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THE PSYCHOLOGY AND NEUROBIOLOGY OF SUICIDAL BEHAVIOR

Thomas E. Joiner Jr., Jessica S. Brown, and LaRicka R. Wingate
Psychology Department, Florida State University, Tallahassee, Florida 32306-1270; email: joiner@psy.fsu.edu, brown@psy.fsu.edu, wingate@psy.fsu.edu

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■ **Abstract** Suicide is a leading cause of death, but it is not well understood or well researched. Our purpose in this review is to summarize extant knowledge on neurobiological and psychological factors involved in suicide, with specific goals of identifying areas particularly in need of future research and of articulating an initial agenda that may guide future research. We conclude that from both neurobiological and psychological perspectives, extant research findings converge on the view that two general categories of risk for suicide can be identified: (*a*) dysregulated impulse control; and (*b*) propensity to intense psychological pain (e.g., social isolation, hopelessness), often in the context of mental disorders, especially mood disorders. Each of these categories of risk is underlain at least to some degree by specific genetic and neurobiological factors; these factors in general are not well characterized, though there is emerging consensus that most if not all reside in or affect the serotonergic system. We encourage future theorizing that is conceptually precise, as well as epistemically broad, about the specific preconditions of serious suicidal behavior, explaining the daunting array of suicide-related facts from the molecular to the cultural level.

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THE NEUROBIOLOGY OF SUICIDAL BEHAVIOR

Of the leading causes of death, there is little doubt that suicide is the least well understood and the least well researched. It is the cause of death for more than half a million people a year worldwide, and agonizes many more. Our purpose in this review is to summarize extant knowledge on neurobiological and psychological factors involved in suicide, with specific goals of identifying areas particularly in need of future research and of articulating an initial agenda that may guide future research.

Family History and Genetics

TWIN STUDIES Initial studies attempting to determine the genetic contribution to suicidal behavior were conducted with twin samples. Roy (1992) reviewed four of the early twin studies and found that overall, 13.2% of the monozygotic (MZ) twin pairs were concordant for death by suicide as compared to only 0.7% of the dizygotic (DZ) twin pairs, a significant difference. Roy & Segal (2001) conducted two more twin studies and summed those with the previous four to find a MZ concordance rate of 18.5%, as compared to a DZ concordance rate of 0.7%.

With such studies having clearly indicated that there is some genetic component to suicidality, more recent studies have sought to clarify the role of genetics in suicide by evaluating variables that may account for this association. One study assessed 3401 female twins in Missouri, and identified a concordance rate for suicide attempts of 25% for MZ twins and 12.8% for DZ twins. Based on these results, they estimated the additive genetic effects to be 48%, the unique environmental factors to be 44%, and shared environmental effects to be 8% of the contribution to suicide attempts. When controlling for other psychopathology, they found major depression, childhood physical abuse, social phobia, African-American ethnicity, alcohol dependence, and conduct disorder to be significant predictors of suicide attempts, whereas alcohol abuse, generalized anxiety disorder, simple phobia, and parental education did not predict suicide attempts (Glowinski et al. 2001).

A similar study conducted on 5995 adult twins in Australia yielded similar results. This study examined three categories: the presence of suicidal thoughts; persistent thoughts of suicide, a plan to commit suicide, or a minor suicide attempt; and serious suicide attempts. In all categories, concordance was higher for MZ than for DZ twins. In comparison to the earlier studies, the concordance rates for serious attempts were 23.1% in MZ twins and 0% in DZ twins. Estimates of heritability of these types of suicidality were 43% for any ideation, 44% for persistent thoughts/plan/minor attempt, and 55% for a serious attempt, comparable to the estimate of the prior study. When controlling for other psychopathology, a history of major depressive disorder, conduct disorder, alcohol dependence, and panic disorder, each increased risk of persistent thoughts/plan/minor attempt in both men and women. In women, risk of a serious attempt was increased by a history of major depressive disorder, panic disorder, social phobia, and childhood sexual abuse.

Risk of a serious attempt in men was increased by a history of major depressive disorder, conduct disorder, panic disorder, and childhood sexual abuse. However, when controlling for these psychiatric and psychosocial variables, the cotwin's history of suicidal thoughts was a significant predictor of both increased serious attempts and persistent thoughts/plan/minor attempts in MZ twins, indicating a genetic link to suicide beyond the contribution of mental illness (Statham et al. 1998). This is a key point about the relation of mental disorders to suicidality—mental disorders, though very important in understanding suicidality, do not fully explain it (and a simplistic view of the association between mental disorders and suicidality does not explain why most people with mental disorders do not attempt, or die by, suicide).

Finally, a study on 6744 adult male twins in Missouri also identified a similar pattern of results (Fu et al. 2002). This study examined suicidal ideation as well as suicide attempts and calculated a heritability estimate for suicide attempts of 30%, lower than the two prior studies. It identified nearly identical psychiatric risk factors: History of major depressive disorder, adult antisocial personality disorder, post-traumatic stress disorder, panic disorder, and drug and alcohol dependence predicted both suicidal ideation and attempt when controlling for psychiatric history. Childhood conduct disorder was also a significant predictor of suicidal ideation, but unlike in the two prior studies, suicide attempts were not a significant predictor. Like the Statham et al. study (1998), the Fu et al. (2002) study also evaluated the role of cotwin ideation or attempt while controlling for other psychiatric and psychosocial risk factors. Here, too, genetic risk remained even when various mental disorders were controlled. Also, for MZ twins, risk of both suicidal ideation and attempt increased regardless of whether the cotwin endorsed ideation or attempt. However, in DZ twins, a more specific pattern emerged: A cotwin's suicidal ideation increased risk of ideation only, and a cotwin's suicidal attempt increased risk of attempt only. This suggests a broader effect on various forms of suicidality among MZ twins, and a more specific effect among DZ twins.

FAMILY STUDIES Further evidence of the role of genetics in suicide is shown through family studies. One early study (Egeland & Sussex 1985) examined the Old Order Amish over a 100-year period. During this time 26 people died by suicide, the majority of whom came from only four families. Interestingly, while these four families also had a high genetic loading for affective disorders, other families had a similarly high loading for affective disorders but no suicides, again consistent with the argument that an independent genetic component to suicide exists.

In examining familial risk factors for individuals who died by suicide, a family history of suicide contributed about a twofold increase in risk, even when controlling for family psychiatric history, which is also a significant predictor (Qin et al. 2003, Runeson & Åsberg 2003). These results also add support to the argument that there is a genetic contribution to suicide independent of the genetic contribution to mental illness. Interestingly, Runeson & Åsberg (2003) found no gender differences in the relation of family history to personal risk for suicide, whereas

Qin et al. (2003) found that a family history of suicide increases risk for suicide in females more than in males. Clearly, further research on the interaction between gender and family history of suicide is necessary.

Research on the parent-child transmission of suicide risk has also been utilized to identify risk factors for suicide attempts. One study found a sixfold increase in risk for suicide attempt in children of suicide attempters versus nonattempters. Additionally, 82% of the offspring who attempted suicide also had a mood disorder. A history of sexual abuse and increased impulsive aggression in both the parent and child also increased risk for suicide in the children of suicide attempters (Brent et al. 2002). This same group conducted another study (Brent et al. 2003), which divided the parents into three groups: those who had attempted suicide and had a sibling who had attempted suicide (highest genetic loading), those who had attempted suicide but none of whose siblings had attempted suicide (moderate genetic loading), and those who had not attempted suicide and whose siblings had not attempted suicide (low genetic loading). As expected, offspring with the highest genetic loading had the highest risk for suicide attempt, those with a moderate genetic loading had a moderate risk for suicide attempt, and offspring with a low genetic loading had the lowest risk for suicide attempt; greater genetic loading was associated with earlier age of first suicide attempt in offspring. Similar to their prior study, impulsive aggression predicted both familial transmission of suicide attempt and earlier age at first attempt, though in contrast to the earlier study, history of physical or sexual abuse did not (Brent et al. 2003). These two studies of parent-child transmission of suicidal behavior illustrate the important role of impulsive aggression as a mediator, but contribute mixed results regarding the role of childhood abuse in risk for suicidal behavior.

STUDIES OF CANDIDATE GENES In recent years, one gene that has received much attention is the serotonin transporter gene. The serotonin transporter (5-HTT) maintains control over the availability of serotonin in the synaptic cleft. In humans, 5-HTT is encoded by one gene (SLC6A4), located on chromosome 17q12. The transcriptional control region of this gene, denoted 5-HTTLPR, has been identified as having a polymorphism consisting of a 44 base pair insertion or deletion. These two alleles have been called the long (*l*) and short (*s*) (Lesch et al. 1996). These two alleles combine in individuals to form three different genotypes—the homozygous short (s/s), homozygous long (l/l), and heterozygous (s/l). Studies to date examining the link between these various genotypes and suicidality have generally shown mixed results. A recent study that followed 103 suicide attempters over the course of a year found that having the *s* allele increased the risk for subsequent suicide attempt, and that the frequency of the s/s genotype rose as the number of suicide attempts rose. Additionally, subjects carrying the s/s genotype had significantly higher scores on a measure of impulsivity (Courtet et al. 2004). Joiner et al. (2002a) reported that those with a significant family history of suicide were more likely to have the s/s genotype than were those without a family history. Mann et al.'s (2000) postmortem study found that short alleles were more

common among suicide victims than among others, but this difference did not reach statistical significance. However, a recent meta-analysis (Brown & Joiner, in preparation) has indicated that suicide completers are significantly *less* likely to carry the *s* allele than are controls. Suicide attempters showed no significant genotype differences from controls. These apparently contradictory findings highlight the need for further research on this gene as it relates to suicidality. In particular, the serotonin transporter gene's potential link to impulsivity warrants further investigation, as impulsivity appears to be involved in risk for suicide (a point that will be expanded on below).

Perhaps the most commonly studied gene with relation to suicidality is the tryptophan hydroxylase (TPH) gene. TPH is the rate-limiting enzyme in the synthesis of serotonin, making it an obvious candidate for speculation regarding suicide. This gene is located on chromosome 11q7, and two polymorphisms in particular have been studied: A218C and A779C. A meta-analysis of the association between the A218C polymorphism and suicidal behavior (combined attempted and completed suicides) found that presence of the 218A allele was significantly related to increased risk for suicide (Rujescu et al. 2003a). Other studies (e.g., Bennett et al. 2000, Pooley et al. 2003) have examined the A779C polymorphism and its relationship to suicide, with mixed results. One study (Nielsen et al. 1998) evaluated suicidality in male violent offenders and classified offenses as impulsive or nonimpulsive. Interestingly, suicidal impulsive offenders were more likely to carry the 779C allele, but suicidal nonimpulsive offenders were less likely to carry the 779C allele. The A218C polymorphism and the A779C polymorphism have been shown to be linked, such that almost all individuals have the same genotype for both polymorphisms (Kunugi et al. 1999). This suggests that the results regarding the A218C polymorphism likely hold true for the A779C polymorphism as well, and vice versa. Currently, the implications of these results are unclear, given that these two polymorphisms do not seem to have any functional influence on TPH gene transcription. Research is needed to identify the possible mechanisms of this gene's influence on suicidality as well as its potential moderating effect of impulsivity.

A third serotonergic gene that has been examined in relation to suicide is the 5-HT_{2A} receptor gene. A polymorphism has been identified on chromosome 13q14.1–14.2 and has been labeled T102C. This gene has come into question based on findings that suggest abnormalities in the 5-HT_{2A} receptors in suicidality (discussed below). However, the polymorphism in question has shown no functional relationship with the receptor, with one study (Du et al. 1999) showing no association between genotype of the T102C polymorphism and 5-HT_{2A} receptor density. Given these results, it is not surprising that most studies to date have found no association between the T102C polymorphism and suicidality (see Arango et al. 2003 for a review). However, these findings should not be taken to mean that the 5-HT_{2A} receptor gene has no effect on suicidality. It is more accurate to say that we have not yet identified the polymorphism that regulates the effect of the 5-HT_{2A} receptor gene on suicidal behavior.

Finally, one gene that has only recently been studied with regard to suicide is the catechol-O-methyltransferase (COMT) gene. The COMT enzyme is responsible for degradation of catecholamines (dopamine, epinephrine, and norepinephrine). A polymorphism on chromosome 22q11 codes for COMT activity and is composed of two alleles, the *H* allele and the *L* allele, which trigger high or low COMT activity, respectively. As with most other research on candidate genes, results have been mixed. One study (Russ et al. 2000) identified no difference in COMT genotype between patients at high risk for suicide and controls. However, other studies have suggested that the COMT gene is associated only with violent suicide. In one sample (Rujescu et al. 2003b), the *L* allele was more frequent in violent suicide attempters versus nonviolent attempters and nonattempters. The nonviolent suicide attempters and nonattempters showed no difference in COMT genotype. A similar study (Nolan et al. 2000) stratified the results by gender and found that the *L* allele was more frequent in males with a history of suicide attempts than in females. Furthermore, males who carried the *L* allele were more likely to have made violent suicide attempts and more attempts overall, but this relationship did not hold for females. Clearly, additional studies must be conducted to replicate these results, which suggest an interesting gender difference in suicide with regard to the COMT gene. The results also suggest that the COMT gene is linked to violent behaviors. Though recent studies have not evaluated the COMT gene with regard to impulsivity, this is an important area for future research.

To summarize, twin and family studies of suicidality have clearly shown a genetic component to suicidal behavior. Current research estimates the genetic contribution to suicidality to be between 30% and 50%. This genetic risk for suicidality appears to be partly independent of risk for mental illness and other psychological stressors. With advances in the study of the human genome and readily available procedures for genotyping, several candidate genes for the transmission of suicide risk have been identified. The serotonin transporter gene, the TPH gene, and the COMT gene have all shown links to suicidal behavior. The effects that these genes may have on impulsive and violent behaviors have only begun to be assessed and are a promising area of future research, as they may be the mechanisms through which the genetic risk is expressed. It is also important to note that suicidal behavior is not simple enough to be caused by any one gene, and haplotype analysis—the analysis of the effects of multiple genotypes in combination—may help to differentiate levels of genetic risk.

Abnormalities in the Serotonergic System

PERIPHERAL MEASURES OF SEROTONIN FUNCTION To date, one of the most well replicated findings in suicidal behavior is decreased levels of 5-hydroxyindoleacetic acid (5-HIAA), a major metabolite of serotonin, in the cerebrospinal fluid (CSF) of suicidal individuals. A meta-analysis comparing levels of 5-HIAA as well as homovanillic acid (HVA, a dopamine metabolite) and 4-hydroxy-3-methoxyphenyl glycol (MHPG, a metabolite of norepinephrine) found consistent evidence for

lowered 5-HIAA in suicide attempters and completers but no evidence for consistent changes in HVA or MHPG, indicating specificity to the serotonergic system (Lester 1995). A subsequent review came to similar conclusions and indicated that low levels of 5-HIAA in suicide attempters are predictive of subsequent attempts (Åsberg 1997).

Given the robust findings regarding decreased 5-HIAA in the CSF of suicide attempters and completers, recent research has begun to investigate possible moderators of this relationship. Some research (Mann & Malone 1997, Placidi et al. 2001) has divided suicide attempters based on the lethality of their attempts and has found that levels of 5-HIAA are significantly lower in high-lethality versus low-lethality attempters and that levels of HVA and MHPG do not vary by group. Other research (Cremniter et al. 1999) has evaluated impulsivity as a potential moderator. In violent suicide attempters, those who were identified as having high impulsivity had significantly lower 5-HIAA levels than did nonimpulsive attempters and controls. When evaluating serotonin in blood samples, plasma levels of 5-HIAA were lower in impulsive suicide attempters than in nonimpulsive attempters and controls (Spreux-Varoquaux et al. 2001). Taken together, these more recent studies suggest that lethality and impulsivity may serve as a link between low 5-HIAA and suicidal behavior.

One study (Nielsen et al. 1994) examined the association between CSF 5-HIAA levels and the TPH gene in impulsive alcoholic offenders. Individuals who carried the 779C allele were more likely to have lower 5-HIAA concentrations than individuals who did not. As mentioned previously, impulsive offenders with a suicide history were also more likely to carry the 779C allele, again supporting the link between low 5-HIAA and increased impulsivity and suicidality.

FENFLURAMINE CHALLENGE STUDIES Another mechanism for documenting abnormalities in the serotonin system is by administration of a fenfluramine challenge. This task is useful in that it stimulates serotonin release and inhibits reuptake, and the degree to which it stimulates serotonin can be measured by levels of prolactin. Results have generally shown a decreased prolactin response in suicide attempters versus depressed patients and controls, indicating less serotonergic activity in suicidality specifically (Coccaro et al. 1989, Corrêa et al. 2000, Duval et al. 2001). However, this difference has not always been found (Prochazka et al. 2000).

Similar to the 5-HIAA studies, lethality and impulsivity have been evaluated as moderators of this relationship. Not surprisingly, higher-lethality suicide attempters show decreased prefrontal cortex functioning as compared to low-lethality attempters, particularly after fenfluramine challenge (Oquendo et al. 2003). These high-lethality attempters also show decreased prolactin response to the fenfluramine challenge as compared to low-lethality attempters (Corrêa et al. 2000, Malone et al. 1996). Blunted prolactin response to the fenfluramine challenge is also seen in impulsive (Coccaro et al. 1989, Dolan et al. 2001, Sher et al. 2003) and aggressive individuals (Coccaro et al. 1989, Sher et al. 2003) as

compared to controls. One study (Malone et al. 1996) examined the interrelationships between suicide attempt lethality, Diagnostic and Statistical Manual (DSM) Cluster B personality disorders (characterized by erratic and impulsive behaviors), and fenfluramine-induced prolactin response. Again, the evidence to date suggests that hypoactivity of the serotonin system may influence aggression, impulsivity, and the lethality of suicide attempts.

TRANSPORTER AND RECEPTOR BINDING ABNORMALITIES Another method of evaluating the serotonin system is by postmortem analysis of the brains of individuals who have died by suicide. This area of research is not as clearly defined as the CSF 5-HIAA and fenfluramine literature, as some have found no difference in serotonin transporter binding between suicide victims and control subjects (Arango et al. 2001, Du et al. 1999). However, another study (Mann et al. 2000) found decreased serotonin transporter binding in the ventral prefrontal cortex that was specific to suicide as compared to major depression. Findings also indicated that abnormalities in the ventral prefrontal cortex are associated with disinhibition and impulsivity. Clearly, further research—either in vivo using imaging techniques or by postmortem analysis—regarding serotonin transporter binding in suicidal individuals is necessary.

Similar techniques have also been used to study serotonin receptor activity in suicidal individuals. Studies of the serotonin 2A receptor have indicated increased binding in suicide victims as compared with controls (Du et al. 1999, Turecki et al. 1999). Results for the serotonin 1A receptor, however, are less consistent. Increased serotonin 1A receptors have been seen in the dorsal raphe nucleus in suicide victims as compared with controls (Stockmeier et al. 1998). It has also been reported (Arango et al. 2001) that the receptor density in the dorsal and median raphe nucleus is equivalent between suicide victims and controls, but that the binding capacity is decreased in suicide victims. Again, this area of research is still in the preliminary stages and clear differentiation between suicidal individuals and controls regarding serotonin receptors has not yet been identified.

Other Brain Systems

Thus far, research has primarily focused on the role of the serotonin system in suicidal behaviors. As reported in the CSF studies, metabolites of dopamine and norepinephrine are generally no different in these groups than in others (see Placidi et al. 2001 for a review). However, it has been suggested that other brain systems, such as the hypothalamic-pituitary-adrenal (HPA) axis, may be involved in suicidal behavior. One way to measure HPA axis activity is by administering the dexamethasone suppression test (DST) and measuring cortisol response. Nonsuppression of cortisol in response to the DST indicates hyperactivity of the HPA axis. A meta-analysis has indicated that nonsuppression of cortisol in response to the DST may be predictive of later death by suicide (Lester 1992). While some more recent studies have not found an association between cortisol response to the DST and suicidality (Pitchot et al. 1995, 2003), others have shown that nonsuppressors show greater suicidality and severity of depression (Westrin & Niméus 2003).

One study (Coryell & Schlesser 2001) followed a group of patients over 15 years and found that those with nonsuppression of cortisol at baseline went on to have a 14-fold greater risk of death by suicide than those who did suppress cortisol output in response to the DST. These studies suggest that hyperactivity of the HPA system may be involved in suicidal behavior, though the evidence is not conclusive.

In summary, neurobiological research to date has clearly shown that there are serotonergic differences in suicidal individuals as compared to others. These differences appear to be specific to serotonin and may not involve other neurotransmitters. Studies of CSF and fenfluramine challenge responses indicate decreased serotonergic function in suicide attempters and completers, and point to impulsivity, aggression, and lethality as being influenced by this serotonin hypoactivity. More specific biological mechanisms underlying this hypoactivity are not yet clear, as there is no conclusive evidence for abnormalities in either the serotonin transporter or serotonin receptors in the brains of those who die by suicide. The twin and family genetic studies also implicate impulsivity as a factor, as well as mood and anxiety disorders; they further document that the genetic contribution to suicide exists beyond these factors. Continued research in this area is clearly necessary. Research has also implicated the HPA axis in suicidality, and further research on the nature of this system and its link to suicidal behavior promises to be an exciting new avenue of inquiry.

PSYCHOLOGICAL AND CLINICAL RISK FACTORS FOR SUICIDALITY

Mental Disorders

The presence of a psychiatric disorder and particularly major depressive disorder is a well-established risk factor for suicide across all age groups (Prigerson et al. 2003). Approximately 90% of completed suicides have a diagnosable psychiatric disorder at the time of death (Bertolote 2003, Cheng 1995, Conwell et al. 1996, Henriksson et al. 1993, Vijayakumar & Rajkumar 1999). A number of other psychiatric disorders have also been repeatedly and specifically linked to suicide. The specific disorders with strong empirical support for a relation to suicide include mood disorders, borderline personality disorder (BPD), disruptive behavior disorders, alcohol and drug use disorders, anxiety disorders, anorexia nervosa, and schizophrenia.

Depression is a long-established risk factor for suicide (see, e.g., Brent et al. 1988, Driessen et al. 1998, Friedman et al. 1983, Kessler et al. 1999, McGlashan 1986, Preuss et al. 2002, Yen et al. 2003), and mood disorders are the disorders most frequently associated with suicide and suicide ideation and discussed as risk factors for the presence of suicidality (Chioqueta & Stiles 2003, Hawton 1987). The majority of the studies that evaluate the relation of psychiatric disorders to suicide report major depression as the most significant diagnosis related to suicide (Asnis et al. 1993, Chioqueta & Stiles 2003, Isometsa et al. 1996, Spalletta et al. 1996). Overall, the lifetime risk for suicide in depressed patients is estimated at 2.2%

(Bostwick & Pankratz 2000, Papakostas et al. 2003). In a study of published cases specifically examining the diagnosis of people who died by suicide, Bertolote et al. (2003) reported that 53.7% of those who died by suicide were diagnosed with depression. This finding is consistent with Lonnquest (2000), who found a diagnosis of depression ranging from 29% to 88% in his review of psychological autopsy studies. It has been suggested that patients with depressive disorders have a suicide risk 60% to 70% higher than the general population (Khan 2002).

In addition to depression, the rates of suicide have also been found to be substantial for other mood disorders, especially bipolar disorder (Chen & Dilsaver 1996; e.g., Chioqueta & Stiles 2003, Vieta et al. 1997), and perhaps dysthymia (Angst 1995, Chioqueta & Stiles 2003, Hintikka et al. 1998, Isometsa et al. 1996). People diagnosed with bipolar disorder represent a diagnostic group of especially high suicide risk (Goodwin & Jamison 1990). Epidemiologic studies have found that 29% of bipolar disorder patients admit to at least one suicide attempt in their lifetime (Chen & Dilsaver 1996). Previous studies have identified bipolar disorder in 10% to 15% (Arato et al. 1988, Beautrais et al. 1996, Rihmer et al. 1995) and up to 47% (Rihmer et al. 1990) of suicide victims or suicide attempters. In their review of studies of bipolar disorder Balazs et al. (2003) reported that suicidal behavior is more frequent in bipolar II than in bipolar I disorder (Dunner et al. 1976, Endicott et al. 1985, Rihmer et al. 1990, Rihmer & Pestality 1999), attempts are more common in bipolar than in unipolar depression patients (Bulik et al. 1990, Dunner et al. 1976, Endicott et al. 1985, Rihmer et al. 1990, Rihmer & Pestality 1999), and bipolar patients are overrepresented among suicide victims (Rihmer et al. 1995).

The relation of dysthymia to suicide is less clear and studies have reported mixed results. Chioqueta & Stiles (2003) studied suicide risk in outpatients with specific mood and anxiety disorders and found that both a major depressive episode and bipolar disorder, but not dysthymia, were significantly associated with higher levels of suicidal ideation. The data supported an interaction effect in which higher levels of anxiety in patients with dysthymia were associated with more suicidal ideation.

Mood disorders have long been established as a risk factor for suicidality and particular emphasis and study have been placed on the relationship between depression and suicide. An obvious candidate for a neurobiological explanation of the association is dysregulated serotonergic functioning, which characterizes both depression and suicidality (Papakostas et al. 2003). From a psychological standpoint, hopelessness may be a mediator, in that hopelessness is clearly associated with both depression and suicidality, perhaps causally (as will be expanded on below).

Specific personality disorders have also been associated with suicidality. A diagnosis of a personality disorder is found in 9% to 28% of completed suicides and the significance of a personality disorder as a risk factor for attempted suicide is even greater, with rates reported as high as 55% among attempters (Soloff et al. 1994). BPD is frequently associated with suicide and is a long-established risk factor for suicide (see, e.g., Friedman et al. 1983, McGlashan 1986, Yen

et al. 2003). BPD is characterized by affective instability, interpersonal storminess, a diffuse sense of self, and behavioral impulsivity, including self-harm. BPD is described as among the most lethal of all psychiatric disorders, with the usual mechanism of death being suicide (Gunderson 1984, Keel et al. 2003). Approximately 50% of BPD patients have made a minimum of one very severe suicide attempt (Gunderson 1984); and among patients with this syndrome, an average of more than three lifetime suicide attempts has been documented (Soloff et al. 1994). Findings from the Collaborative Longitudinal Personality Disorders Study (Yen et al. 2003) report that BPD was the strongest predictor of a suicide attempt. In this study, a majority (77.6%) of those who attempted suicide met criteria for BPD, and conversely, 20.5% of borderline participants had made a suicide attempt during the two-year study interval (Yen et al. 2003). Further, a history of a previous suicide attempt among BPD patients is a stronger predictor of completed suicides than for any other diagnostic group (e.g., in 65% of suicides among BPD patients a prior attempt had been made, versus 33% among patients with major depression; Stone et al. 1987). The most significant link between suicide and BPD may be the instances of repeated self-injury characterized by the disorder. People diagnosed with this disorder will commonly engage in repeated self-harm behavior involving self-cutting, scratching, hitting, and swallowing harmful objects. Through repeated self-injury, people with BPD become practiced regarding suicidal behavior, and thus may lose fear regarding suicide and become competent about suicide, and as a consequence, engage in increasingly dangerous self-harm (Joiner 2002).

Another mechanism connecting BPD to suicidality may be emotion dysregulation. Many have hypothesized that when people with BPD engage in self-harm behaviors they do not actually intend to die; rather, they are attempting to regulate their emotions (Kemperman et al. 1997, Yen et al. 2003). Linehan (e.g., 1993) has emphasized emotion dysregulation as a core problem in and cause of suicidal behavior. The interpersonal strains associated with emotional dysregulation are likely to contribute to feelings of disconnection and ineffectiveness, which are significant predictors of suicidal behavior (Joiner 2002). Dialectical behavior therapy is an empirically supported therapy for BPD in which the main ingredient of the therapy is the reduction of self-injury. This is accomplished by teaching skills to regulate emotion.

Antisocial personality disorder, and its youth analogue, conduct disorder, are associated with suicidality. These disorders are characterized as a long-standing pattern of aggressive behavior and reckless and impulsive disregard for others as well as disregard for rules and norms. Substantial evidence exists for a relation between one aspect of antisociality—antisocial deviance—and suicidal acts, but not between another aspect of antisociality—unemotional callousness—and suicidality (Verona 2001; Verona et al. 2001, 2004). One mechanism explaining the link between antisocial personality disorder and suicide may be the combination of aggression and negative emotionality (e.g., anger). There is a heightened risk for suicidal behavior among individuals manifesting reactive aggressiveness,

persistent criminality, and antisocial personality disorder (Verona 2001). Additionally, a history of violent crime and juvenile delinquency has been associated with suicide attempts and completions in adulthood (Bland et al. 1998, Ivanoff & Jang 1991, Marcus & Alcabes 1993). Aggression is discussed further as an independent risk factor for suicide below.

Another possible explanation for the relationship between antisocial personality disorder and conduct disorder and suicide may be the cumulative effects of repeated instances of self-harm, both direct and indirect (e.g., through recklessness). Repeated self-harm is related to higher risk for eventual suicide (Ivanoff 1992, Marcus & Alcabes 1993). Antisocial personalities characterized by undercontrolled behaviors would be at a higher risk for suicide because their recklessness gives them opportunity to habituate to pain and injury, a potentially key process in serious suicidal behavior (Joiner 2002).

Of course, impulsivity may be another mechanism for the relationship between suicide and Cluster B personality disorders such as BPD and antisocial personality disorder. Impulsive personality characteristics are a well-documented risk factor for serious suicidality (see, e.g., Apter et al. 1993). Soloff et al. (1994) suggested that many suicide attempts in patients with BPD arise from a background of anger or impulsivity ("impulsive-aggression"), which may represent a primary behavioral dyscontrol in this disorder. Aggression, impulsivity, and antisocial traits have been associated with suicidal behavior in many studies (Soloff et al. 1994). As was noted above, there is converging evidence that the serotonergic system is a neurobiological substrate underlying the association between impulsivity, aggression, and suicidality.

Substance use disorders confer risk for suicidality as well (American Psychiatric Association 1994, Borges et al. 2000, Harris & Barraclough 1997, Miles 1977, Pokorny 1983). Koller et al. (2002) report that approximately 30% to 40% of male suicide attempters and 15% to 20% of female suicide attempters have alcohol-abuse or alcohol-dependence diagnoses (Rygnestadt et al. 1992), and approximately 7% to 8% of alcohol-dependent subjects die by suicide (Inskip et al. 1998). The relative lifetime risk for suicide in alcoholics is seven times higher than that of the general population (Gorwood 2001, Soyka et al. 1993). Darke & Ross (1997) report that in all studies they reviewed, the prevalence of attempted suicide among those with substance use disorders is many orders of magnitude greater than that of community samples. In studies of heroin users specifically, the lifetime prevalence of attempted suicide was reported at 35% (Vingoe et al. 1999) and 40% (Darke & Ross 2001). High levels of polydrug use have also been associated with attempted suicide (Murphy et al. 1983, Rossow & Lauritzen 1999). The number of drug classes used is a stronger predictor of suicidal behavior than is any individual drug class (Borges et al. 2000). Empirical evidence suggests that the risk is often associated with comorbidity with other disorders. Prigerson et al. (2003) states that there is a well-established suicide risk of comorbid diagnosis with substance abuse disorders in the general population. In his review of studies of death by suicide, Bertolote et al. (2003) found that comorbidity of mood disorder with

substance-related disorder was the most frequently found multiple diagnosis. Suicide risks associated with substance abuse and associated dual diagnoses among differing age groups are less well understood (Prigerson et al. 2003).

Koller et al. (2002) found that alcohol-dependent subjects with a history of suicide attempts have more aggressive and impulsive traits, and suggest that these traits may be significant factors in the pathogenesis of suicide attempts in alcoholics, largely independent of the suicide attempt method used. Additionally, it is important to note the confluence of general suicide risk factors in those who abuse drugs. Darke & Ross (1997) describe the social profile of heroine users (and likely other drug abusers) as one of predominant unemployment, low educational levels, social isolation, repeated incarceration, and high rates of parental alcoholism, general psychopathology, and divorce (Darke & Ross 2001; Harlow 1990; Johnsson & Fridell 1997; Marx et al. 1994; Murphy et al. 1983; Rossow & Lauritzen 1999, 2001; Segest et al. 1990; Tunving 1998). Given their widespread exposure to suicide risk factors, it is not surprising that the rates of both completed and attempted suicide are many times those observed in the general community (Darke & Ross 1997).

Symptoms of anxiety disorders have been implicated in serious suicidality, though findings on this point appear to be mixed. Data linking anxiety and suicide risk have been described as unclear (Khan et al. 2002, Placidi et al. 2000) and controversial (Cox et al. 1994). Noyes (1991) reported that suicide rates for those with an anxiety disorder range from 6% to 60%. An analysis of the Food and Drug Administration database of treatment outcome studies found a significant association between anxiety disorders and suicide (Khan et al. 2002). This study reported a suicide risk higher than described in many previous studies, and regardless of the type of anxiety disorder with which the subject was diagnosed, reported a high risk of suicide. Fawcett and colleagues have repeatedly shown that severe anxious agitation is an important sign of acute suicide risk (see, e.g., Busch et al. 2003), and others have reported the highest amount of suicidal ideation was associated with co-occurring major depression and anxiety disorder (Bartles et al. 2002). However, in a study by Beck et al. (1991), no patients with panic disorder, and 1.3% with panic disorder and agoraphobia, reported they had made a suicide attempt. In a study of suicide risk in outpatients with specific mood and anxiety disorders (Chioqueta & Stiles 2003), none of the anxiety disorders were associated with increased levels of suicide risk, and specific phobia was actually associated with significantly lower levels of suicidal ideation.

Of all the anxiety disorders, panic disorder probably has received the most attention with regard to associations with suicidality, and indeed, according to some researchers there does seem to be a significant association between panic disorder and suicidal symptoms (Noyes 1991, Weissman et al. 1989). It is possible, though, that the connection may be explained partly through comorbidity with mood disorders (Cox et al. 1994, Schmidt et al. 2000). The findings regarding panic disorder are mixed as are the findings regarding anxiety in general (Yen et al. 2003); some studies have not found associations between panic disorder and suicidality. Chioqueta & Stiles (2003) reported that panic disorder, whether

or not associated with agoraphobia, was not found to be associated with either hopelessness (a significant predictor of suicide) or suicidal ideation. Their findings were in accordance with Overbeek et al.'s (1998) study, which did not find higher suicide risk for the panic-disordered patients, even though they found higher levels of hopelessness in comparison with the control group, and with other more recent prospective studies in which panic disorder was not associated with an increased risk of suicide attempt (Brown et al. 2000, Placidi et al. 2000, Warshaw et al. 2000).

The diagnosis of schizophrenia has long been associated with an increased risk for suicide and suicide-related behaviors. It has been estimated that up to 13% of patients with schizophrenia will die of suicide, a rate comparable to that of mood disorder patients, and more than 20 times higher than in the general population (Allebeck 1989, Altamura et al. 2003, Black 1988, Meltzer 2003, Meltzer et al. 2000). As many as 40% of people diagnosed with schizophrenia spectrum disorders attempt suicide at some time in their lives (Axelsson & Lagerkvist-Briggs 1992, Meltzer & Fatemi 1995, Meltzer et al. 2000, Planasky & Johnston 1971). Many studies have investigated clinical variables linking schizophrenia to suicide. Not surprisingly, depressive symptoms in patients with schizophrenia are one of the most reported symptom sets related to suicidal behavior (Cohen et al. 1990, Heila et al. 1997, Mann et al. 1999, Potkin et al. 2003, Radomsky et al. 1999, Rossau & Montensen 1997, Roy & Draper 1995, Tandon & Jibson 2003; but not in Allebeck et al. 1987 or Young et al. 1998). In addition to depressive symptoms, Altamura et al. (2003) described many other variables related to suicide in schizophrenic patients, including male gender, a younger age, unemployment, a positive family history for suicidal attempts, comorbid substance abuse, and the lack of a supportive environment (Black & Winokur 1988, Breier & Astrachan 1984, Caldwell & Gottesman 1990, Siris 2001). Positive symptoms have also been associated with an increased risk for suicide (Addington & Addington 1992, Amador et al. 1996, Falloon & Talbot 1981, Fenton et al. 1997, Kaplan & Harrow 1999; Messias et al. 2001, Miller & Chabrier 1988). However, others have found that the presence of delusions did not increase the risk for suicide attempts (Grunenbaum et al. 2001). Meltzer (2003) reported five variables that were most predictive of suicidality among schizophrenic people, including number of lifetime suicide attempts, number of hospitalizations within the last three years, current or lifetime substance abuse, depression, and the severity of Parkinsonism. The relationship between hopelessness and suicide has been demonstrated in schizophrenic patients (Murphy 1983). In a study of patients' charts, hopelessness accounted for the relationship between depression and suicide in a group of schizophrenic inpatients who eventually died by suicide (Drake & Cotton 1986).

Joiner et al. (2001) provided data relating a particular aspect of depressive symptoms (self-hatred) that combines with schizophrenia to encourage suicidality. Their findings were consistent with Bleuler's (1911/1987) suggestions that self-hate may be one aspect of depressive symptoms that takes on an especially pernicious quality in people with schizophrenia-spectrum symptoms. The relation

of self-hate to suicidal symptoms was stronger among those with schizophrenia-spectrum symptoms than among others; this finding was specific to self-hate, and did not apply to depression in general (Joiner et al. 2001).

Finally, there is evidence that anorexia nervosa is associated with high rates of death by suicide. Herzog et al. (2000) followed 246 eating-disordered women (some with anorexia nervosa, some with bulimia nervosa) for more than 10 years. Seven died, three from suicide. All of those who died were anorexic; no bulimic women died. The risk of death by suicide among the anorexic participants was 58 times the expected rate (see also Keel et al. 2003).

Up until this point, we have focused on the specific relationships between psychiatric disorders and suicide. Much research supports these relationships; however, as has been noted, research has focused on other specific factors and their relationship to suicide. In addition to the several disorders that have been repeatedly linked with suicide, other factors such as hopelessness, social isolation, aggression, and ineffectiveness have been consistently linked to suicide.

Hopelessness

Hopelessness is significant in the etiology and maintenance of depression, and is a significant predictor of suicide. Hopelessness is defined as "a system of cognitive schemas whose common denominator is negative expectations about the future" (Beck et al. 1974, p. 864), or a "lowered expectation of obtaining certain goals and a diminished belief in the likelihood of achieving success" (Melges & Bowlby 1969). Beck (1963) considered hopelessness to be the mechanism, or the key factor, in the relationship between depression and suicide. Hopelessness has been found to correlate better with suicidal ideation than depression in prospective studies (Beck et al. 1974, Chioqueta & Stiles 2003, Silver et al. 1971, Wetzel 1976, Wetzel et al. 1980), and is a better predictor of suicide than of depression in some studies (Beck et al. 1985, 1990). Empirical research strongly supports the central role of hopelessness in suicidal ideation (Bedrosian & Beck 1979, Chioqueta & Stiles 2003, Dyer & Kreitman 1984, Minkoff et al. 1973, Nekanda-Trepka et al. 1983). Hopelessness is arguably the best predictor overall of suicide completions in clinical populations (Steer et al. 1993).

The development of hopelessness is often related to interpersonal factors (Perez-Smith et al. 2002). Joiner's (2002) Interpersonal-Psychological Theory of Attempted and Completed Suicide hypothesizes that suicidal people are specifically hopeless about feelings of being a burden on others and of failed belongingness. Concepts like burdensomeness and failed belongingness are interpersonal, and there is evidence that interpersonal factors are among the strongest predictors of serious suicidality.

Social Isolation

Social isolation—a state in which interpersonal contacts and relationships are disrupted or nonexistent (Trout 1980)—has been consistently related to suicidal

behavior. Many studies cite Durkheim (1897) as the first to propose and study the theory that suicide results in part from failure in social integration. It has been suggested that the fact that those who die by suicide experience isolation and withdrawal before their deaths is among the clearest in all the literature on suicide (Trout 1980). Studies of adolescents found that those with histories of suicide attempt often chose not to seek support from others (Greholt et al. 2000), and did not tell anyone what they were thinking during the period of suicidal ideation (Negron et al. 1997). In a study of suicidal and death ideation in older primary care patients, fewer social supports were associated with greater overall ideation (Bartles et al. 2002). Darke & Ross (1997) suggested that indices of social isolation and disadvantage were associated with risk of suicide (Appleby et al. 1999, Beautrais et al. 1996, Hassan 1995, Shepherd & Barraclough 1980).

Baumeister & Leary (1995) proposed that the need to belong is a fundamental human motive, and they provided many diverse lines of empirical support for their model. Baumeister & Leary (1995) argued that the need to belong to valued groups or relationships is a powerful, fundamental, and extremely pervasive motivation. When this need is thwarted, numerous negative effects on health, adjustment, and well-being have been documented. Joiner's (2002) theory of suicide suggests that this need to be social is so powerful that, when satisfied, it can prevent suicide; however, when the need for social connection is thwarted, risk for suicide is increased.

In addition to social isolation in the general population, isolation has been studied specifically in correctional settings. According to Felthous (1997), several authorities have argued from a clinical or theoretical viewpoint that isolation can adversely affect an inmate's mental state and increase the likelihood of suicide. Research shows that a large percentage of inmates who killed themselves while incarcerated were in isolation, and two of every three jail suicides occurred in isolation (Felthous 1997, Hayes & Kajdan 1981). In their study of an incarcerated group, Anderson et al. (2000) found that isolation presented an increased suicide risk, and the incidence of psychiatric disorders developed in the prison was significantly higher in prisoners in solitary confinement.

There is not only support for the fact that social isolation is detrimental to mental health, but data suggest that the presence of a social network is a protective factor against suicide. In their study of risk and protective factors for suicidal behavior in abused African American women, Kaslow et al. (2002) found that social support was a significant protective factor associated with nonattempter status. Hoyer & Lund (1993) studied nearly one million women in Norway and reported that women with six or more children had one-fifth the risk of death by suicide as compared to other women. These findings support Durkheim's (1897) hypothesis that parenthood is of great importance when it comes to suicide prevention in married women. Hoyer & Lund (1993) also found the highest rates of suicide in single women. This is consistent with statistics compiled by McIntosh (2002) that indicate the following suicide rates in the United States in 1999: divorced—32.7 per 100,000, widowed—19.7 per 100,000, single—17.8 per 100,000, married—10.6 per 100,000.

Impulsivity and Aggression

As has been touched on above, lifetime aggression and impulsivity are known correlates of suicidal behavior (Mann et al. 1999). Conner et al. (2003) explain that no matter how aggression is defined (as a psychiatric diagnosis, psychological construct, or overt violent behavior), it confers risk for suicide. Reactive aggression (Dodge & Coie 1987, Vitiello & Stoff 1997), characterized by proneness to reflexive anger in the context of aversive events, particularly perceived interpersonal threat, has been proposed as a diathesis for suicide risk, with acute risk occurring in the context of psychiatric illness (Conner et al. 2003, Mann et al. 1999).

Several studies focusing on violence and suicide found clear support for their association. In a study that compared 50 persons attempting suicide with 50 nonsuicidal psychiatric patients and with 50 nonpsychiatric control patients attending a heart clinic, suicidal patients had experienced an array of violent episodes to a significantly higher degree than either control group (Whitlock & Broadhurst 1969). Similar results were found in a study of coroners' statistics in 32 inner-city boroughs in London (Kennedy et al. 1999). Rates for suicide, violence, and homicide were highly correlated with one another. The more violence and homicide occurred in a given borough, the higher the suicide rate.

Conner et al. (2001) reported on a representative survey of next-of-kin and other respondents close to people who had died by suicide and by other means in the previous year. Findings suggest that those who had died by suicide had more frequently threatened and attempted violence in the previous year, as compared to accident victim controls. Brent et al. (1994) found that a lifetime history of aggression differentiated adolescent suicide victims from matched controls, even after controlling for differences in psychopathology between suicides and controls.

Other factors also point to an association of experience with violence and related suicidality. As Conner et al. (2003) pointed out, prison inmates are at increased risk for suicide compared to community dwellers, and inmates completing suicide are more likely to have been incarcerated for manslaughter or murder as compared to other prisoners (DuRand et al. 1995).

Ineffectiveness

The view that ineffectiveness is painful has informed and been informed by prominent theories of psychopathology, including those related to the learned helplessness model (Abramson et al. 1978, 1989). Extending this perspective to include the particularly painful aspects of personal ineffectiveness affecting others is consistent with work on the possible roles of shame and guilt in psychopathology generally (Tangney et al. 1992) and suicidality in particular (Hastings et al. 2000). Factors such as unemployment, low income, physical illness, and less education can make it more difficult to be an effective agent of change in one's environment. These factors likely make it more difficult to negotiate tasks of daily living, obtain help from others, and cope with stressors. If individuals are able to obtain material resources, they may be somewhat protected against suicide (Kaslow et al. 2002);

if not, this can lead to feelings of hopelessness and feelings that one is a burden on others. To perceive oneself as ineffective is painful, and it is even more painful to perceive oneself as so ineffective that loved ones are threatened and burdened. Joiner's (2002) suicide theory proposes that feelings of ineffectiveness contribute to the desire for suicide, and that feeling ineffective to the degree that others are burdened is among the strongest sources of all for the desire for suicide.

To our knowledge, four studies have directly assessed perceived burdensomeness in suicidality. Brown et al. (1999) conducted a questionnaire study of college students, and found the predicted correlation between feeling a burden on kin and suicidality. Burdensomeness stood out as a unique and specific predictor of suicide-related symptoms even when key variables were controlled. Joiner et al. (2002b) trained raters to evaluate suicide notes regarding the following dimensions: perceived burdensomeness, hopelessness, and generalized emotional pain. Unknown to the raters, half of the notes were from people who died by suicide, and half were from people who attempted suicide and survived. In correlation/regression analyses in which predictors were controlled for each other, the notes from those who died by suicide contained more perceived burdensomeness than did notes from attempters; no effects were found regarding hopelessness and emotional pain. A second study in the Joiner et al. (2002b) report took a similar approach, except that all notes were from those who died by suicide, and perceived burdensomeness, hopelessness, and generalized emotional pain were used as predictors of lethality of suicide method (e.g., self-inflicted gunshot wound was viewed as relatively more lethal than overdose). Here again, perceived burdensomeness was a significant predictor of lethality, whereas hopelessness and generalized emotional pain were not. DeCatanzaro (1995) conducted a survey on reproductive behavior, quality of family contacts, and suicidal ideation on several hundred community participants, as well as on five high-suicide-risk groups (e.g., general psychiatric patients, incarcerated psychiatric patients). Within each of these samples, of all the many variables assessed, perceived burdensomeness toward family and social isolation were especially correlated with suicidal ideation.

Although not direct tests of the burdensomeness view of suicidality, several other studies have reported results consistent with this perspective. For example, Brown et al. (2002) reported that genuine suicide attempts were often characterized by a desire to make others better off, whereas nonsuicidal self-injury was often characterized by desires to express anger or punish oneself. As in other studies (e.g., two studies from Joiner et al. 2002b), burdensomeness emerged as a key variable even as compared to other powerful correlates of suicidality (see also Filiberti et al. 2001, Magne-Ingvar & Oejehagen 1999, Motto & Bostrom 1990).

CONCLUSIONS

From both neurobiological and psychological perspectives, extant research findings converge on the view that two general categories of risk for suicide can be identified: (*a*) dysregulated impulse control; and (*b*) propensity to intense

psychological pain (e.g., social isolation, hopelessness), often in the context of mental disorders, especially mood disorders. Each of these categories of risk is underlain at least to some degree by specific genetic and neurobiological factors; these factors in general are not well characterized, though there is emerging consensus that most, if not all, reside in or affect the serotonergic system. The specific ways in which these categories of risk are translated into actual suicidal behavior is not clear, and is a main frontier for future research.

In this connection, we would counsel against simplistic theorizing of the sort that one factor or class of factors is a main cause of suicide. For example, the evidence is clear that mental disorders comprise a significant risk for suicide. Yet, the genetic contribution to suicide exists beyond the effects of mental disorders, and the majority of people with mental disorders do not attempt or die by suicide. Similarly, impulsivity is a documented risk factor for suicidal behavior, leading some to imagine that "impulsive suicide"—that is, spur-of-the-moment death by suicide—is common. Yet, it is exceedingly difficult to document a case like this, where it is clear that spur-of-the-moment processes were operative apart from more long-standing processes.

We therefore believe that a full understanding of suicide will involve multivariate, interactive models that are constrained to account for the facts summarized in this review. Joiner's (2002) interpersonal-psychological theory is an attempt at this—the theory contends that people gradually acquire the ability to enact lethal self-injury through prior experience with self-injury (which in turn is encouraged by impulsive behavior underlain by serotonergic dysregulation). The theory further asserts that this ability is not acted upon unless the desire for death is instantiated by a strong sense of perceived burdensomeness coupled with a sense of failed belongingness; these two factors are relevant to why hopelessness, social isolation, and the mental disorders of which they are associated features comprise a clear risk for suicidal behavior. This model is presented as a tentative example of the kind of theorizing that will be necessary to be simultaneously conceptually precise about the specific preconditions of serious suicidal behavior as well as epistemically broad, explaining the daunting array of suicide-related facts at levels ranging from the molecular to the cultural.

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