to stay in individual therapy and (3) had fewer inpatient psychiatric days, in comparison with a treatment as usual group. At the initial 6-month follow-up, DBT subjects had significantly less parasuicidal behaviour, less anger and better self-reported social adjustment. At the final 6-month follow-up, DBT subjects were found to have significantly fewer psychiatric inpatient days and better interviewer-rated social adjustment (Linehan et al. 1993).

Schema Therapy (ST) is an integrative psychotherapy that combines elements of cognitive-behavioural, attachment, object relations, psychodynamic and emotion-focused models. ST was developed by Jeffrey Young for the treatment of people with chronic characterological problems and has been found to be an effective treatment for patients with BPD (Farrell et al. 2009; Giesen-Bloo et al. 2006; Nadort et al. 2009).

The construct of an early maladaptive schema (EMS) is central to ST. An EMS is defined as a broad, pervasive life theme or pattern comprised of memories, emotions and cognitions regarding oneself and one's relationship with others developed during childhood or adolescence and elaborated throughout one's lifetime and dysfunctional to a significant degree. Suicidal risk and behaviour could be conceptualized around the EMS and schema modes. Of the full range of 18 EMS which have been defined (Table 1), the ones (based on clinical observations) that are consistently associated with the most intense painful affect and greatest risk of suicidal behaviour are those involving disconnection and rejection (e.g. the emotional deprivation, social exclusion, mistrust/abuse, and abandonment schemas), especially when they have been developed early in childhood. This is clearly linked to the maternal deprivation animal model of suicide described in the previous section.

Suicidal behaviour, as distinct from risk, could conceptualize in terms of schema modes. There are four distinct types: child modes, maladaptive coping modes, maladaptive parent modes and a healthy adult mode (Table 2). The child modes (Vulnerable, Angry, Impulsive/Undisciplined, Contented) are ones that humans come into the world

Table 2 Description of the schema modes of schema therapy [taken and adapted from Young et al. (2003)]**Child modes**

Involve feeling, thinking and acting in a “childlike” manner

Vulnerable child (including abandoned, abused, humiliated, or lonely types) Feels overwhelmed by painful feelings, e.g. anxiety, depression, grief, shame/humiliation, or loneliness

Angry child Feels and expresses uncontrolled anger or rage in response to perceived or real mistreatment, abandonment, humiliation, or frustration; often feels treated unjustly. Acts like a child throwing a temper tantrum

Impulsive, undisciplined child “Wants what he wants when he wants it”. Cannot tolerate the frustration of limits

Maladaptive parent modes

Involve internalized dysfunctional parent “voices”

Punitive/critical parent Internalized, critical or punishing parent voice; harsh criticism directed towards the self; feelings such as shame, guilt or self-loathing

Demanding parent Unrealistically high expectations; Pushy, controlling, demanding

Maladaptive coping modes

Involve maladaptive attempts to protect self from pain

Avoidance modes

Detached protector Emotional detachment used as protection from painful feelings; unaware of feelings; feels “nothing”; appears emotionally distant, flat, or robotic; avoids getting close to other people

Detached self-soother/self-stimulator Uses repetitive, “addictive”, compulsive or self-stimulating behaviours to calm and soothe himself; uses pleasurable or exciting sensations to distance himself from painful feelings

Angry protector A “wall of anger” used to keep others at a safe distance; anger is more controlled than in Angry Child mode

Surrender mode

Compliant surrenderer Gives into real or perceived demands/expectations of others seen as more powerful in an anxious attempt to avoid pain; get needs met

Over-compensator modes

Self-aggrandizer Feels superior, special or powerful; looks down on others; sees the world in terms of “top dog” and “bottom dog”; shows off or acts in a self-important, self-aggrandizing manner; concerned about appearances rather than feelings or real contact with others

Bully/attacker Uses threats, intimidation, aggression, coercion, retaliation to get what he wants; asserts his dominant position; feels sadistic pleasure in attacking others

Con man/manipulator Cons, lies or manipulates to achieve goals; victimizes others; seeks to escape punishment

Predator Focuses on eliminating threats, rivals, obstacles or enemies in a cold, ruthless and calculating manner

Over-controller (Paranoid and obsessive–compulsive) Focuses attention, ruminates and exercises extreme control in attempt to protect self from perceived or real threats; paranoid types try to locate/uncover hidden threats; obsessive types use order, repetition, or ritual

Healthy adult mode

Serves as an “executive function” in which the healthy adult part nurtures and protects the vulnerable lonely child, sets limits for the angry child and battles or moderates the maladaptive coping modes so helping to meet the child’s emotional needs

with and have close parallels to the child emotional systems that have been identified in mammalian brains (fear, panic, rage, seeking and play; Panskeep 1998). The Vulnerable Child mode, in the case of individuals who have suffered parental neglect and/or abuse, is characterized by an ongoing sense of deprivation and/or abuse and is labelled the Deprived/Abandoned or Abused Child mode. The Deprived/Abandoned/Abused Child mode is the one most commonly driving suicidal behaviour. Each mode is seen as having characteristic signs and symptoms, its own function and as requiring its own strategies to be effectively treated. The Deprived/Abandoned/Abused Child mode is characterized by neediness, frantic efforts to avoid abandonment, clinging, an idealized view of nurturers and feelings of

depression, loneliness, hopelessness, despair, fear, panic, worthlessness and victimization. The individual feels helpless to get their needs met or find protection. One of the main strategies when this mode is activated and suicidal risk is high is to connect to, soothe, reassure and protect the “Vulnerable Child” part of the patient and provide enough ongoing contact (with the therapist or significant others) for the crisis to be weathered and core needs for connection to be met. This mode and these strategies have close parallels to the aforementioned animal models involving the central role of maternal deprivation in suicidal risk. Two other modes, the Detached Protector (one of the maladaptive coping modes) and the Punitive Parent (one of the maladaptive parent modes) are also involved with suicidal

risk but involve a sense of self that other animals and even primates do not have. While these may be unique to *Homo sapiens*, the most important and central factor in the development and resolution of suicidal risk involves the Vulnerable Child mode; one we share with all other mammals.

All of the EMS (except for Entitlement/Grandiosity and Self-Sacrifice) have shown significant correlations with the temperament dimension “negative affectivity” and the trait “neuroticism” in child, adolescent and adult samples (Muris 2006; Thimm 2010; Rijkeboer and de Boo 2010). As mentioned above, consistent and strong correlations have been found between various measures of BPD and neuroticism. Consistent with this finding, it is observed clinically that when BPD patients fill out the Young Schema Questionnaire (Young 2005), a self-report inventory used to assess EMS, they almost always score highly on almost all 18 of the schemas making up the inventory.

Negative affectivity and anxiety proneness (precursors to neuroticism in adulthood) are associated with greater parental needs of the child (Van den Boom and Hocksma 1994). A prospective study that focused on the issue of how to best parent a needy child and that lends support to the plasticity hypothesis in relation to neuroticism and the *s* allele was conducted by Suomi (1997). The study investigated the developmental outcome of insufficient, normal and exceptionally good parenting of infant rhesus macaque monkeys with both normal and “neurotic” temperaments. One of the findings was that infant monkeys with normal temperament raised by inadequate parents (i.e. peers) developed behavioural and physiological characteristics of neurotic infants raised by normal parents. Infant monkeys with a neurotic temperament raised by normal mothers developed deficits in early exploration, exaggerated startle responses to minor stressors and a less secure attachment and were more likely to remain at the bottom of the dominance hierarchy. Interestingly, infant monkeys with a neurotic temperament raised by parents with exceptionally good parenting skills (i.e. being notably loving, nurturing and patient; qualities that are known to be essential for effective ST) expressed an even better developmental trajectory than infants with a normal temperament raised by normal parents. For example, they explored their environment more, displayed less behavioural disturbance during weaning, had an unusually secure attachment, rose to and maintained top positions in the dominance hierarchy and became highly nurturing parents themselves. The developmental trajectory of normal infants raised by exceptionally good parents was the same as that when raised by normal parents so the extra nurturance seemed to make no difference. Being a prospective study with primates, it allowed for control of all relevant variables throughout the period of investigation, making conclusions about causality more reliable than even the most tightly controlled prospective

studies possible with humans. We therefore view this study as a striking example of the potential advantages of a responsive and affirmative stance towards the needs of patients with a temperament characterized by neuroticism, negative affectivity and increased risk of suicidal behaviour such as those diagnosed with BPD.

An outcome study in which ST was compared to transference focused therapy (TFP) in the treatment of BPD produced findings consistent with those discussed above (Giesen-Bloo et al. 2006). ST was found to be twice as effective as TFP and led to a significant reduction in all BPD manifestations and related psychopathology including suicidal risk and behaviour. ST also had a significantly lower dropout rate. It is worth noting that ST was still found to be twice as effective even when controlling for the lower dropout rate. This strengthens the greater impact of ST on suicidal behaviour and risk since it retained more patients who would otherwise be left at higher risk and more quickly and effectively reduced suicidal behaviour and other BPD symptomatology in the patients that remained in the study. The Schema Therapists in the study were selected and trained with a focus on being warm and highly nurturing in response to the BPD patient's intense affect and needs for soothing. This involved the therapists making direct contact with the patient's Vulnerable Child mode and providing emotional nutrients such as soothing, reassurance, validation, understanding and praise, along with empathic limits when needed. The experiences are seen as being internalized and thereby building the healthy adult part of the patient. TFP therapists, on the other hand, focused on the adult part of their patients, helping them gain a better insight into the nature of their needs and feelings and through this, learn how to better tolerate painful affect and self-soothe. A key difference between these two approaches, and between ST and almost all other therapies including DBT, is captured in this distinction between the internalization of “other-soothing” and training in “self-soothing”. The former involves the assumption that the ability to self-soothe will grow spontaneously out of gratifying dependency needs. The latter involves a belief that directly gratifying patients' longings to be soothed and nurtured will do the opposite—impede and undermine the development of the capacity to self-soothe. Notably, the nurturing monkey parents were operating on the basis of internalization of other-soothing. We do not necessarily see this as a difference between good and bad. For children with less sensitive temperaments, there appears to be little difference between normal and exceptionally loving parenting and many young children and patients with either temperament can be trained to self-soothe. Moreover, a large percentage of the patients treated with TFP derived significant benefit. We believe, however, that providing training in self-soothing in response to these early core emotional

needs could facilitate the development of compulsive self-reliance and risks promoting detachment from self and others as a means of coping with intense affect. This can result in individuals with more sensitive natures (e.g. *s* allele carries) not having full access to the nutrients that allow them to flourish. ST seems to be especially effective in its ability to capitalize on the plasticity associated with the *s* allele and more sensitive temperaments, including patients with BPD, and in so doing, to more effectively reduce or eliminate suicidal risk and behaviour.

The importance of “other-soothing” in relation to BPD is seen in the third significant correlation (in the negative direction) between this diagnosis and the Agreeableness scale of the NEO PI-r (Samual and Widiger 2008; Saulsman and Page 2004). This reflects the great difficulty of those diagnosed with BPD to trust and get along with others. The latter, in combination with the intense emotional suffering BPD patients endure, leaves them cut off from the soothing and responsiveness they need, thus falling back on compulsive self-reliance. The patients in the Giesen-Bloo et al. (2006) study attributed a large part of ST effectiveness to the extent the therapist actively reached out to form a connection with, and be responsive and soothing to, their vulnerable or “child side”. This was also believed to be a major factor in the lower dropout rate.

The NEO PI-r Neuroticism, Conscientiousness and Agreeableness scales were all found to correlate with BPD. The combination of correlations on these three dimensions is unique to BPD. The strength of the correlation with neuroticism is also central. While, for example, APD also correlates significantly in a negative direction with Agreeableness and Conscientiousness, it correlates negatively rather than positively with neuroticism. The correlations found with BPD overlap well with the mode model that forms a central framework for the ST approach to this disorder. ST views BPD as made up of four distinct modes: the Vulnerable Child, Angry/Impulsive Child, Detached Protector and Punitive Parent modes. The Vulnerable Child mode is associated with reactions such as fear, anxiety, sadness, loneliness and hopelessness and thus has a clear link to neuroticism. The Angry/Impulsive Child mode corresponds with low Conscientiousness since the latter is associated with difficulties with restraint and impulse control. The Detached Protector mode is characterized by difficulty trusting others and a tendency towards interpersonal vigilance and keeping an emotional distance from oneself and others. This pattern is consistent with what is defined as low Agreeableness. The Punitive Parent mode (a critical/punitive aspect of the self) generates feelings such as low self-esteem, self-loathing, shame and guilt and is clearly linked to neuroticism with a focus on the internal activity through which these feelings are generated. This overlap lends support to the mode model as a comprehensive

framework with which to organize the key dimensions of a BPD patient’s functioning and to its emphasis on the Vulnerable Child mode as the core of the treatment process. In addition to the “other-soothing” aspect of ST (a key element of a process called “limited reparenting”), the mode model was seen by the patients in the study as being one of the most helpful features of the treatment.

The results of this study were replicated by Nadort et al. (2009) in a second large-scale trial of ST in the treatment of BPD testing to see if ST could be successfully implemented in regular treatment settings. A randomized control trial of Group ST in comparison with treatment as usual in the treatment of BPD found Group ST to be significantly more effective and to have a significantly lower dropout rate (Farrell et al. 2009). The results of these studies were as strong as or stronger than the Giesen-Bloo et al. (2006) study suggesting that ST shows considerable promise as an approach to decrease the risk and incidence of suicidal behaviour.

Lending support to the hypothesized link between rhesus macaques, humans and neuroticism discussed above and for the previous discussion on animal models of suicide is that fact that animals, and especially primates such as rhesus macaques, exhibit individual differences in behaviour that mirror most of the major temperament dimensions in childhood and Big Five personality traits in adults (Weinstein et al. 2008). Only effortful control (Conscientiousness) is not widely evident in other species, although it can be observed in chimpanzees.

Conclusions

It has been argued that, from a neurobiological perspective, suicidal behaviour is related to functional abnormalities in specific brain regions that have been associated with a person’s experience of the continuity of self, goal setting, decision making and emotion regulation. Biological suicide research has largely focused on low serotonin turnover. In current neurobiologically informed models, genetic predisposition and adverse childhood experiences (i.e. biological and psychosocial factors) are thought to interact during the developmental years, eventually resulting in the manifestation of neurobiological and clinical factors associated with suicidal behaviour. Clinically, these characteristics appear to be related to traits such as impulsivity and aggression, hopelessness and impaired problem-solving capacities.

Emerging studies on the nature of the genetic polymorphisms that underlie these abnormalities suggest that a paradigmatic shift is unfolding that sheds a new and brighter light on what has been viewed strictly in terms of the neurobiology of vulnerability. It appears that many of those who have less efficient serotonergic systems suffer

the most and who are at the greatest risk of suicide suffer greatly in toxic and depriving environments and benefit the most from highly nurturing environments. These individuals may in fact have an especially strong capacity for deep and meaningful relationships, and ST seems to be especially well suited to capitalizing on these strengths, allowing these individuals to move beyond coping and reduced suicidal risk to living rich and deeply connected lives.

The developments in the field of neuroscience are now leading to a deeper and more precise understanding of how and why approaches such as ST are especially effective in the treatment of suicidal risk. The continuing integration of psychotherapeutic models with neurobiological concepts has the potential to help build on these early successes and to lead to the development of better therapies for suicidal individuals. It is conceivable that in the future, neuroimaging studies will help to identify which treatments are effective in increasing resilience to stressful experiences after one or several suicide attempts. Neurobiological perspectives of understanding are no contradiction to patient-oriented models of suicide.

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